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# THE CHINESE PHYTOTHERAPY: ORIENTAL AND WESTERN PATHOPHYSIOLOGICAL ASPECTS AND PERSPECTIVES: THE EXAMPLE OF *EPHEDRAE DECOCTUM*

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Dissertação de Mestrado em Medicina Tradicional Chinesa

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Dissertação de Candidatura ao grau de Mestre em Medicina Tradicional Chinesa submetida ao Instituto de Ciências Biomédicas de Abel Salazar da Universidade do Porto.

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## Abbreviations

11-β-OHSD - 11-β-hydroxysteroid dehydrogenase

3MGA - 3β-monoglucuronyl-18β-glycyrrhetic acid

A1C - glycated hemoglobin or HbA1c

ACO - acyl-CoA oxidase

ADP - adenosine diphosphate

AGE - advanced glycationend product

ALB - albumin

ALT - alanine aminotransferase

AMPK - AMP-activated protein kinase

AST - aspartate transaminase/Aspartate aminotransferase

ATP - adenosine triphosphate

AUC - area under the plasma curve

BUN - blood urea nitrogen

CAM - complementary and alternative medicine

CC - *Cinnamomum cassia*

CCL - CC chemokine ligand

CD36 - fatty acid transporter

CE - cinnamon water extract

CECs - cerebral endothelial cells

CFS- chronic fatigue syndrome

CHC - chronic hepatitis C

CHM - Chinese herbal medicines

CMV - cytomegalovirus

CNS - central nervous system

COX-2 - cyclooxygenase-2

CP - Chinese pharmacopoeia

CPM - Chinese proprietary medicines

Cr - creatinine

Cyt-C - cytochrome C

D-Gal N - galactosamine

DGL - deglycyrrhizinated licorice

DHEA - dehydroepiandrosterone

DHS - dropped head syndrome

DIN - Drug Identification Number

DIO - diet-induced obesity

DM - differentiated medium

DPP-4 (DDP IV) - dipeptidyl peptidase IV

EAT - *Ehrlich* ascites tumor

EKG - electrocardiography

ELISA - enzyme-linked immunosorbent assay

EP - European pharmacopoeia

ER - estrogen receptor

ET-1- endothelin-1

FAS - fatty acid synthase

FBG - fasting blood glucose

FDA - Food and Drug Administration

FER - food efficiency ratio

FFA - free fatty acids

FHF - fulminant hepatic failure

fMRI - functional magnetic resonance imaging

FST - forced swimming test

GC - gas chromatography

GC/MS- GC/mass spectrometry

GEPRs - genetically epilepsy prone rats

GER - gastric emptying rate

GG - *Glycyrrhiza glabra*

GGT - gamma-glutamyltransferase

GLP-1- glucagon-like peptide-1

GLS - *G. uralensis* saponins

GLU - glucose

Glut4 - glucose transporting protein 4

GLUTs - hexose transporter protein

GP - glycyrrhiza polysaccharide

GPMT - guinea pig maximization test

GRAS - Generally Recognised As Safe

Grb2 - growth factorreceptor-binding protein 2

HbA1c - A1C or glycated hemoglobin (glycosylated hemoglobin A1c)

HBsAg - hepatitis B surface antigen

HC - hypercholesterolaemic animals

HCC - hepatocellular carcinoma

HDL- high-densitylipoprotein

HDL-C - high-density lipoprotein cholesterol

HFD - high-fat diet

HGG-I - hypercholesterolaemic animals administered with 5 gm% Glycyrrhiza glabra root powder

HGG-II - hypercholesterolaemic animals administered with 10 gm% Glycyrrhiza glabra root powder;

HIV - human immunodeficiency virus

HMG-CoA - 3-hydroxy-3-methylglutaryl-coenzyme A

HPLC - high performance liquid chromatography

HPLC -DAD - high performance liquid chromatography with diode array detection

$IC_{50}$ - inhibitory concentration reducing activity to 50% of controls

IFN - interferon

IKS - Interkantonale Kontrollstelle fur Heilmittel

IL-1β - interleukin-1β

iNOS - inducible nitric oxide synthase

IPGTT- intraperitoneal glucose tolerance test

IR - insulin receptor

IRS - insulin receptor substrate

IRS -1 and IRS-2- insulin receptor substrate-1 and insulin receptor substrate-2

JP - Japanese pharmacopoeia

LBD - ligand-binding domain

$LD_{50}$ - mean lethal dose (lethal dose killing 50% of animals)

LDH - lactate dehydrogenase

LDL - low-density lipoprotein

LDL - low-density lipoprotein

LDL-C - low-density lipoprotein cholesterol

LicA - licochalcone A

LPL - lipoprotein lipase

LPS - lipopolysaccharide

MHCP - methylhydroxychalcone polymer

MIC - minimum inhibitory concentration

MPA - Medical Products Agency

mRNA - messenger ribonucleic acid

MRSA - methicillin-resistant *Staphylococus aureus*

MS - mass spectrometry

NC - normal controls

NF- Kb - nuclear factor kB

NGG-I - normal animals administered with 5 gm% *Glycyrrhiza glabra* root powder

NGG-II - normal animals administered with 10 gm% *Glycyrrhiza glabra* root powder

NK - natural killer

NLT- not less than

NMDA - receptor- N-methyl D-aspartate receptor

NMT- not more than

NO - nitric oxide

NOS - nitric oxide synthase

OPC - oligomeric procyanidin

OTC - over-the-counter

OVA - ovalbumin

PARP- poly (ADP-ribose) polymerase

PB2 - post prandial 2h blood glucose levels

PCA- passive cutaneous anaphylaxis

PEL- primary effusion lymphoma

$PGE_2$ - prostaglandin $E_2$

PI - phosphatidylinositol

PI 3-kinases or PI3Ks - phosphoinositide 3-kinases

PP - Portuguese pharmacopoeia

PPAR - peroxisome proliferator-activated receptor

RDDP - RNA-Dependent DNA-polymerase

rhCK-II - recombinant human casein kinase II

ROS - reactive oxygen species

rRT - reverse transcriptase

RT-PCR - reverse transcription-polymerase chain reaction

SARS - severe acute respiratory syndrome

SARS-CoV - SARS-associated coronavirus

SBP - systolic blood pressure

SDH - succinate dehydrogenase

SHC- src-homology-collagen-like protein

SLE - systemic lupus erythematosus

SNMC - Stronger Neo-Minophagen C

SOD - superoxide dismutase

STZ - streptozotocin

TBIL - total bilirubin

TC - total cholesterol

TCD - traditional Chinese drugs

TCM - traditional Chinese medicine

TG - triglycerides

THM - traditional herbal medicine

TNF-α - tumor necrosis factor alpha

Total-C - total cholesterol

TRLs - triglyceride -rich lipoproteins

TST - tail suspension test

TZD - thiazolidinediones

USFDA - United States Food and Drug Administration

VEGF - vascular endothelial growth factor

VLDL - very low-density lipoprotein

VSV - vesicular stomatitis vírus

WBC - white blood cell count

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## Abstract

One of the most important areas of intervention of Traditional Chinese Medicine is Phytotherapy. The repertoire of Chinese plants includes many well-known plants in the West, and their effectiveness has been tested, but there´s a lot of work to be done.
Although many of the old Chinese formulas continue to be used in the East, many of its therapeutic properties remain little known by the Western scientific community.
The Ephedra Decoction (*Herba ephedrae, Semen armeniacae, Ramulus cassia, Radix Glycyrrhizae*) is one of the oldest Chinese formulas, as described in the *Shang Han Lun*.
In this master thesis I tried to search according to the sensitivity of Eastern and Western knowledge about each of the plants constituents of this formula and make the crossing information. It was concluded that most of the chemical constituents and pharmacological actions resulting from each individual plant explain its conduct traditional Chinese therapy behavior.

## Key words

Traditional Chinese Medicine, traditional Chinese drugs, *Ephedrae Decoctum* (Ephedra Decoction), *Herba ephedrae, Semen armeniacae, Ramulus cassia, Radix glycyrrhizae*

## Resumo

Uma das áreas mais importantes de intervenção em Medicina Tradicional Chinesa é a Fitoterapia. O repertório de plantas Chinesas inclui muitas plantas bem conhecidas no Ocidente e a sua eficácia já foi testada. Apesar de muitas das antigas fórmulas chinesas continuarem a ser utilizadas no Oriente, muitas das suas propriedades terapêuticas persistem pouco conhecidas pela comunidade científica ocidental, à luz dos conhecimentos do Ocidente.

A decocção de efedra (*Herba ephedrae, Semen armeniacae, Ramulus cassia, Radix glycyrrhizae*) é uma das mais antigas fórmulas chinesas, já descrita no *Shang Han Lun*. Nesta tese procurou-se pesquisar de acordo com a sensibilidade oriental e ocidental o conhecimento acerca de cada uma das plantas constituintes desta fórmula e proceder ao cruzamento da informação. Concluiu-se que muitos dos constituintes químicos e consequentes acções farmacológicas individuais de cada planta explicam o seu comportamento terapêutico tradicional chinês.

## Palavras - chave

Medicina tradicional Chinesa, plantas tradicionais Chinesas, *Ephedrae Decoctum* (Decocção de Efedra), *Herba ephedrae, Semen armeniacae, Ramulus cassia, Radix glycyrrhizae*

# 1. Objectives

One of the most important areas of intervention of Traditional Chinese Medicine is Phytotherapy. The repertoire of Chinese plants includes many well-known plants in the West, and their effectiveness has been tested, but there is still a lot of work to be done. The aim of this Master Thesis is to link the Chinese pathophysiological aspects of a Chinese standard formulation (Ephedrae Decoction) with the western pathophysiological, pharmacological and chemical aspects.

# 2. Motivation

When I began studying Chinese medicine 4 years ago, a new world opened before my eyes. I found great interest in Chinese Pharmacology once my scientific background being Pharmaceutical Sciences. With this master thesis I will try to bring Western and Chinese perspectives on the Chinese herbs pharmacology together, and to bridge two worlds with the example of the ancient formula Ephedra Decoction (Mahuang Tang).

# 3. Research design and methods

***Search methodology***

To be included in this research, I conducted a systematic literature search of Medline/ PubMed, Scirus, Scopus, Proquest and Google Scholar, with no date or language restriction. I used the following medical subject headings and keywords: efedra, ephedra(e), mahuang, Mahuang, cinnamon, cinnamomum, cinnamomum cassia, cinnamomum zeylanicum, cinnamomum verum, cinnamomum aromaticum, cassia, ramulus cinnamomi, cortex cinnamomi, ramuli cinnamon, cortex cinnamon, cinnamon twig, cinnamon bark, guizhi, gui zhi, rougui, rou gui and other variations, semen armeniaca(e), apricot kernel, xingren, xing ren, radix glycyrrhiza(e), gancao, gan cao, licorice alone or in combination with: tradicional Chinese medicine, TCM, mao-to, ma-huang tang, traditional Chinese herbs, Chinese herbology, alone or other variations. A manual search of retrieved articles was also performed. Reference lists and citations of included studies were also checked. In addition, the following additional databases were consulted: Chinese Herb Dictionary, Complementary and Alternative Healing University, eNatural Health Center, Sacred Lotus Arts-Traditional Chinese Medicine-TCM Herbs, Traditional Chinese Medicine and Acupuncture Health Information Organization, Natural Medicines Comprehensive Database.

# 4. Introduction

Traditional Chinese medicine (TCM) has developed over more than 4000 years and is one of the most tested and applied sciences in mankind. Today, a tremendous amount of medical knowledge has been accumulated. For example, much knowledge of herbal drugs, such as sapor, nature, channel tropism, efficacy and compatibilities, has been discovered and verified. Each herbal drug has its own particular medical efficacy, and when combined with some others, we obtain a formula or decoction with more curative effects. Formulae that have proven medically effective have been treasured as part of the TCM legacy and recorded in text for future use or instruction (Cao *et al.,* 2004).

Traditional Chinese drugs (TCD), being natural materials, appeal to many people, because of their high activity, low toxicity, and rare complications. Building new TCM pharmacology theories relies heavily on thorough understanding of their chemical action. One of the most important tasks in revealing this is to analyze the composition of each TCD. It is well known that the determination of TCD is a rather complex problem compared with analysis of pharmaceutical medicine. For example, even a TCM for treating the common cold contains hundreds of chemical components. It is difficult to analyze such complex systems with a conventional single-wavelength detector unless demanding conditions are imposed to the chromatographic separation process. This calls for specific tools to handle these complicated systems. Fortunately, modern hyphenated chromatographic instruments, for example high performance liquid chromatography (HPLC) with diode array detection (HPLC–DAD) and gas chromatography mass spectrometry (GC–MS), and related chemometric methods, provide powerful tools to accomplish such an arduous job (Xu *et al.,* 2001). Traditional Chinese pharmacology, pharmacology in the broad sense, is an integral part of TCM. It deals with the origin, collection, processing, actions and used of TCD, or Chinese Materia Medica, under the guidance of the basic theory of TCM (Ganzhong *et al.,* 2003).

There are very rich resources of TCD. According to a recent survey, the number of TCD is 12.807. Among them, 11.146 are drugs of plant origin; the rest are of animal or mineral origin. Hence, traditional Chinese pharmacology is sometimes called traditional Chinese herbal pharmacology (Ganzhong *et al.,* 2003). The theories that govern the prescription of medicinal plants are taken from traditional Chinese pharmacology, itself based on long centuries of clinical observation and practice (WHO, 1997).

## 5. The Development of Modern TCD Pharmacology

The modern pharmacology of TCD started in China 70 years ago, when Dr. KK Chen (Chen Kehui) published a paper on ephedrine. There were around 30 TCD studied from the 1920s to the 1940s by phytochemists and pharmacologists, such as *Radix Angelicae Sinensis* (danggui), *Rhizoma coptidis* (huangglian), *Radix Aconiti* (chuanwu), *Radix Dichroae* (changshan), *Radix Stephaniae Tetrandrae* (fangji), *Bulbus Fritillariae* (beimu), *Rhizoma Corydalis* (yanhusuo), etc (Ganzhong *et al.,* 2003).

Beginning in the 1950s, the Chinese government has paid great attention to the development of TCM. TCM colleges have been established in every province and autonomous region, and TCM hospitals and research institutes at the national provincial, municipal and even county level have been set up. The development of TCM has thus entered a new era (Ganzhong *et al.,* 2003). The trend of development of TCD is in two directions: One treats TCD as ordinary natural resources, plants and/or animals, and endeavors to extract new chemical ingredients from them. A number of compounds have been isolated and identified. Their actions have been studied and they have undergone clinical trial. Hence, a number of new drugs have been developed and marketed, such tetrandine, artemisinine and its derivatives, ferric acid, etc (Ganzhong *et al.,* 2003). The other is the study of TCD under the guidance of TCM theory, mainly studying the actions of prescriptions experimentally and clinically. The traditional pharmaceutical preparations are also undergoing transformation. New forms of patent TCD are instant powders, tablets, injections and capsules. In order to elucidate the actions of prescriptions, both classical and contemporary, actions of drugs in the prescription individually and in combination have been studied and clarified. Chemical constituents in prescriptions are also being investigated. Hence there is both a need and the conditions to form a modern pharmacology of TCD which will include both the classical descriptions of actions and uses in TCM and the new information and data obtained from the study of TCD using modern technology and expertise. As a result, since the 1980s, the pharmacology of Chinese materia medica has been listed as a course in the curriculum of colleges of TCM, and textbooks have been published. Yet, TCM pharmacology is still at the infant stage, and there is still a lot of work to be done (Ganzhong *et al.,* 2003).

# 6. Designing of a Chinese formula

Westerners learning about Chinese herbs are often exposed to unusual concepts regarding the form of herbal administration.
It is known that each formula is composed of certain herbs but it is more than a random group of herbs combined at one´s pleasure. Simple addition of the effects of some herbs does not entirely equate to the efficacy of a formula, in fact, is a process in which some proper herbs, guided by the principle of treatment based on syndrome differentiation, are chosen to constitute the formula in a certain formula-forming pattern. Among the herbs which constitute the formulas, there exists a certain formulating relationship such as the relationship of supplementing each other, relationship of both opposing and complementing each other, relationship of both opposing and complementing each other, etc. Generally the constitution of a formula has three purposes:

- Adapting to the condition of the disease and increasing the therapeutic efficacy;
- Harmonizing the partial property of the herbs and inhibiting their side-effects;
- Reducing the toxicity (Gongwang, 2002).

A formula consists of ruler/emperor, minister/*medicamentum ministrale,* assistant, and nuncio medication/signaling medication (Greten, 2007). Other authors use other terms like monarch (principal herb), minister, adjuvant and dispatcher, respectively.

1. The most important is the ruler, or the emperor (principal herb): the herb which is aimed at producing the leading effects in treating the cause and main symptoms of a disease.
2. The minister: the herb which helps the ruler to increase the effects of the principal herb, or treats the accompanying symptoms of a disease.
3. The assistant: it can be divided into the following three types:
   a) The herb which helps to reinforce the actions of the principal and minister herbs, or the one which treats the minor accompanying symptoms of a disease.
   b) The herb which eliminates or restrains the drastic actions of the principal and minister herbs or the toxicity of these herbs.
   c) The herb which can reduce the overly potent action of the principal ingredients. For instance, adding one or two cool or cold-natured herbs to the formula dominated by the herbs of warm or heat nature can prevent the warm or heat property of the principal herbs from damaging the body fluid.

4. Signaling medication: the herb which mediates or coordinates the effects of various ingredients in the formula, or the herb which directs the actions of other herbs in the formula to the affected site.

As a whole, the establishment of principal, assistant, adjuvant and dispatcher herbs in a formula should be based on their respective importance of efficacy, potency and dosage in the formula. Generally, there is only one principal herb in a formula though there may occur a case where there are two or three principal herbs in a complex formula. In a formula, the principal herb is absolutely necessary while the assistant, adjuvant and dispatcher herbs may be rejected according to the state of disease or herbal property. For some simple formulas, it is common that there are only the principal and assistant herbs, or the principal and adjuvant herbs (Gongwang, 2002).

### The example of Ephedrae Decoction

- The the ruler, or the emperor is *H. ephedrae*. This part of a concoction acts as the principal medication representing the main direction of impact or main attack on disease. As this is the most important constituent, we take e.g. 4 once a day (the Chinese ounce is 3 grams), or about 60g per week. *H. ephedrae* is known to liberate the extima and to unfold the pulmonary orb. If it is taken roasted in honey it takes of pituita and humor thereby facilitating breathing and stopping cough. In other words, this medication works double-fold. The main action is to enhance the orb function.

- A suitable *medicamentum ministrale*, suitable minister to this ruler should work in the same direction. Under the condition that we want to treat bronchitis with difficulties to breathe, such as is spastic bronchitis or asthma, we would to get rid of mucus and stop coughing. A suitable minister in this sense is S*emem armeniacae*. This medication belongs to Group XIII c) which removes pituita and stops coughing. So, in a way one could say that the minister acts dependent on the ruler and in a related direction of impact. It is the second main attack which complements the first, the principal impact. In this sense we add the effect on coughing and enhance ephedra´s liberation of airways. If you follow the idea of proportional dosage, we should have about 45g a week. The dosage therefore represents the hierarchy of the effects necessary.

- The assistant drug also cannot work independently of the boss and the second boss of this prescription. It also must fit into the general direction of attack. If it would contradict, e.g. by cooling, it would take away some of the effect of the ruler, thereby weakening the whole prescription instead of making it more effective. Ephedra, the ruler, is very hot. In so far it is directed against a cold attack. Its group is *liberantia extimae acria et calida*. Therefore we can assume that the concept is good for coughing as a result of cold as often seen in asthma. It is therefore a good complement to warm up the *extima* in order to get rid of the cold. For this propose we need a warming liberantium, a warming medication liberating the *extima* and to support the idea of *H. ephedrae*. *Ramuli cassia* does not only liberate the *extima* but also is warm in nature and therefore warms the pulmonary orb, as the *extima* is part of the pulmonary orb. 30g a week would correspond to its function as the assistant of this prescription. Now we have a medication which "opens" the airways and the pulmonary orb, gets rid of pituita, stops coughing and acts against cold which covers the main features of common cold, bronchitis and asthma.

- The nuncio medication or signaling medication here is *R. glycyrrhizae* with itself is supplective in nature and belongs to the *supplentia qi* group. This medication has a special effect not known by other. It distributes and guides the qi of the decoction not only in one conduit but in all 12 conduits at the same time. It is also sweet as a sapor and therefore harmonizes by strengthening the center. This is a desired effect within the overall purpose of the medication. If you want to get rid of pituita strengthening the center makes sense. The whole prescription actually is strongly guided to the pulmonary orb by the first three constituents already. This medication does not need to be directed to the pulmonary orb any more. On the contrary, it is necessary to soften this strong and very unilateral effect. Following the ideal of proportional usage, 15g per week is suitable. With this medication the much accentuated effect on the pulmonary orb is softened and spread over the whole medication has a genius double effect. You open the extima and all conduits, remove humor and pituita and warm it up tremendously, as especially ephedra and *Ramuli cassia* are warm liberanting substances. On the other hand, you also open and unfold the intima by S*emen armeniacae* and strengthening the center with *R. glycyrrhizae* (Greten, 2007).

The example of this concoction shows that that the hierarchy within a concoction is extremely important for the effects in clinical usage. It shows that some of the herbs are not harmless and that we have to determine the primary objective of a concoction before composing it (Table 1) (Greten, 2007).

**Table 1.** Hierarchy in Ephedrae Decoction (adapted from Greten, 2007)

| | | | |
|---|---|---|---|
| I | ***Herba ephedrae roasted in honey*** | 60g | Opens the extima and unfolds the pulmonary orb, there by leading qi down, enhancing breathing, stopping anhelitus, and removes pituita |
| II | ***Sem. Armeniacae*** | 45g | Removes pituita, warms and stops coughing |
| III | ***Ramuli cassiae*** | 30g | Warms the extima and the pulmonary orb, thereby eliminating algor |
| IV | ***Radix glycyrrhizae*** | 10g | Softens and connects the 3 others by leading into 12 conduits, being sweet and strengthening the center |

In the literature we find several references to Ephedra Decoction where the usual quantity of its constituents can vary widely (Table 2). Some examples:

**Table 2.** Examples of diferent constituent quantitys according diferents authors

| | (Liu *et* Tseng, 2005) | (Gongwang, 2002) | (Ling, 2005) |
|---|---|---|---|
| *H. ephedra* | 9 g | 6g | 6g |
| *Ramuli cassia* | 9 g | 6g | 4g |
| *Semen armeniacae* | 9 g | 9g | 9g |
| *Radix glycyrrhizae* | 3 g | 6g | 3g |

Of course we can play a little with the constituents. If we change the position within the hierarchy of the 4 constituents, we could e.g. give *Ramuli cassiae* the position of S*em. armeniacae*. In this case we would happen between *H. ephedrae* and *Ramuli cassiae* whith both liberate the *extima*. This would be the classical usage of this concoction which is for the earliest phases of colds. We would maybe also not roast *H. ephedrae* in honey in order to enhance the extima liberanting effect and not the pituita dissolving effect. This little change would make this concoction useless for chroric asthma, as *H. ephedrae*, the ruler, would not anymore take away edema and mucus from the bronchi. We would rather promote sweating. Chronic asthma, however, is a condition which normally complies with stage IV of the ALT, an intimal event. Therefore, this second variation which is classical and older now is not as frequent as the alteration given as an example for a concoction (Greten, 2007).

Pulses for the original extima liberating form of this concoction should be superficial in the right policar, right clusal position and mostly intent, whereas superficiality is not seen in intimal disease. Also in the typical Stage IV (yin major), the intent pulses are often overlaid by slippery pulses (*pulsus lubricus*) indicating pituita and humor rather being effective than algor. The dosage of the concoctions varies a lot. One can say that a concoction is not a prescription but a therapeutic constellation that has to be adapted to the individual case. In those cases in which coughing and mucus are tremendous, *Semem armeniacae* can be enhanced, in other cases in which breathlessness, dyspnea, is the leading symptom, *H. ephedrae* can be augmented. In cases in which cold syndromes appear on the skin, in the muscles, etc. also *Ramuli cassiae* can be raised (Greten, 2007).

**Note:** *H. ephedrae* can raise blood pressure, lead to palpitations and mydriosis. These effects are less common within the concoction as a whole. This may be due to roasting it in honey and by the beneficial effects of *R. glycyrrhizae* or other molecules in the concoction. *H. ephedrae* was the first substance to show genomic differences in the pharmacodynamics, as 9 out of 10 Chinese persons do not have mydriasis in a certain dosage, whereas 9 out of Caucasians respond sensitive with their sympathetic nervous system. Within the range of the dosage and in the combination given we have rarely seen this. Again it is necessary to start with one third of the daily dosage and then individually regulate the dosage required (Greten, 2007).

## 7. Characterization of Ephedra Decoction (Ma-Huang Tang) 麻黃湯

### Constituents

*Herba ephedrae, Semen armeniacae, Ramulus cassia, Radix glycyrrhizae*

### Category

Formulas that Release the Exterior (Anonymous, 2009a).

### Uses

The main indications for Ephedra Decoction are absence of sweating and presence of wheezing which is a result of algor constricting the extima leading to Lung *Qi* rebellion. Thus, *H. ephedrae* is used as a chief herb to promote sweating and calm wheezing which follows the principle of using acrid warm herbs and promoting sweating (Liu *et* Tseng, 2005). Exterior syndrome of excess due to wind-cold (Cold stroke syndrome of Taiyang channel) (Anonymous, 2009a; Anonymous, 2009c; Cheng, 2008; Gongwang, 2002) that causes chills and fever, headache body ache, absence of sweating (Anonymous, 2009a;

Gongwang, 2002; Ling, 2005; Liu *et* Tseng, 2005), wheezing, decreased taste sensitivity (Ling, 2005; Liu *et* Tseng, 2005), stuffy and running nose (Anonymous, 2009a; Gongwang, 2002), cough or asthma (Cheng, 2008; Gongwang, 2002), thin white tongue coat (Anonymous, 2009a; Gongwang, 2002), floating, and tight pulse (Anonymous, 2009a; Gongwang, 2002; Ling, 2005; Liu *et* Tseng, 2005).

### Actions

Releases the Exterior Cold and arrests wheezing. Opens the Lung Qi (Anonymous, 2009c) and induces sweating (Anonymous, 2009a; Anonymous, 2009c; Cheng, 2008; Ling, 2005), relieving the exterior syndrome (Anonymous, 2009a; Cheng, 2008; Ling, 2005), dispersing the lung to relive asthma (Gongwang, 2002), disperses algor, favors the dispersive action of the lung and eliminate asthma (Cheng, 2008).

### Western uses

This medication is commonly used in asthma (Anonymous, 2009a; Cheng, 2008; Greten, 2007), common cold (Anonymous, 2009a; Cheng, 2008), and chronic obstructive pulmonary disease (COPD) (Greten, 2007), influenza (Cheng, 2008; Chu, 2008), recommended for cases of flu accompanied by nasal congestion, sinusitis (Cheng, 2008) and cough (Anonymous, 2009a). Also used in rheumatoid arthritis, nocturia, cystitis and measles (Cheng, 2008).

### Originally Appeared In

On Cold Damage (Shang Han Lun) (*Discussion of Cold-induced Disorders*) (Anonymous, 2009a; Ling, 2005), Algor Leadens Theory (Greten, 2007).

## Brief description of the action of the constituents

***Herba ephedrae:*** pungent and slightly bitter, warm. Relieves the surface, disperse lung, and eliminates liquids and edema. Sweat to disperse syndrome superficial; encourages the dissemination and relaxes cough wheezing. Related to the pulmonary and vesical orbs.

***Semen armeniacae:*** bitter, slightly toxic; warm. Descends Lung Qi, relieves cough and asthma, and moistens intestines. Slow down wheezing cough. Related to the crass intestinal and pulmonary orbs.

***Ramulus cinnamomi:*** sweet, warm. Relieves the surface, warm the Yang and facilitates the flow channels, warms and unblocks channels to strengthen Yang, stimulates nutrient layer and defensive, supports *Herba ephedrae* to strengthen diaphoretic and dispersive action. Related to the cardial, pulmonary and vesical orbs.

***Radix glycyrrhizae:*** sweet, neutral. Approximate the actions of the other ingredients, moderate the diaphoretic action of *Herba ephedrae*, and coordinate the other plants. Related to all the orbs.

## Action of associations in the formula

***Herba ephedrae* + *Ramulus cinnamomi***

When ephedra is combined with cassia twig, because of the pungent flavor and warm nature of the herbs, the formula has the effect of inducing perspiration and is applicable for the exterior syndrome of excess without presence of seat due to attack of Taiyang channel (Stage I of the ALT) by algor (Yanfu, 2002a).

This association maximizes the diaphoretic effect and this combination very effective for reliving the exterior (Cheng, 2008). Both *Ramulus cinnamomi* and *Herba ephedrae* are diaphoretics for dispersing algor venti, whereas Ramulus Cinnamomi is moderate in action and weaker than *H. ephedrae* in inducing sweating. Since H. ephedrae is a medicinal herb mainly attributive to the lung and has the strong action of perspiration, it is often used for exterior syndrome with anidrosis due to ventus and algor and can disperse the lung and relieve asthma, promote diuresis to relieve edema (Yanfu, 2002a).

***Herba Ephedrae* + Semen Armeniacae Amarum**

Ephedra is pungent in flavor and apricot kernel is bitter and when they two are combined, promotes the role of dispersive and descends Lung Qi, expelling the pathogen, relieving asthma, eliminate algor and relieve the surface (Cheng, 2008; Gongwang, 2002). Both apricot seed and ephedra belong to the pulmonary orb and can treat cough and asthma caused by algor venti attacking the lung co-operatively. Ephedra tends to disperse the algor venti to promote the flow of lung qi to allay asthma; apricot seed tends to lower the flow of qi to relieve cough. One for dispersing, the other for lowering, they can regulate the flow of qi to relieve cough and asthma. In addition ephedra can disperse lung qi to induce diuresis and reduce edema caused by attacking wind (Gongwang, 2001d).

***Plus Radix Glycyrrhizae***

The use of roasted licorice root has the action of preventing the ephedra and cassia twig from perspiring too much. It also has the effects of resolving phlegm and stopping cough (Gongwang, 2002).

## Preparation

Decoction. Take the warm decoction in three doses until mild sweating is induced (Liu *et* Tseng, 2005).

## Precautions and ontraindications

- Used only in exterior excess Wind Cold, and its use is ceased once sweating occurs.
- Not for exterior deficient Wind Cold patterns (Anonymous, 2009a).
- Not for exterior Wind Heat patterns (Anonymous, 2009a; Gongwang, 2002).
- Not for patients that are prone to bleeding.
- Use caution in patients with hypertension.
- This formula contains one or more toxic substances (while some Chinese herbs are toxic, it must be noted that many come prepared, or are combined, to mitigate their toxicity) (Anonymous, 2009a).
- This formula is not suitable for those with weak and fragile constitutions (Gongwang, 2002).

## Combined orbs of all herbs in this formula

Pulmonary, Vesical, Cardial, Crass intestinal.

## The use of Ramulus cassia versus Cortex in Ephedra Decoction

Mao-to (Ma-Huang-tang in Chinese) is traditionally used in Japan and China for treatment of influenza-like illness (high fever, headache, pain and cough) since ancient times. According to Shijie *et al.,* 2008 in Japan the component herb names (botanical names) of Mao-to are as follows: *H. ephedra* (stem of *Ephedra Sinica* Stapf), *Cinnamomi Cortex* (bark of Cinnamomum cassia Blume), *Armenicae Semen* (semen of Prunus Armeniacae Linne) and *Glycyrrhizae Radix* (root of *Glycyrrhizae uralensis* Fisher).

This exchange between the Cortex and he Ramulus of cinnamon is very pertinent. Is so important to use one or another part of this herb? I will try to answer this question later in this master thesis.

## *7.1. Herba Ephedrae*

### Introduction

Many members of the genus Ephedra have been used medically. The most common include *E.sinica* Satpf. (草麻黄 - cao Mahuang) (Fig. 1-2) (Bensky *et al.*, 2004; Chen *et* Chen, 2004; Chu, 2008; CP, 2005 ; Ganzhong *et al.,* 2003b; Soni *et al.*, 2004; Yanfu, 2002a), *E. major* Host. (Fig. 5), *E. vulgaris*, *E.altissima*, *E.distachya* (Fig. 4-5), *E. helvetica*, C.A. Meyer and *E. nevadensis* Watson (Soni *et al.*, 2004). *E. equisetina* Bunge, (木賊麻黄- mu zei Mahuang) (Chen *et* Chen, 2004; Chu, 2008; CP, 2005 ; Yanfu, 2002a) and E. *intermedia* Schrenk et Mey. (中麻黄 -zhong Mahuang) are also refered as standard species (Bensky *et al.*, 2004; Chu, 2008; CP; 2005; Ganzhong et al., 2003b; WHO, 1997a; Yanfu, 2002a).

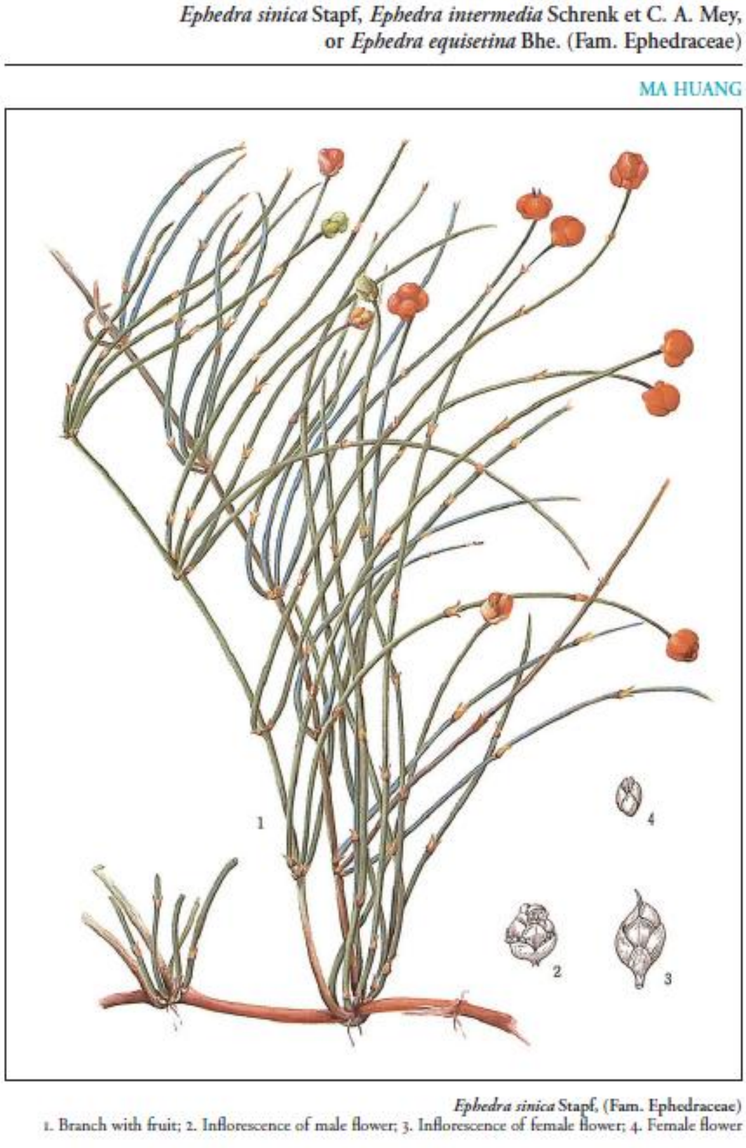



**Fig. 1.** *Ephedra sinica* (adapted from Wu, 2005).

**Fig.** ***2***. *Ephedra sinica* (adapted from http://www.ktbotanicals.com/ephedra-sinica-Mahuang-p-6931.html) (visited 10-6-2009).

**Fig. 3.** *Ephedra major* Host (adapted from http://vanherbaryum.yyu.edu.tr/flora/famgenustur/ephedraceae/ephedra/emajor/index.htm) (visited 10-6-09)

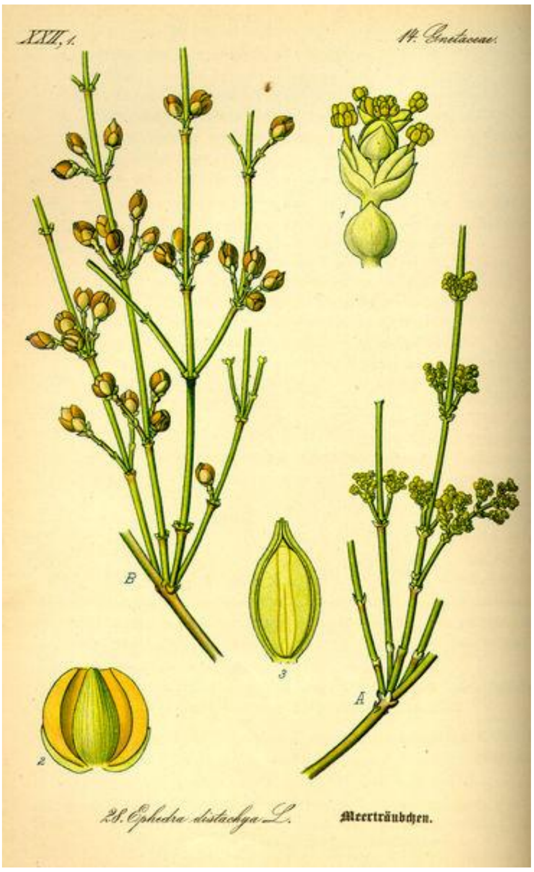



**Fig. 4.** *Ephedra distachya* (adapted from http://commons.wikimedia.org/wiki/File:Illustration_Ephedra_distachya0.jpg) (visited 10-6-2009).

**Fig. 5.** *Ephedra distachya* (adapted from http://www.hlasek.com/ephedra_distachya_6552.html) (visited 10-6-2009).

By definition, *Herba ephedrae* consists of the dried stem or aerial part of *Ephedra sinica* Stapt or other ephedrine-containing Ephedra species (Lee *et al.*, 2000; Soni *et al.*, 2004;

WHO, 1999), that belongs to the Family Efedraceae (Abourashed *et al.*, 2003; Bensky *et al.*, 2004; Ganzhong *et al.,* 2003b; Lee *et al.*, 2000; Leite, 2005a; Soni *et al.*, 2004; WHO, 1999; Yanfu, 2002a) or Gnetaceae (Lee *et al.*, 2000; Soni *et al.*, 2004; WHO, 1999).

The Chinese term '*Mahuang*' may be loosely translated as 'yellow astringent' (Abourashed *et al.*, 2003; Andraws *et al.*, 2005), 'yellow horsetail' or 'hemp yellow' (*huang* is yellow; *ma* has different meanings) and is more specific to the aerial parts of *Ephedra sinica* Stapf., *E. equisietina* Bunge., or *E. intermedia* Schrenk et Mey. Other species that are not official in the Chinese Pharmacopoeia but that are also considered as sources of Mahuang include *E. minuta* Florin, *E. distachya* L. and *E. gerardiana* Wall., as well as at least 6 more ephedrine-containing species (Abourashed *et al.*, 2003).

Other names commonly used are: ma hoàng, mao, maoh, mao-kon, môc tac ma hoàng, mu-tsi-Mahuang, san-Mahuang, phok (WHO, 1999), desert herb, Chinese ephedra (Anonymous, 2009i; WHO, 1999), horsetail, soma, amsania, budshur, chewa, hum, huma, khama (WHO, 1999), joint fir (Anonymous, 2009i; WHO, 1999), mormon tea (WHO, 1999; Soni *et al.*, 2004), yellow horse (Anonymous, 2009i; WHO, 1999; Soni *et al.*, 2004), sea grape, joint fir, squaw tea, teamster´s tea (Soni *et al.*, 2004), popotillo, yellow astringent (Anonymous, 2009i; Soni *et al.*, 2004), xin jiang xue lian hua (Chu, 2008), Cao Mahuang, Chinese Joint-Fir, Cao Ma-Huang, Ephedra Sinisa, Ephedrine, Ephedrine Alkaloid, Herbal Ecstasy, Indian Jointfir, Mahuang, Mahuanggen (Mahuang root), Mongolian Ephedra, Muzei Mahuang, Pakistani Ephedra, Sea Grape, Shuang Sui Mahuang, Teamster's Tea, Zhong Mahuang (Anonymous, 2009i). Mormon tea and ephedra are often confused. Mormon tea or American ephedra comes from *Ephedra nevadensis*, and ephedra or Mahuang comes primarily from *Ephedra sinica*. Mormon tea is alkaloid-free and lacks both the therapeutic effects and the toxicity of ephedrine (Anonymous, 2009i).

## Historical perspective

One of the oldest medicinal herbs known to mankind is probably ephedra, or "*Mahuang*", as it is known in TCM. *Ephedra sinica* is the primary species that has been used in China for more than 5000 years (Abourashed *et al.*, 2003; Bent *et al.*, 2003; Soni *et al.*, 2004) and is still being used in ephedra preparations and extracts all around the world. Although originally examined by Emperor Shen Nung (ca. 3200 BC), the use of Mahuang as a stimulant and as an antiasthmatic was not documented until the time of the ancient Chinese Han Dynasty (ca. 207 BC–220 AD). Ephedra has a long story of use as a stimulant and for the management of bronquial disorders (Soni *et al.*, 2004). *Ephedra gerardiana* has been similarly employed in Indian folk medicine since old times (Abourashed *et al.*, 2003). Reports also indicate that the ancient Aryans discovered ephedra or Soma plant as an energizer-cum-euphoriant. Use of ephedra juice for longevity was a part of ancient Indian Aryan custom mentioned in the Rigveda (the oldest of sacred Sanskrit Vedas) and followed even by ancient Romans. In Asian medicine, ephedra is recommended for colds and flu, fever, chills, headaches, edema, coughing, wheezing (Soni *et al.*, 2004), and for the treatment of asthma (Bent *et al*., 2003; Soni *et al.*, 2004). Even during the time of the Roman Empire, ephedra was well known and described until it was eventually dropped from medieval European literature. More recently, the importance of some ephedra species as potential cash crops in India and the United States (US) has been contemplated. In spite of its long history and its agronomic promise, the use of ephedra herb has declined throughout the years, but in the beginning of the 20th century, interest in the herb gradually revived, as demonstrated by its use in the US for weight loss and performance enhancement. Over the past decade, however, the use of ephedra in the US has been under increasing scrutiny due to the mounting evidence of possible hazards caused by misuse or abuse of the herb (Abourashed *et al.*, 2003).

## Geographical distribution

The genus Ephedra includes ca. 40 species distributed throughout the temperate and subtropical zones of Europe, Americas and Asia (Abourashed *et al.*, 2003; Andraws *et al.*, 2005; WHO, 1999 Soni *et al.*, 2004) (China, India, Japan, and Southern Siberia) (Soni *et al.*, 2004). In China, it is mainly produced in Liaoning Inner Mongolia, Hebei, Shanxi (Chu, 2008; Wu, 2005; Ganzhong *et al.,* 2003b; Yanfu, 2002a), Gansu (Ganzhong *et al.,* 2003b; Wu, 2005; Yanfu, 2002a), Heilongjiang, Jilin, Shaanxi, Henan (Chu, 2008) and Sichuan provinces (Wu, 2005). Although China has been the main supplier of the herb, India and Pakistan are currently accepted as major suppliers as well (Abourashed *et al.*, 2003).

## Description

Ephedra is an erect postrate undershrub, 20-40 cm high but according to Abourashed *et al.* (2003) the plants are herbaceous perennials that can exceed 1 m in height. Branches erect, short, glaucous green, somewhat flat, 1.0-1.05 mm thick, with sparse longitudinal striae, fascinated at the nodes; internode 2.5-5.5 cm long by 2 mm, acute triangular. Flowers in summer, unisexual, dioecious; male flowers pedunculate or nearly sessile, grouped in catkins composed of 4-5 pairs of flowers with 8 anthers; female flowers biflorous, pedunculate with 3-4 pairs of bracts, the naked ovule with the outer coat produced into a styliform tube, fruiting with often freshy red succulent bracts, 2-seeded (WHO, 1997a). The medicinal parts of the plants are collected between August and October and dried in the shade. After being cut into pieces (segments) (Fig. 6), they are left raw, or further prepared with honey, or made into fibers for clinical use (Wu, 2005; Ganzhong *et al.,* 2003b).

**Fig. 6.** Pieces from *Ephedra sinica* (adapted from http://tcm.health-info.org/Herbology.Materia.Medica/mahuang-properties.htm) (visited 10-6-09).

## Plant material of interest

Stem or arterial part (Cunha *et al*., 2003; Soni *et al.*, 2004; WHO, 1997A; WHO, 1999).

## Organoleptic properties

Odor, slight (WHO, 1999), with a strong pine odor (Abourashed *et al.*, 2003); taste, slightly bitter (WHO, 1997A; WHO, 1999), and astringent (Abourashed *et al.*, 2003; WHO, 1997A; WHO, 1999), giving a slight sensation of numbness on the tongue (WHO, 1999); colour: dark brown; solubility: partly soluble in water (Soni *et al.*, 2004).

## General Identity Tests

Macroscopic and microscopic examinations and microchemical tests for the presence of alkaloids with *Mayer´*s reagent (WHO, 1999). The VIII Portuguese Pharmacopoeia (2005) and the European Pharmacopoeia (2005) inscribes the monography of ephedrine (*Ephedrinum anhydricum, Ephedrinum hemihydricum*, *Ephedrini hydrochloridum* and *Ephedrini racemici hydrochloridum*), but not the ephedra monography.

## Purity Tests

### *Microbiology*

The test for *Salmonella* spp. in *Herba Ephedrae* products should be negative. The maximum acceptable limits for other microorganisms are as follows. For preparation of decoction: aerobic bacteria—not more than $10^7$/g; fungi—not more than $10^5$/g; *Escherichia coli*—not more than $10^2$/g. Preparations for internal use: aerobic bacteria—not more than $10^5$/g or ml; fungi—not more than $10^4$/g or ml; enterobacteria and certain Gram-negative bacteria—not more than $10^3$/g or ml; *Escherichia coli*—0/g or ml (WHO, 1999).

***Foreign organic matter***

Woody stems, not more than 5% (CP, 2005; WHO, 1999). Does not contain stems of Equisetaceae or Gramineae plants, nor any other foreign matter (WHO, 1999).

***Total ash***

Not more than 9% (WHO, 1999) or according to Chinese Pharmacopoeia (2005) not more than 10%.

***Acid-insoluble ash***

Not more than 2% (WHO, 1999).

***Moisture***

Not more than 9% (CP, 2005; WHO, 1999).

***Pesticide residues***

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for *Herba Ephedrae* is not more than 0.05 mg/kg (WHO, 1999).

***Heavy metals***

Recommended lead and cadmium levels are no more than 10 and 0.3mg/kg, respectively, in the final dosage form of the plant material (WHO, 1999).

***Radioactive residues***

Analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239 (WHO, 1999).

***Other purity tests***

Chemical, dilute ethanol-soluble extractive and water-soluble extractive tests to be established in accordance with national requirements (WHO, 1999).

***Chemical assays***

Contains not less than 0.7% total alkaloids, calculated as ephedrine by high performance liquid chromatography in the Japanese pharmacopoeia; or not less than 0.8% of total alkaloids, calculated as ephedrine in the Chinese pharmacopoeia. Thin-layer, gas–liquid or HPLC analysis for ephedrine and related alkaloids are available (WHO, 1999).

## Chemical constituents

The main active components are alkaloids (Ganzhong *et al.,* 2003b). The yield of alkaloids of ephedra ranges from 0.5% to 2.5% (Soni *et al.,* 2004; Zaacks et al, 1999), but according to Abourashed *et al.* (1993), the aerial parts of different ephedra species contain from 0.02% to 3.4% of 6 optically active alkaloids (Fig. 7) concentrated in the internodes. (-)-Ephedrine (EPH) is the major isomer (Cheng *et al.*, 2004; Abourashed *et al.*, 2003) comprising 30–90% of the total alkaloids. It was the first alkaloid isolated from ephedra by Nagai in 1887. (+)-Pseudoephedrine (PSE), the diastereomer of (-)-EPH, was subsequently isolated by Ladenburg and Ölschlägel in 1889 followed by the remaining isomers in the late 1920s (Abourashed *et al.*, 2003).

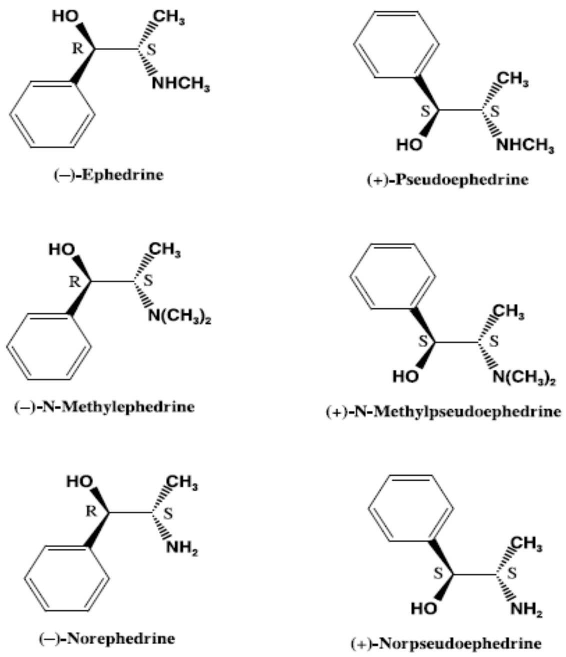



**Fig.7.** Naturally occurring ephedra alkaloids (adapted from Abourashed *et al.*, 2003)

The natural form of ephedrine is the L isomer (levorotatory), while the synthetic compound is generally a racemic mixture of L and D-isomer. The roots and fruits of the ephedra plant are generally devoid of alkaloids, while the woody basal stems are low in alkaloids (Soni *et al.,* 2004). Other trace alkaloids in the alkaloid complex include (-)-norephedrine, (+)-norpseudoephedrine, (-)-methylephedrine, (+)-methylpseudoephedrine (Andraws *et al.*, 2005; Bent *et al.*, 2003; Soni *et al.,* 2004; WHO, 1999) and phenylpropanolamine (a synthetic, racemic mixture of the stereoisomers of norephedrine) (Andraws *et al.*, 2005). The Asian species (*E. sinica, E. intermedia,* and *E. equisetina*) have the highest alkaloid content and the greatest amount is found in the branches, the remainder of the shrub being devoid of the compounds. Extracts of the branches contain varying amounts of the different alkaloids and each alkaloid differs somewhat in its pharmacodynamic properties

(Andraws *et al.*, 2005). It is to be noted that not all ephedra species contain ephedrine-type alkaloids (Abourashed *et al.*, 2003; WHO, 1999). *Ephedra nevadensis*, known as Mormon or desert tea, *E. trifurca*, and *E. antisyphilitica*, as well as most North and Central American species are believed to be devoid of these alkaloids. In addition to the ephedrine-type alkaloids, other alkaloids and amino compounds have been isolated from different species of ephedra. The macrocyclic spermine alkaloids, ephedradines A-D have been isolated from the roots *E. sinica*. Kynurenic acid derivatives have been found in the fresh stem extracts of *E. foeminea* and *E. foliata*. The fresh stems of *E. foeminea* and *E. altissima* have been reported to contain cyclopropylglycine and methanoproline aminoacids. Different types of secondary metabolites, such as flavones, flavanols, tannins carboxylic acids and volatile terpenes have also been reported (Abourashed *et al.*, 2003). The tannins contribute to the adstringent taste of ephedra products (Soni *et al.,* 2004), (ellagic and gallic tannins) (Cunha *et al.*, 2003). Some other active components, such as volatile oil, are also present (Ganzhong *et al.,* 2003b). A minor bioactive oxazolidone derivative of (-)-EPH, ephedroxane, has also been isolated from the aerial parts of *E. intermedia* and has been detected in at least 6 more species containing ephedrine alkaloids (Abourashed *et al.*, 2003). Some of these constituents are shown in Fig. 8-9.

**Fig. 8.** Non-ephedrine alkaloids and amino compounds in ephedra species

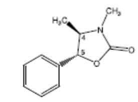
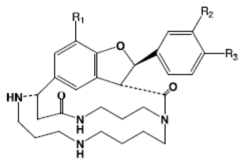
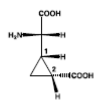
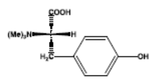
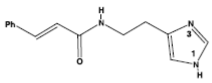
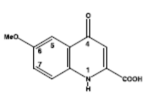
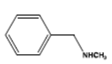
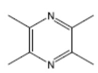
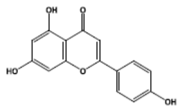
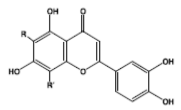
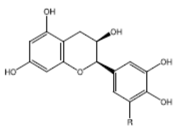
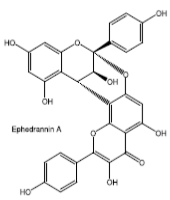
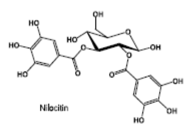
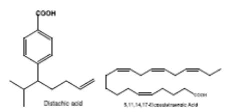
| Compound Name | Chemical Structure | Source/Organ |
|---|---|---|
| Ephedroxane |  | Aerial parts of *Ephedra* herb |
| Ephedradine A, $R_1 = R_2 = R_3 = H$ Ephedradine B, $R_1 = R_3 = H$, $R_2 = OMe$ Ephedradine C, $R_1 = H$, $R_2 = OMe$, $R_3 = Me$ Ephedradine D, $R_1 = OMe$, $R_2 = R_3 = H$ |  | Aerial parts of *Ephedra* herb |
| Cyclopropyl-$\alpha$-amino acids |  | Stems of *E. altissima* *E. foeminea* |
| Maokonine |  | *Ephedra* root |
| Feruloylhistamine |  | *Ephedra* root |
| 6-Methoxykynurenic acid |  | Fresh stem of *E. pachyclada* |
| *N*-methylbenzylamine |  | Ephedra herb |
| Tetramethylpyrazine |  | Ephedra herb |

**Fig. 9.** Miscellaneous non-alkaloidal natural constituents of ephedra species (adapted from Abourashed *et al.*, 2003).

| Compound Class | Chemical Structure and name | Source |
|---|---|---|
| Flavones |  Apigenin | *E. antisyphylitica* |
| |  Lucenin 1, R = xyl, R' = glu Lucenin 3, R = glu, R' = xyl | |
| Flavanols (Tannin precursors) |  Catechin, R = H Gallocatechin, R = OH | Twigs and barks of *E. helvetica* |
| Bisflavanols |  Ephedrannin A | *E. sp.* |
| Carboxylic Acids |  Nilocitin | *E. alata* |
| |  Distachic acid 5,11,14,17-Eicosatetraenoic Acid | *E. sp.* |

The pharmacological action of ephedra is dependent upon its chemical composition. As the primary alkaloid found in most ephedra species is ephedrine, the effects of ephedrine can represent a surrogate for the expected pharmacological action of ephedra. Because other constituents of ephedra may alter the pharmacological action of ephedrine, understanding the effects of ephedrine may provide insight into the biological action of this herb. The profile of all alkaloids is also important, because although the individual alkaloids have similar pharmacological activity, they vary significantly in potency and thus alter the net effect. Recent studies suggest that the potency of the adrenergic activity and the cytotoxicity of ephedra extracts, correlate with the ephedrine content; however, the cytotoxicity of all ephedra extracts could not be completely accounted for their ephedrine content alone (Soni *et al.,* 2004).

The pharmacology of ephedra is complex, but for both traditional and more recent popular uses, the established pharmacological effects appear to be attributable to its ephedrine-type alkaloids, mainly (-)-EPH and (+)-PSE. Current Western therapies utilize these two alkaloids (and until recently norephedrine, also known as phenylpropanolamine) in their optically pure forms or as their synthetic racemates. Due to their stability, they are often incorporated in oral dosage forms (Abourashed *et al.*, 2003). Ephedrine and pseudoephedrine are potent sympathomimetic drugs that stimulate α, β1 and β2 adrenoceptors (Abourashed *et al.*, 2003; Maglione, 2005; Soni *et al.,* 2004; WHO, 1999). Pseudoephedrine´s activity is similar to ephedrine, but its hypertensive effects and stimulation of the central nervous system (CNS) are somewhat weaker (WHO, 1999). Also has a weaker cardiac effect, but a greater diuretic activity (Soni *et al.,* 2004). Part of ephedrine´s peripheral action is due to the releases of norepinephrine (Maglione, 2005; Soni *et al.,* 2004; WHO, 1999) and dopamine (Maglione, 2005; Soni *et al.,* 2004; WHO, 1999), from neuronal storage sites in the symphathetic nerves (Soni *et al.,* 2004) and direct action on α- and β-postsynaptic receptors at effector organs (Soni *et al.,* 2004; WHO, 1999). This basic pharmacological mechanism seems to account for most of ephedrine's therapeutic efficacy, as well as its most prominent adverse effects. Hallmark effects of α- and β-adrenergic receptor stimulation include enhanced cardiac rate and contractility, peripheral vasoconstriction, bronchodilation, and CNS stimulation. The vasoconstrictor and bronchodilator effects explain the traditional use of ephedra as a nasal decongestant and anti-asthmatic. Ephedrine is metabolized to norephedrine (phenylpropanolamine) which may be responsible for the CNS stimulant effects. In current usage, the CNS stimulant and perhaps thermogenic effects are purported to afford enhanced weight loss in obesity, and improved performance in endurance training or body-building. Although ephedrine does suppress appetite, the main mechanism for promoting weight loss appears to be by increasing the metabolic rate of adipose tissue.

The actions of ephedrine and its congeners as sympathomimetics have been studied extensively, but variations in the compounds tested, species, target tissue, and study conditions vary sharply (Abourashed *et al.*, 2003).

Their molecular structures are isomers of one another or are closely related, substituted molecules that demonstrate significant similarity with amphetamines and other catecholamines (Fig. 10). It is not surprising, then, that these molecules possess significant α- and β-adrenergic agonist activity. In addition, they enhance the release of endogenous catecholamines. This latter effect, through depletion of endogenous catecholamine stores, is thought to explain the tachyphylaxis noted with repeated dosing (Andraws *et al.*, 2005). Tachyphylaxis develops to its peripheral actions, and rapidly repeated doses become less effective owing to the depletion of norepinephrine stores (WHO, 1999).

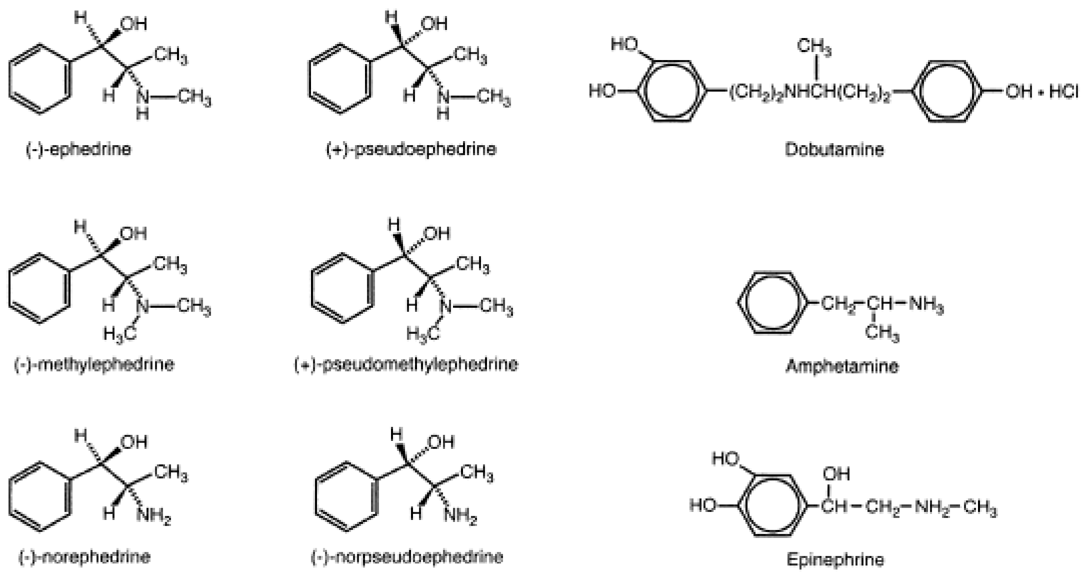



**Fig. 10.** Chemical structures of the ephedra alkaloids (left). The structures of epinephrine, amphetamine, and dobutamine (right) are shown for comparison (adapted from Andraws *et al.*, 2005).

In addition to the ephedrine alkaloids, some of the minor compounds isolated from Ephedra species exhibited other biological activities. Ephedroxane, was found to have anti-inflammatory activity; while others, such as ephedrannine A and maokonine (present in root) exhibited hypotensive activity in animals. It is interesting to notice that the reported hypotensive activity is exhibited by compounds present only in the roots of ephedra, which agrees with Chinese belief that the roots constitute a drug (Mahuang gen, or mao-kon in Japanese) that produces opposite effects to those of the aerial parts (Mahuang) (Abourashed *et al.*, 2003).

## Effects and uses

Ephedra alkaloids have a long history as traditional folk remedies, particularly among the Chinese (Andraws *et al.,* 2005). In Oriental medicine, the ephedra herb (Mahuang) is the chief medicine used in the treatment of asthma and bronchitis (Soni *et al.,* 2004). Herbal ephedra has been used as part of Chinese traditional medicine for over 5,000 years (Morton, 2005) for asthma (Cunha *et al*., 2007; Kliger *et* Lee, 2004; Soni *et al.,* 2004; Cunha *et al*., 2003; Abourashed *et al.*, 2003; Ang-Lee *et al*., 200; Lee *et al.*, 2000), common cold (Abourashed *et al.*, 2003; Andraws *et al.*, 2005; Cunha *et al*., 2003; Kliger *et* Lee, 2004; Lee *et al.*, 2000; WHO, 1997 ; Soni *et al.,* 2004), fever (Abourashed *et al.*, 2003; Lee *et al.*, 2000 ; Soni *et al.,* 2004), bronchitis (Ang-Lee *et al*., 2001) and cough (Abourashed *et al.*, 2003; Andraws *et al.*, 2005; Cunha *et al*., 2007; Lee *et al.*, 2000; WHO, 1997 ). Other uses supported by clinical data include nasal congestion (Abourashed *et al.*, 2003; Cheng *et al.*, 2004; Cunha *et al*., 2003; Kliger *et* Lee, 2004; Lee *et al.*, 2000 ; Soni *et al.,* 2004), lung congestion (Lee *et al.*, 2000), allergic rhinitis, (Cunha *et al*., 2007; Cunha *et al*., 2003 ; Kliger *et* Lee, 2004) acute coryza (Cunha *et al*., 2003 ; Kliger *et* Lee, 2004;), flu (Abourashed *et al.*, 2003 ; Cunha *et al*., 2007; Soni *et al.*, 2004), chills (Abourashed *et al.*, 2003 ; Soni *et al.,* 2004) lack of perspiration, (WHO, 1997 ; Soni *et al.,* 2004) headache, aching joints and bones (Abourashed *et al.*, 2003 ; Soni *et al.,* 2004), wheezing (Soni *et al.,* 2004) and oedema (WHO, 1997A).

In the West, ephedra preparations have been used, alone or with caffeine, as CNS stimulants and mood enhancers. Moreover, new uses for ephedra have recently emerged. Many ephedra-containing products are claimed to be effective for weight-loss, as energy/performance boosters (Abourashed *et al.*, 2003; Ang-Lee *et al*., 2001), euphorics or aphrodisiacs, claims that are especially appealing to young adults. Such claims, however, have not been adequately substantiated and, in an attempt to probe their validity, the role of EPH in thermogenesis and cold tolerance in humans was investigated (Abourashed *et al.*, 2003). Also, ephedrine acts on the hypothalamus reducind appetite, so it is often associated with caffeine in products for weight loss (Cunha *et al.*, 2007).

In Germany, ephedra is approved by the E Comission for respiratory problems with bhroncospasm in adults and children over 6 years of age (Cunha *et al.*, 2007; Cunha *et al.*, 2003; Soni *et al.,* 2004). The Expanded Commision E monograph describes at length, dosage and administration (Soni *et al.,* 2004).

## Pharmacological effects

Ephedra causes dose-dependent increases in blood pressure and heart rate. Ephedrine, the predominant active compound, is a noncatecholamine sympathomimetic agent that exhibits α1, β1, and β2 activity by acting directly at adrenergic receptors and by indirectly releasing endogenous norepinephrine (Abourashed *et al.*, 2003; Ang-Lee *et al*., 2001; Maglione, 2005; Soni *et al.,* 2004; WHO, 1999) and dopamine (Maglione, 2005; Soni *et al.,* 2004; WHO, 1999).

***Cardiovascular actions***

The principle cardiovascular effects of ephedra alkaloids include increases in systolic and diastolic blood pressure (Andraws *et al.*, 2005; Ang-Lee et al, 2001; Chen *et* Chen, 2004; Chu, 2008; Ganzhong *et al.,* 2003b; WHO, 1999), heart rate (Andraws *et al.*, 2005; Ang-Lee et al, 2001; Ganzhong *et al.,* 2003b; Soni *et al.,* 2004; WHO, 1999) and indices of cardiac performance (Andraws *et al.*, 2005; Ganzhong *et al.,* 2003b). Like epinephrine (adrenaline), ephedrine excites the sympathetic nervous system, causing vasoconstriction and cardiac stimulation (Ganzhong et al., 2003b; WHO, 1999).The drug stimulates the cardiac output, and increases the peripheral resistance, thereby producing a lasting rise in the blood pressure (Soni *et al.,* 2004; WHO, 1999). Ephedrine differs from epinephrine in that it is orally active, has a much longer duration of action, and has more pronounced activity in CNS, but is much less potent. The cardiovascular effects of ephedrine persist up to ten times as long as those of epinephrine. Renal and splanchnic blood flows are decreased, while coronary, cerebral, and muscle blood flow are increased (WHO, 1999). Reports of hypoglycemic activity were found about *Ephedra distachya* (Konno *et al.,* 1985)

***Respiratory effects***

Ephedrine, like epinephrine, relaxes bronchial muscles and is a potent bronchodilatador (Chen *et* Chen, 2004; Soni *et al.,* 2004; WHO, 1999) owing to its activation of the β-adrenoreceptors in the lungs (Soni *et al.,* 2004; WHO, 1999). Bronquial muscle relaxation is less pronounced but more sustained with ephedrine than with epinephrine (WHO, 1999). Ephedrine has a more rapid onset of action, but its effectiveness may decrease if it is used repeatedly in a short period of time (Chen *et* Chen, 2004). The sympathomimetic action of ephedrine leads to an increase in respiratory rate and pulmonary ventilation and it is used to eliminate the cough also in non asthmatics subjects (Cunha *et al.*, 2007). Ephedrine promote the release of noradrenaline and adrenaline and inhibit the release of sensitizing substances as histamine, resulting in the dilation of bronchial smooth muscle, the contraction of intra-mucosal blood vessels of the respiratory tract, and eventually, free movement in the air passage. Mahuang can relieve the respiratory system symptoms related to cough, sputum and asthma (Ganzhong et al., 2003b). Water extract of *Mahuang a*dministered via oral or intraperitoneal injection is also associated with an antitussive effect (Chen *et* Chen, 2004).

### *Nasal decongestant effect*

Ephedrine, like other sympathomimetics with α-receptor activity, causes vasoconstrition and blanching when applied topically to nasal and pharyngeal mucosal surfaces. Both ephedrine and pseudoephrine are useful orally as nasal decongestants in case of allergic rhinitis, but they may not be very effective for the treatment of nasal congestion due to colds (WHO, 1999). On the other hand, the most popular application of pseudoephedrine is in flu medications to relieve nasal decongestion and perhaps due to its anti-inflammatory effect. Also ephedroxane was found to have anti-inflammatory activity (Abourashed *et al.*, 2003).

### *Central Nervous System actions*

Ephedrine is a potent stimulant of the central nervous system (Chen *et* Chen, 2004; Maglione, 2005; Soni *et al.,* 2004; WHO, 1999), its immediate effects are attributable to stimulation of dopamine release (Maglione, 2005) and the effects may last for several hours after oral administration (WHO, 1999). The combination of adrenergic and dopaminergic effects of ephedrine leads, in the short therm, to improved mood and heightened alertness with decrease fatigue and lessened desire for sleep (Maglione, 2005).

### *Hypoglycemic effects*

The hypoglycemic effect of *E. distachya* has been investigated in Japan, in order to show that the hydroalcoholic extract produced long lasting hypoglycemia in mice following transient hyperglycemia. Activity-guided fractionation resulted in the isolation of five active glycans, ephedrans A, B, C, D and E which significantly reduced blood glucose levels in normal and alloxan-induced diabetic mice (Fig. 11). In a similar investigation of the hypoglycemic activity of selected plants growing in Egypt, the alcoholic extract of *E. alata* exhibited a persistent lowering of blood glucose one hour after administration to fasting rats. In alloxanized rats, however, the same extract failed to reduce blood glucose levels as compared to the positive control, glibenclamide (Abourashed *et al.,* 2003; Konno *et al.,* 1985).

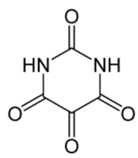


**Fig. 11.** Chemical structure of alloxan (adapted from http://en.wikipedia.org/wiki/File:Alloxan.png) (visited 10-5-09)

***Diaphoretic effect***

The diaphoretic components of mahuang are the volatile compounds and alkaloids. The decoction prepared from mahuang also shows a diaphoretic effect (Ganzhong et al., 2003b). In humans, administration of ephedrine alkaloids is associated with increased perspiration, but only in subjects with elevated body temperature (Chen *et* Chen, 2004).

***Diuretic effect***

Pseudoephedrine has a diuretic function (Chen *et* Chen, 2004; Ganzhong et al., 2003b; Soni *et al.,* 2004), greater than ephedrine (Soni *et al.,* 2004), which exerts its diuretic effect possibly through dilating renal vessels, increasing renal blood flow, or inhibiting sodium ion reabsorption of renal tubes (Ganzhong et al., 2003b).

***Anti-infeccious effect***

Decoction of *Mahuang "Mahuang Tang"* has varying degrees of inhibitory effect *in vitro* against *Staphylococcus aureus,* α-*streptococcus*, β-*streptococcus*, *Bacillus anthracis, Corynebacterium diphtheriae, Pseudomonas aeruginosa, Bacillus dysenteriae,* and *Salmonella typhi.* The essential oil of *Mahuang* has an inhibitory effect against *E. coli*, *Candida albicans* and various types of influenza virus (Chen *et* Chen, 2004). *Herba* e*phedra* was reported to show the *in vitro* anti-influenza viral effects and augments the production of inflammatory cytokines including interleukin-6 and interleukin-1 (Shijie *et al.,* 2008).

***Effects on Weight Loss and Athletic Performance***

Dietary supplements containing ephedra have primarily been used in the United States, since the 1980's, to promote weight loss or to enhance athletic performance. Approximately three billion servings were consumed in the U.S. in 1999 according to a survey conducted by ephedra product manufacturers (Morton, 2005; Andraws *et al.*, 2005). Dietary supplements containing ephedra used as ''herbal ecstasy'' are widely available, and it is estimated that at least 1% of the adult population have taken these products (Cheng *et al.*, 2004) and nearly one third of young, obese women have used a weight-loss supplement containing ephedra (Andraws *et al.*, 2005). Several studies on these compounds (particularly ephedrine) have been undertaken to assess their efficacy and safety in humans for the treatment of obesity. Doses of ephedrine and related compounds ranged from 60 to 150 mg/d. Overall, studies have found statistically significant reductions in weight in obese patients treated with ephedra alkaloids versus those treated with placebo. Treatment with these carefully controlled doses resulted in a modest incidence of cardiovascular side effects, including increases in blood pressure (both systolic and diastolic), heart rate, and palpitations that were often mild and transient. No clinical trial has reported major adverse cardiovascular events (stroke, myocardial infarction, or malignant arrhythmias) associated with the use of ephedra alkaloids for weight loss. However, several caveats must be noted. The studies to date have examined small cohorts for relatively short periods of time, usually 6 months or less. They have also suffered from high attrition rates (Andraws *et al.*, 2005). In addition, most studies have looked at ephedrine in combination with caffeine (Andraws et al, 2005; Soni et al, 2004) and, in several cases, aspirin (the rationale for this combination is that it better stimulates increases in fat metabolism and energy expenditure) (Andraws *et al.*, 2005). Perhaps the most sobering finding is that weight loss, although statistically significant, may not be clinically significant (<1 kg) with anywhere from a 2- to 4-fold increase in side effects compared to placebo. Moreover, side effect profiles may be quite different in cohorts with preexisting cardiovascular disease. Thus, it is difficult to generalize these results to the various ephedra products on the market that contain variable amounts of active compound and are sold to a variety of consumers with different risk factors who may consume higher doses than those studied (Andraws *et al.*, 2005). According to Morton (2005), ephedra promotes modest short-term weight loss. The most rigorous review to date assessed studies with at least 8 weeks of follow-up and concluded that *E. sinica* and ephedrine promote a small short-term weight loss of about 0.9 kg per month more than placebo (Pittler *et* Ernst, 2005).

Ephedrine is thought to cause thermogenesis and modest short-term weight loss, possibly by stimulating norepinephrine release. Some evidence suggests that aspirin and caffeine might act synergistically with ephedrine for weight loss by inhibiting prostaglandin, which increases norepinephrine release (Anonymous, 2009i). There is some evidence that ephedrine alone or in combination with caffeine can improve anaerobic exercise performance. Ephedrine causes catecholamine release and increases CNS stimulation, which may lead to better performance. Although ephedra is often included in muscle development products, preliminary research suggests ephedra does not affect muscle precursor cells called satellite cells, which are thought to cause muscular hypertrophy (Anonymous, 2009i). However, the intake is associated with an increased risk of psychiatric, autonomic or gastrointestinal symptoms and heart palpitations (Pittler *et* Ernst, 2005). Again, studies tend to be small and contain young healthy individuals who may not reflect the general population. Thus, once more, the limited available safety assessments are difficult to extrapolate to the general population (Andraws *et al.*, 2005).

***Other effects***

Mydriasis occurs after local application of ephedrine to the eye, but the effect last only for only a few hours. Ephedrine is of little value as a mydriatic in the presence of inflammation (WHO, 1999). The activity of the smooth muscles of the uterus is usually reduced by ephedrine; consequently, the drug has been used to relieve pain of dysmenorrhoea. Ephedrine stimulates the α-adrenoreceptors of the smooth muscle cells of the bladder base, which increases the resistance to the outflow of urine (used in the treatment of urinary incontinence and nocturnal enuresis) (WHO, 1999).

## Pharmacokinetics

Ephedrine is absorbed faster if it is consumed as the powdered extract. However, onset of action and extent of absorption does not differ greatly between the powdered extract and the powdered herb. Some sources claim ephedra is safer than pure ephedrine and pseudoephedrine because ephedrine from ephedra is absorbed more slowly. However, pharmacokinetic studies have found no differences in the pharmacokinetics of ephedrine from ephedra versus the purified form. The time to maximum concentration (t max) for ephedra is 2.4 hours. The half-life is 6.1 hours (Anonymous, 2009i).

Ephedrine and pseudoephedrine are well-absorbed (Chen *et* Chen, 2004). Ephedrine is active when given orally, parenterally, and ophthalmically. Because of the rapid and complete absortion of ephedrine, the onset of pharmacological effects is generally evident within an hour of ingestion (Soni *et al.,* 2004). Ephedrine is rapidly and completely absorbed from the gastrointestinal tract (Andraws *et al.*, 2005; Soni *et al.,* 2004). After oral administration, absorption of ephedrine is complete within 2-2.5h (Soni *et al.,* 2004). According to Andraws *et al.* (2005), time to peak serum levels varies between 2 and 4 hours and according to Chen *et* Chen (2004) peak plasma concentration is reached 1-2 hours after oral ingestion of the herb. The pure alkaloid is absorbed most quickly; herbal alkaloid mixtures may retard the rate of absorption. The rate of absorption of ephedrine may be increased with heat stress. Additionally, elevations in blood pressure are significantly greater when ephedrine is taken during heat stress. The importance of this finding lays in the fact that ephedra extracts have been marketed as enhancers of athletic performance and are often taken prior to exercise in a warm environment (Andraws *et al.*, 2005). Thus, they may add to the cardiovascular stress already being experienced during physical activity. Once absorbed, ephedrine has a large volume of distribution and is not bound to plasma proteins (Andraws *et al.*, 2005). Ephedrine and pseudoephedrine are distributed throughout the body, with higher concentrations found in the liver and kidneys, followed by the brain, spleen, fatty tissues, and saliva (Chen *et* Chen, 2004). Ephedrine and related alkaloids are lipophilic and cross the blood–brain barrier. It is this physical property that accounts for their effects on the CNS, which include appetite suppression, anxiety, and changes in gastric motility (Andraws *et al.*, 2005). The effects of ephedrine last for approximately 1 hour, but the serum half-life ranges from 3 to 11 hours (Andraws *et al.*, 2005) (2.7-3.6h, according to Soni *et al.* (2004)). In humans, the primary route of ephedrine excretion is via the urine and within 24h of administration (Andraws *et al.*, 2005; Soni *et al.,* 2004). Approximately 95% of the ephedrine may be excreted unchanged (55-75%) or as metabolites (Soni *et al.,* 2004). According to Chen *et* Chen (2004) up to 75% of these compounds can be recovered unchanged in the urine.

Because of the presence of ionizable groups, the urinary excretion of ephedrine is pH-dependent, with excretion increasing in acidic urine and decreasing in alkaline urine (Andraws *et al.*, 2005; Soni *et al.,* 2004). It has been estimated that approximately 8-20% of the administered ephedrine is metabolized by N-demethylation to norephedrine, while 4-13% undergoes oxidation deamination resulting in the formation of 1-phenylpropan-1,2-diol and further side-chain oxidation to benzoic acid and hippuric acid. Studies in animals and humans suggests that the metabolism of ephedrine primarily takes place through aromatic hydroxylation, N-demethylation and oxidative deamination reactions. The extent of metabolism and the major metabolites formed, vary between species. Elimination from the plasma was reported to occur monoexponentially, with a half-life of 30.6minutes (Soni *et al.,* 2004). According to Chen *et* Chen (2004) the half-lives of ephedrine and pseudoephedrine range from 4.73 to 7.1 or 13.4 hours (when the urinary pH is 5.2, 6, and 7, respectively) and according to Ang-Lee *et al*. (2001) ephedrine has an elimination half-life of 5.2h. In addition to renal excretion, ephedrine is also found to be excreted in breast milk and crosses the placenta, which poses concerns for younger women who may be using extracts for weight loss purposes while pregnant or after delivery (Andraws *et al.*, 2005). The pharmacokinetics of other alkaloids present in ephedra, including pseudoephedrine and phenylpropanolamine are similar to ephedrine (Soni *et al.,* 2004).

## Precautions and contraindications

*Herba Ephedrae* should not be used in patients with coronary thrombosis, impaired circulation of the cerebrum, (Soni *et al.,* 2004; WHO, 1999), diabetes (Abourashed *et al.*, 2003; Anonymous, 2009i; Cunha *et al.*, 2003; Soni *et al.,* 2004; WHO, 1999) (ephedra might interfere with blood sugar control, and exacerbate high blood pressure and circulatory problems in people with diabetes) (Anonymous, 2009i), glaucoma (Soni *et al.,* 2004; Abourashed *et al.*, 2003; WHO, 1999), heart disease (Soni *et al.,* 2004; Cunha *et al.*, 2003), arrhythmia (ephedra might exacerbate arrhythmia; has been linked to tachycardia and arrhythmias, due to its cardiac stimulant effects (Anonymous, 2009i), hepatitis (Charalampopoulos *et al*., 2007, Skoulidis *et al.*, 2005), hypertension

(Anonymous, 2009i; Bensky *et al.,* 2004; Soni *et al.,* 2004; Abourashed *et al.*, 2003; Cunha *et al.*, 2003, WHO, 1999) (ephedra might exacerbate hypertension; contraindicated in uncontrolled hypertension) (Anonymous, 2009i) or other cardiovascular diseases (Abourashed *et al.*, 2003), hyperthyroid, thyrotoxicosis (theoretically, ephedra might stimulate the thyroid and exacerbate hyperthyroid symptoms) (Anonymous, 2009i), mental health problems like anxiety (Anonymous, 2009i; Soni *et al.,* 2004) (large doses of ephedra might cause or exacerbate anxiety due to central nervous system (CNS) stimulant effects (Anonymous, 2009i), depression or psychosis (Soni *et al.,* 2004), thyroid disease (Cunha *et al.*, 2003; Soni *et al.,* 2004; WHO, 1999), autonomic insufficiency (Soni *et al.,* 2004), pheochromocytoma (Anonymous, 2009i; Soni *et al.,* 2004; WHO, 1999), hyperthyroidism, (Abourashed *et al.*, 2003; Anonymous, 2009i) (ephedra might exacerbate the symptoms of pheochromocytoma) (Anonymous, 2009i), prostate trouble (Soni *et al.,* 2004; Cunha *et al*., 2003, WHO, 1999), in people with angina (it might induce or exacerbate angina due its cardiac stimulant effects) (Anonymous, 2009i), essential tremor (ephedra might exacerbate essential tremor) (Anonymous, 2009i), kidney stones (nephrolithiasis) (ephedra and ephedrine can cause kidney stones) (Anonymous, 2009i), long QT interval syndrome (ephedra appears to prolong the QT interval; it might increase the risk of ventricular arrhythmias in patients with long QT interval syndrome (Anonymous, 2009i), narrow-angle glaucoma (ephedra might exacerbate narrow-angle (angle-closure) glaucoma by causing mydriasis) (Anonymous, 2009i), seizure disorders (ephedra might cause an exacerbation or precipitation of a seizure in patients with an underlying seizure disorders) (Anonymous, 2009i).

***Pregnancy***

*E. sinica* did not have any teratogenic effects in vivo, and is not abortifacient in rats. Clinical studies in humans are not available (WHO, 1999); It is known that ephedrine crosses the placenta, therefore, use of the drug during pregnancy is not generally recommended (Andraws *et al.*, 2005; Cunha *et al.*, 2003; WHO, 1999).

***Nursing Mothers***

No reliable studies on this subject, breastfeeding is not generally recommended (WHO, 1999).

***Other precautions***

Continued, prolonged use may cause dependency (WHO, 1999). Use not for children under 6 years of age (WHO, 1999). Patients suffering from renal insufficiency may be at an increased risk to ephedrine toxicity (Soni *et al.,* 2004). Patients under surgery: although ephedrine is widely used as first-line therapy for intraoperative hypotension and bradycardia, the unsupervised preoperative use of ephedra raises certain concerns. Vasoconstriction and, in some cases, vasospasm of coronary and cerebral arteries maycause myocardial infarction and thrombotic stroke. Do to the increased heart rate and blood pressure through direct and indirect sympathomimetic effects, the preoperative concerns are: Risk of myocardial ischemia and stroke from tachycardia and hypertension; ventricular arrhythmias with halothane (see Drugs Interactions); long-term use depletes endogenous catecholamines may cause intraoperative hemodynamic instability; life-threatening interaction with monoamine oxidase inhibitors (see Drugs Interactions); Long-term use results in tachyphylaxis from depletion of endogenous catecholamine stores and may contribute to perioperative hemodynamic instability. The preoperative discontinuation should be at least 24 hours before surgery (Ang-Lee *et al*., 2001).

## Drugs Interactions

- Mahuang should not be combined with other ***sympathomimetic drugs***, such as ephedrine, pseudoephedrine, theophylline, caffeine (Chen *et* Chen, 2004), monoamine oxidase inhibitors (MAOI) (Anonymous, 2009j; Beers, 2008; Chen *et* Chen, 2004), or substances with similar properties (Chen *et* Chen, 2004).
- Concomitant use of ephedra and ***MAOI*** can result in life-threatening hyperpyrexia (Ang-Lee *et al*., 2001), hypertension (Anonymous, 2009j; Ang-Lee *et al*., 2001; Anonymous, 2009i; Soni *et al.,* 2004; WHO, 1999) and coma (Ang-Lee *et al*., 2001). Myocardial ischemia has also been reported with this association (also bupropion) (Andraws *et al.*, 2005).
- ***Oxytocin*** may increase the risk of high blood pressure (Beers, 2008; WHO, 1999).
- ***Gaunethidine***, which leads to the enhancement of the sympathomimetic effect (WHO, 1999).
- ***Cardiac glycosides*** may cause heart rhythm disturbances (Chu, 2008; Bensky *et al.,* 2004; Chen *et* Chen, 2004; WHO, 1999).
- ***Halothane*** may cause heart rhythm disturbances (WHO, 1999). Patients who have consumed ephedra and are later anesthetized with halothane may be at risk of developing intraoperative ventricular arrhythmias because halothane sensitizes the myocardium to ventricular arrhythmias caused by exogenous catacholamines (Abourashed *et al.*, 2003; Ang-Lee *et al*., 2001). (See Other Precautions)
- Cautions with ***tea, cola, guarana, coffee*** (Anonymous, 2009i; Cunha *et al.*, 2003; Soni *et al.,* 2004) because caffeine enhances the ephedra action (Cunha *et al.*, 2003) and may lead to an increased heart rate and blood pressure (Soni *et al.,* 2004).

- ***Beta blockers:*** The effect may be reduced when combined with *Mahuang* because of increased levels of norepinephrine caused by the herb (Chen *et* Chen, 2004).
- ***Diuretics:*** *Mahuang* has a diuretic effect. Though this potential interaction has not been documented, concurrent use with diuretic drugs may lead to increased elimination of water and/or electrolytes (Chen *et* Chen, 2004).
- ***Anticonvulsants:*** theoretically, concomitant use of ephedra might interfere with the effectiveness of anticonvulsant drugs. Ephedra is associated with seizure activity. Some anticonvulsant drugs include phenobarbital, primidone, valproic acid, gabapentin, carbamazepine, phenytoin, and others (Anonymous, 2009i).
- ***Antidiabetes drugs:*** ephedra can raise blood glucose levels and might decrease the effectiveness of drug therapy (Anonymous, 2009i; Beers, 2008). Monitor blood glucose concentrations closely. Some antidiabetes drugs include glimepiride, glyburide, insulin, pioglitazone, rosiglitazone, and others (Anonymous, 2009i; Beers, 2008).
- ***Dexamethasone:*** theoretically, concomitant use might reduce the effectiveness of dexamethasone, due to the ephedrine contained in ephedra. Ephedrine increases the clearance rate of dexamethasone (Anonymous, 2009i).
- ***Ergot derivatives:*** theoretically, concomitant use of ephedra and ergot alkaloids might cause hypertension, due to the ephedrine contained in ephedra (Anonymous, 2009i).
- ***Methylxanthines:*** the use of ephedra with caffeine or other methylxanthines such as theophylline might increase the risk of stimulatory adverse effects. There is also some evidence that using ephedra with caffeine might increase the risk of serious life-threatening or debilitating adverse effects such as hypertension, myocardial infarction, stroke, seizures, and death (Anonymous, 2009i; Beers, 2008).
- ***QT interval-prolonging drugs:*** ephedra may have an additive effect with drugs that prolong the QT interval. This may increase the risk of ventricular arrhythmias. Drugs that prolong the QT interval include amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, sotalol, thioridazine, and many others (Anonymous, 2009i).
- ***Stimulant drugs:*** theoretically, drugs with CNS stimulant properties, such as phenylpropanolamine, pseudoephedrine, and diethylpropion, and many others might increase the risk of hypertension and adverse cardiovascular effects of ephedra due to its ephedra content (Anonymous, 2009i).
- ***Amitriptiline:*** may decrease hypertensive effects of herb (Beers, 2008).

### Interactions with Herbs & Supplements

- ***Ergotamine***: theoretically, concomitant use might cause excessive vasoconstriction and hypertension due to the ephedrine contained in ephedra (Anonymous, 2009i).
- ***Herbs and supplements with stimulant properties:*** Use of ephedra and other stimulant herbs, such as those containing caffeine, can increase the risk of common side effects such as insomnia, jitteriness, tremulousness, dizziness, etc. Using ephedra with other stimulants might also increase the risk of more serious adverse effects such as hypertension, myocardial infarction, stroke, and death. There are several reports of serious life-threatening or debilitating adverse events in patients taking ephedra in combination with caffeine and other stimulants. Some herbs and supplements with significant caffeine content include black tea, coffee, cola nut, green tea, guarana, mate, and others, as referred before (Anonymous, 2009i).
- ***Panax ginseng:*** *Panax ginseng* can cause prolonged QT interval with initial use. It might have an additive effect with ephedra on the QT interval, increasing the risk for arrhythmias (Anonymous, 2009i).

### Side effects

The risk for an adverse reaction after the use of ephedra is substantially greater than with other herbal products (Anonymous, 2009i; Bent *et al*., 2003). The researchers reported that there was sufficient evidence to conclude that ephedrine and ephedra are associated with an increase of two to three times in the risk of psychiatric symptoms, autonomic symptoms, upper gastrointestinal symptoms and heart palpitations (Kliger *et* Lee, 2004). Adverse effects are consistent with catecholamine excess (Anonymous, 2009i). Although ephedra products make up a modest amount of overall supplement sales (0.82%), they account for an inordinately large number of reported adverse events (64%) (Andraws *et al.*, 2005). Because these products are not regulated as drugs, many of these ephedra dietary supplements have extreme variability in the content of ephedrine related to differences in ephedra species and place of origin (Chen *et al.*, 2004). Insight into the potential toxicity of these agents may be obtained, by considering their pharmacologic properties and toxicity may not be limited to the pharmacologic effects of the alkaloids themselves (Andraws *et al.*, 2005).

By the year 2000, the Food and Drug Administration (FDA) had received more than 1000 injury reports related to use of ephedra products. With the assumption that such reports have been adequately substantiated, the causes can be attributed to at least one of the following practices linked to ephedra:

(1) *Misuse*: [administration of overdoses of ephedra/ephedrine-containing products in an attempt to achieve better or faster response for the desired effect]. Overdosing may also result from regular administration of ephedra products spiked with ephedrine alkaloid(s). Even at sub-toxic levels, spiked products may result in alkaloid levels deemed illegal in many sporting events. (2) *Abuse*: [the use of illicit amphetamine derivatives (e.g. methylenedioxymethamphetamine-MDMA) chemically synthesized from ephedrine and used in illegal preparations or to spike ephedra products]. The conversion is relatively simple, cheap and high yielding.

(3) *Contraindication, hypersensitivity and/or drug interaction*: [natural hypersensitivity to the pharmacological effects of ephedra alkaloids, or possible conditions in which ephedra administration may lead to serious side effects] (Abourashed *et al.*, 2003). The unsupervised preoperative use of ephedra poses a risk to patients who are later anesthesized with halothane (Abourashed *et al.*, 2003; Ang-Lee *et al*., 2001). Moreover, the concomittent use of ephedra with such drugs as antihypertensives or antidepressants may have a drastic influence on their intended effects. In view of the outlined information, it becomes clear why ephedra has arrived at its precarious situation in contrast to most other herbal supplements. It is mainly due to the specific nature of the pharmacological effects of ephedra alkaloids, aggravated by misuse and/or abuse that the damage has been so obvious and the reaction so intense. Other risks associated with herbal products in general may apply to ephedra, including problems of misidentification or adulteration with other toxic plants (Abourashed *et al.*, 2003).

***Adverse Cardiac Events***

Ephedra alkaloids have been linked to myocarditis and myocardial infarction. This has been attributed to coronary artery vasoconstriction and possibly vasospasm caused by ephedra. Ephedra might also cause cardiac arrhythmia due to adrenergic effects that shorten the cardiac refractory period, causing re-entrant arrhythmias (Anonymous, 2009i). In addition to effects on blood pressure (which can lead to hypertensive urgencies/emergencies) and cardiac performance, they cause vasoconstriction and vasospasm, including coronary vasospasm. The latter effect may be more pronounced in individuals with higher vagal tone, a group which includes well-conditioned, athletic individuals. Moreover, there is some evidence that, along with spasm, ephedra alkaloids may induce hypercoagulable states, low flow, and oxygen supply–demand imbalance within the coronary circulation. This could account for reported cases of myocardial infarction in otherwise healthy young people without significant underlying coronary artery disease. Catecholamines also decrease myocardial refractoriness, which can predispose the heart to arrhythmias, and indeed ventricular arrhythmias have been reported in pregnant women using over-the-counter decongestants as well as in others using ephedra alkaloids recreationally (Andraws *et al.*, 2005). While cardiotoxicity is usually due to a dose-related α- and β- receptor activity, vasculitis due to ephedrine and other sympathomimetics has been primarily limited to the cerebral arteries (Zaacks *et al.*, 1999). Sympathomimetics, including cocaine and amphetamine derivatives such as MDMA or "ecstasy" have been shown to induce cardiomyopathy, and it is reasonable to conclude that ephedra may also have this propensity, perhaps through the similar mechanism of repetitive sympathetic stimulation of myocardium and potential myocardium damage. Ephedra, combined with caffeine, also produces electrocardiographic abnormalities, specific QT prolongation, when given to healthy volunteers (Peters *et al.*, 2005). Commercial preparations of ephedra alkaloids have been associated with adverse cardiovascular events, including hypertension (Anonymous, 2009i; Song *et al.*, 2008; Simsek *et al*., 2006; Bensky *et al.,* 2004; Soni *et al.,* 2004; Srikanth *et al.*, 2004; Chen *et al.*, 2004; Woolf, 2003), cardiomyopathy (Anonymous, 2009i), palpitations (Anonymous, 2009i; Inchiosa Jr, 2007, Soni *et al.,* 2004; WHO, 1999), stroke (Simsek *et al*., 2006; Soni *et al.,* 2004; Srikanth *et al.*, 2004; Woolf, 2003), myocardial infarction (Anonymous, 2009i; Chen *et al.*, 2004; Simsek *et al*., 2006; Song *et al.*, 2008; Soni *et al.,* 2004; Srikanth *et al.*, 2004), myocarditis (Ang-Lee *et al*., 2001; Anonymous, 2009i; Peters *et al.*, 2005; Song *et al.*, 2008; Srikanth *et al.*, 2004, Zaacks *et al.*, 1999), dysrhythmia (Simsek *et al*., 2006; Soni *et al.,* 2004; Srikanth et al, 2004; Woolf, 2003, WHO, 1999), taquicardia (Anonymous, 2009i; Simsek *et al*., 2006; Soni *et al.,* 2004; Srikanth et al, 2004; Woolf, 2003, WHO, 1999), or lethal cardiac arrhythmia (Anonymous, 2009i; Song *et al.*, 2008; Soni *et al.,* 2004), chest tightness, cardiac arrest and sudden death (Anonymous, 2009i).

***Adverse Cerebrovascular Events***

Cerebrovascular events associated with ephedra use are another area of concern. Cases of stroke in connection with the use of ephedrine and related compounds have been reported (Andraws *et al.*, 2005) as other several reports of adverse neurologic events including ischemic strokes, cerebral hemorrhages (Song *et al.*, 2008; Chen *et al.*, 2004) and seizures (Anonymous, 2009i; Chen *et al.*, 2004; Soni *et al.,* 2004; Srikanth *et al.*, 2004; Woolf, 2003). Cerebral hemorrhage associated with ephedra has been attributed primarily to hypertensive effects and possibly due to cerebral vasculitis, which has been reported with other adrenergic drugs. Ischemic stroke has been attributed to ephedra's vasoconstrictive effects on cerebral vasculature and possibly platelet aggregation effects due to adrenergic stimulation (Anonymous, 2009i). Ischemic strokes are presumably related to vasoconstriction of large cerebral arteries leading to local thrombosis as a result of stasis and sympathomimetic-inducted platelet activation. Ephedrine-related cerebral infarcts occur in the distribution of large or small cerebral arteries. Arteriograms have shown extracranial or intracranial arterial occlusions, arterial beading, arterial narrowing, or normal vessels. Subarachnoid hemorrhage is thought to be a result of the hypertensive action of ephedrine, which can be short lived, or of cerebral vasculitis, which has been described in association with a variety of sympathomimetric drugs. Additionally, hemorrhagic strokes have also been hypothesized to be related to vasculitic changes that occur in the cerebral vessels after ephedrine use (Chen *et al.*, 2004). There is some evidence that people who take doses greater than 32 mg per day, might have more than triple the risk of hemorrhagic stroke, including subarachnoid hemorrhage and intracerebral hemorrhage (Anonymous, 2009i)

***Adverse Psychiatric Events***

At higher doses, the release of norepinephrine causes anxiety, restlessness, and insomnia. Prolonged use of ephedra may lead to neurotoxicity, resulting in depletion of brain monoamines. Neurotoxicity may result in psychosis (Maglione, 2005; Simsek *et al*., 2006), and the structural similarity of ephedrine to amphetamine raises concern about possible abuse (Maglione, 2005). Long-term use or use in high doses has also been associated with dependence and tolerance (Anonymous, 2009i). The most commonly serious psychiatric reported events are psychosis (Maglione, 2005; Miller, 2005; Simsek *et al*., 2006) (psychosis can occur in some people and in some cases it is prolonged for several months after discontinuation) (Anonymous, 2009i), severe depression, mania or agitation, desilutions, violent behavior, hallucinations, and suicidal ideation/ thoughts (Chen *et al.*, 2004; Maglione, 2005;), anxiety, (Andraws *et al.*, 2005; Anonymous, 2009i; Maglione, 2005; Srikanth *et al.*, 2004) hostility, (Maglione, 2005) irritability (Anonymous, 2009i; Chen *et* Chen, 2004; Maglione, 2005;), addiction (Miller, 2005), agitation or nervousness (Maglione, 2005, WHO, 1999), hyperactivity (Srikanth *et al.*, 2004), restlessness (Anonymous, 2009i; Bensky *et al.,* 2004; Chen *et* Chen, 2004; Maglione, 2005), insomnia (Anonymous, 2009i; Bensky *et al.,* 2004; Chen *et* Chen, 2004; Maglione, 2005; WHO, 1999), personality changes, difficulty concentrating (Anonymous, 2009i), appetite suppression, changes in gastric motility (Andraws *et al.*, 2005) and tremor (Chen *et* Chen, 2004; Srikanth *et al.*, 2004, WHO, 1999).

***Other adverse events***

Other adverse effects include: dizziness (Anonymous, 2009i; WHO, 1999), visual impairment (Simsek *et al*., 2006), urine retention (WHO, 1999), vomiting (WHO, 1999), headache (Anonymous, 2009; WHO, 1999), nausea (Anonymous, 2009i; Srikanth *et al.*, 2004; WHO, 1999), diarrhea (Srikanth *et al.*, 2004), hepatitis (Charalampopoulos *et al.*, 2007, Skoulidis *et al.*, 2005), skin flushing and tingling (Anonymous, 2009i; WHO, 1999), increased thirst, dry mouth, anorexia, vomiting, heartburn, difficulty urinating, hyperthermia (Anonymous, 2009i). Rebound effect on prolonged use of topical preparations (>3days) (nasal congestion and chronic rhinitis) (WHO, 1999). Allergic reactions in the form of cutaneous eruptions combined with slightly elevated temperature and measles-like erythema have been reported. Because ephedrine stimulates the sphincter muscle of the bladder, long-term administration may cause oliguria or anuresis (Bensky *et al.,* 2004). Injury to the colon, especially ischemic colitis, in patients using Mahuang is presumably related to reduced splanchnic blood flow due to vasoconstrictions such as those seen in myocardial infarction and ischemic stroke (Song *et al.*, 2008). Rhabdomyolysis, eosinophilia-myalgia syndrome, nephrolithiasis, and acute hepatitis (Anonymous, 2009i). Finally, heavy use of ephedra has been documented as a very rare cause of radiolucent kidney stones (Ang-Lee *et al*., 2001).

## Posology

Ephedra is considered to be potentially safe by the FDA when used orally for a maximum of 7 days and in maximum doses of 24 mg/day of ephedrine equivalent (Cunha *et al.*, 2003; Song *et al.*, 2008).

The organs used in traditional medicine are the dried green stems, which are usually boiled in water and administered as a hot tea. The usual daily dose is 1.5–9 g of the decocted herb (Abourashed *et al.*, 2003) or according to WHO (1999) 1-6g/day. Liquid extract (1:1 alcohol 45%): 1-3 ml/day. Tincture (1:4 alcohol 45%): 6-8 ml/day (WHO, 1999).

## Storage

Ephedra should be kept in a closed container (Soni *et al.*, 2004; WHO, 1999), protect from light (FP, 2005; WHO, 1999). According to Chinese Pharmacopoeia (2005) it should be preserved in a ventilated and dry place, protected from moisture.

## Purity and toxicity

Depending on species, parts used (aerial, stem, leaf or a combination of stem, and leaf), harvesting, and extraction techniques, the alkaloid content of the commercially available products varies considerably. As a result of this natural inconsistency in the contents of alkaloids in ephedra, significant inter-product and intra-product variability occurs in ephedra products (Soni *et al.*, 2004). As ephedrine-type alkaloids (ETA) are the active principles, the quality of Mahuang is determined by the contents of total ETA, with higher contents indicating better quality. However, this practice of grading using only the total ETA contents as sole parameter is inadequate. The profile of alkaloids is also important, because although individual ETA has similar pharmacological activity, they vary significantly in potency. Both the contents and the profile of ETA in Mahuang vary with plant species and varieties, plant parts, sex, seasons of harvest and geographical origins. In order to accurately evaluate the quality of the crude drug, the quantitative analysis of individual ETA in Mahuang is urgently needed. In addition to ETA, Mahuang also contains other phytoconstituents, which may modify its pharmacological and toxicological activities. Therefore, the toxicity of Mahuang cannot be totally accounted for by its ETA contents alone. A bioassay is needed to determine the total toxicity of Mahuang due to the combined effect of the alkaloids and other constituents. In all of the published studies reviewed, the Mahuang samples were ground before extraction. This preparation method is similar to that used in preparing the marketed forms of Mahuang as they are exported from China to foreign countries, either as power or as concentrated extract. However, the practices are different from the traditional use of Mahuang as documented in the Chinese literature. Traditionally, Mahuang was known to be used in whole-herb form and to be extracted for a longer period of time than other herbs in a prescription. Also, with reference to the *Shang Han Lun*, a classical Chinese pharmacopoeia, all herbs were only to be extracted once and then the extract was taken, without extracting the herbs any further. However, the current practice is that all herbs are extracted twice and pooled together before taking. There has been no information found regarding the effects of these different ways of preparation on the biological activities if Mahuang (Lee *et al.*, 2000).

### Safety and regulatory actions in the United States

Given the frequency of reports of adverse cardiovascular and cerebrovascular complications, the FDA recently moved to prohibit the sale of these supplements. However, it is likely these agents will remain available to the public through illicit channels and related compounds will be sold through legitimate vendors (Andraws *et al.*, 2005). Products containing ephedra are classified by the FDA as dietary supplements and are regulated by the Dietary Supplement Health and Education Act (DSHEA) of 1994. This Act differs considerably from the regulations that govern the marketing of drugs. Dietary supplement manufacturers are not required to conduct clinical studies to establish the safety of their products. Manufacturers are forbidden from making disease treatment claims but they are also not required to demonstrate the efficacy of their products. DSHEA places the burden of proof for safety on the government. Specifically, the Act requires that the FDA monitor safety and “grants the FDA the authority to take action against a dietary supplement under certain circumstances, including when the product presents a significant risk, an unreasonable risk, or an imminent hazard, does not comply with good manufacturing practices, or makes an unsubstantiated structurefunction claim" (Morton, 2005). In 1995, FDA convened a special working group on food products containing ephedrine alkaloids to evaluate the potential health effects associated with these alkaloids. The group recommended the establishment of single servings and daily total use limits for ephedrine alkaloids, requiring warning or cautionary statements on the labels of the products and the establishment of good manufacturing practices (Soni *et al.*, 2004). Based on these recommendations and the reports of serious injury and death, on June 4, 1997, the FDA proposed a rule to: (1) limit the daily intake of ephedrine alkaloids to a total of 24mg/day or 8mg/6-h period; (2) the label to state that the product shoud not be used for more than 7 days (Anonymous, 2009g; Cunha *et al.*, 2007; Soni *et al.*, 2004); (3) prohibit the use of ephedrine alkaloids with substances known to have a stimulant effect and (Anonymous, 2009; Cunha *et al.*, 2007; Soni *et al.*, 2004); (4) require a specific warning label (Anonymous, 2009; Soni *et al.*, 2004). The FDA developed its proposed rule in response to what it termed "serious illnesses and injuries, including multiples deaths, associated with the use of dietary supplement products that contain ephedrine alkaloids." However, FDA withdrew this proposal because a lack of sound scientific evidence to support its position. Based on additional reports of adverse events, the FDA is being called on to enact stricter regulations and it has begun a new investigation into safety of ephedra. Some investigators have even claimed that these adverse events are an unintended consequence of the DSHEA of 1994 (Soni *et al.*, 2004). A growing number of consumer complaints were made to the FDA and legal cases were filed against ephedra manufacturers in the 1990s. Several adverse events possibly associated with ephedra use, including deaths of highprofile athletes, were reported and focused attention on the safety and efficacy of ephedra. As a result, the nonprofit consumer group Public Citizen filed a petition with the FDA in 2001 asking for a ban on the production and sale of ephedra to protect public health (Morton, 2005). In February 2003, the FDA and Department of Health and Human Resources announced a series of actions to protect patients from the risks of ephedra containing products including: (1) gathering further evidence to support restrictions on ephedra use, (2) obtaining records of ‘‘signs of unreasonable risk of injury’’, (3) creating new warning labels, (4) minimizing unsubstantiated claims about the effects of ephedra. Even further, public health officials caution against the use of ephedra-containing supplements under strenuous exercise, in combination with other stimulants like caffeine, or by patients with underlying cardiovascular disease, hypertension, diabetes, thyroid disease, prostate problems, anxiety or glaucoma (Chen *et al.*, 2004). Based on the evidence of adverse outcomes, professional sports leagues, college athletics associations, and the military were among the first to prohibit the use of these supplements among its members (Andraws *et al.*, 2005). The action of the stimulant ephedrine explains the prohibition of the use of the plant and its alkaloids by athletes in sports competitions (Cunha *et al.*, 2007). Several states passed legislation banning the sale of ephedra. The FDA was slower in announcing a national ban, likely because the DSHEA demanded such a high burden of proof. This formal ban was finally announced in December 2003 with implementation set for April 2004 (Andraws *et al.*, 2005; Anonymous, 2009). Yet, even after this long and winding road towards regulation, the threat from ephedra still exists. Recent commentaries have noted that the national ban has several loopholes. Extracts sold as dietary supplements and athletic enhancers are prohibited, but those marketed as herbal remedies are not. Moreover, compounds similar to phedra that technically do not fall into the ephedra family of alkaloids are not covered by the ban (Andraws *et al.*, 2005). In April 2005, the dietary supplement industry successfully challenged the FDA Ban on ephedra. A year after the ban on ephedra began, a federal judge in Utah stuck down the FDA's action saying that FDA didn't prove that low doses of ephedra are harmful. In August 2006, an appeals court reversed the Utah judge's decision and upheld the FDA's ban of ephedra-containing dietary supplements. Ephedra use is banned by the National Collegiate Athletic Association, International Olympic Committee, and National Football League. Ephedra is sometimes marketed as a recreational drug "herbal ecstasy." The FDA has announced that ephedra products marketed as recreational drugs are unapproved and misbranded drugs subject to seizure and injunction (Anonymous, 2009). The current ruling does not apply to traditional Chinese herbal remedies, or to products such as herbal teas that are regulated as conventional foods (Nelson, 2004). Examples of ephedra containing products are in Fig. 12-16.

In Portugal it is currently prohibited the marketing of efedra (Cunha *et al.*, 2007a).


**Fig. 12.** Example of ephedra containing products (adapted from http://www.buy-ephedrine.com/images/v.jpg) (visited


**Fig. 13.** Example of ephedra containing products (adapted from http://www.dynapurenutrition.com/ephedra.html) (visited 10-6-2009).


**Fig. 14.** Example of ephedra containing products (adapted from http://www.ephedrafaqs.com/blog/2008/03/24/800-audition-for-nbcs-the-biggest-loser/) (visited 10-6-2009).


**Fig. 15.** Example of ephedra containing products (adapted from http://archives.starbulletin.com/97/03/27/news/story1.html) (visited 10-6-2009).


**Fig. 16.** Example of ephedra containing products (adapted from http://www.cnn.com/HEALTH/9908/04/ephedra.safety/index.html)(visited 10-6-2009).

### 7.1.1. Herba Ephedrae (麻黃) according to Traditional Chinese Medicine

In Oriental medicine, the ephedra herb (Mahuang) is the chief medicine used in the treatment of asthma and bronchitis (Soni *et al.,* 2004). Alternate Chinese names are: Jing Mahuang, Mahuang Rong (Chen *et* Chen, 2004).

Chinese ephedra is mainly produced in Chinese provinces of Hebei, Shanxi, Inner Mongolia, Gansu, etc., and are picked and gathered between the beginning of autumn and the First Frost. The herb is dried in the shade, cut into sections and used in raw, stir-baked with honey (Anonymous, 2009l; Yanfu, 2002a) or pounded to fine hair (Anonymous, 2009l). According to the Chinese Pharmacopoeia (2005) the drug is collected in autumn, and dried in the sun. The text in which first appeared (Original Source) was The *Divine Husbandman's Classic of the Materia Medica,* second century (Bensky *et al.,* 2004; Chen *et* Chen, 2004).

#### Common name

Ephedra (CP, 2005; Gongwang, 2001a; Leite, 2005a; WHO, 1997a; Wu, 2005).

#### Pharmaceutical name

*Herba Ephedrae* (CP, 2005; Flaws, 1999d; Gongwang, 2001a; Greten, 2007; Wu, 2005; Yanfu, 2002a).

#### Botanical name

*E. sinica* Stapf., *E equisitina* Bge (Gongwang, 2001a).

#### Pynin name

Mahuang

#### Part used

Parts that grow above ground (Leite, 2005a; Tierra, 1997), stem (Anonymous, 2009g; Ganzhong et al., 2003b; Liu et Tseng, 2005a; Wu, 2005) or processed twigs (Anonymous, 2009g; Ganzhong et al., 2003b).

#### Classification

Unfolds the lung and extima. Ephedra belongs to the group *"Liberantia extimae acria et calida- I a)"* (Greten, 2007) or by other words, "Warm, acrid herbs that release the exterior" (Bensky *et al.,* 2004).

### Sapor & Temperature

Pungent (acrid), slightly bitter and warm (Anonymous, 2009l; Bensky *et al.,* 2004; Chen *et* Chen, 2004; Chu, 2008; Flws, 1999d; Ganzhong et al., 2003b; Gongwang, 2001a; Greten, 2007; Leite, 2005a; Liu et Tseng, 2005a; Ni, 1991; Tierra, 1997; Wu, 2005; Yanfu, 2002a).

### Orbs

Pulmonar, Vesical (Anonymous, 2009l; Bensky *et al.,* 2004; Chen *et* Chen, 2004; Chu, 2008; Flws, 1999d; Ganzhong et al., 2003b; Gongwang, 2001a; Greten, 2007; Leite, 2005a; Liu et Tseng, 2005a; Ni, 1991; Tierra, 1997; Wu, 2005; Yanfu, 2002a).

### Functions

Induces sweating (Anonymous, 2009g; Anonymous, 2009l; Bensky *et al.,* 2004; CP, 2005; Ganzhong et al., 2003b; Gongwang, 2001a), calms wheezing (Bensky *et al.,* 2004) and unfolds the pulmonary orb and therefore has an opening effect on the *extima* which is enhanced by the orb which controls the extima, i.e. the pulmonary orb (Greten, 2007). Activates *yang* (Leite, 2005a). Expels *wind–cold* (Gongwang, 2001a; Leite, 2005a; Liu et Tseng, 2005a), circulates *Lung Qi* (Anonymous, 2009l; Leite, 2005a, Liu et Tseng, 2005a; Wu, 2005) and promotes urination (Anonymous, 2009l; Bensky *et al.,* 2004; CP, 2005; Gongwang, 2001a; Liu et Tseng, 2005a; Wu, 2005). As pungent and warm disperses *cold* (Anonymous, 2009l; Ganzhong et al., 2003b; Gongwang, 2001a) by exerting warming and dispersing functions (Ganzhong et al., 2003b; Gongwang, 2001a).

### Indications

Common cold and influenza (Ganzhong et al., 2003b), asthma (Anonymous, 2009g; Anonymous, 2009l; Liu et Tseng, 2005a; Soni *et al.,* 2004; Tierra, 1997; Wu, 2005), bronchitis (Leite, 2005a; Soni *et al.,* 2004), cough, wheezing (Leite, 2005a; Liu et Tseng, 2005a; Tierra, 1997). Ephedra is used to treat colds accompanied by chills, slight fever, headache, absence of sweating, and rheumatic complaints accompanied by water retention (Tierra, 1997). Used in upper tract respiratory tract infection, some infectious diseases in the early stages such measles, scarlet fever and parotiditis (Ganzhong et al., 2003b), various kinds of oedema (Anonymous, 2009g; Anonymous, 2009l; Bensky *et al.,* 2004; Ganzhong et al., 2003b; Leite, 2005a; Liu et Tseng, 2005a) especially oedema complicated by an exterior syndrome (Anonymous, 2009g; Bensky *et al.,* 2004; Ganzhong et al., 2003b). Also can be used in chronic cellulitis (ostemyelitis, bone tuberculosis), in the early stage of rheumatic arthritis and acute urticaria (Gongwang, 2001a). Mahuang can be prescribed, in company with other appropriate drugs, to treat arthralgia caused by wind-damp and gangrene of *yin* type by dispelling pathogenic cold exerting warming and dispersing functions (Ganzhong et al., 2003b). Warms and disperses cold pathogens: useful for wind-damp painful obstruction and deep-rooted toxic sores without a head (Bensky *et al.,* 2004). Clear nasal cavity, promoting eruption and relieving itching so it it is used to treat nasal obstruction, allergic rhinitis, rubella itch and measles without adequate eruption due to attack of pathogenic wind-cold (Anonymous, 2009l). On superficial (Bensky *et al.,* 2004; Chen *et* Chen, 2004; Flws, 1999d; Gongwang, 2001a; Leite, 2005a) and tense pulse (Bensky *et al.,* 2004; Chen *et* Chen, 2004; Flws, 1999d; Ganzhong et al., 2003b; Gongwang, 2001a). *H. ephedrae* processed with honey is used in cough in common cold at the later stage when chill is absent, because moistens the lung and relieve cough (CP, 2005).

## Chinese therapeutic actions and examples of major combinations

### *1. Liberates the Extima through Diaphoresis*

*Extima-Repletio,* algor venti condition: acrid and warm, Mahuang ventilates the "lung" and is commonly used to treat exterior-excess, algor venti syndrome characterized by symptoms such as chills, fever, headache, nasal obstruction (Bensky *et al.,* 2004; Chen *et* Chen, 2004; Ganzhong et al., 2003b; Wu, 2005), aversion to cold, absence of perspiration (Anonymous, 2009l; Bensky *et al.,* 2004; Chen *et* Chen, 2004; Flws, 1999d; Ganzhong et al., 2003b; Gongwang, 2001a), body aches and pain (Bensky *et al.,* 2004; Chen *et* Chen, 2004; Flws, 1999d; Ganzhong et al., 2003b; Gongwang, 2001a). Induces sweating and releases the exterior (Anonymous, 2009g; Anonymous, 2009l; Bensky *et al.,* 2004; Ganzhong et al., 2003b; Gongwang, 2001a) so it is used to halt asthmatic attacks by dispersing stagnated qi of the lungs (Ganzhong et al., 2003b) and its dispersing function also opens peripheral channels and collaterals (Chen *et* Chen, 2004). Facilities the flow of the lung-qi to relieve asthma (Anonymous, 2009l).

- With *Ramulus Cinnamomi* (Guizhi) for patterns of wind-cold exterior excess presenting with fever and chills but no sweating, plus *Semen Pruni Armeniacae* (Xingren), and *Radix Glycyrrhizae Uralensis* (Gancao) in "The Ephedra Decoction" (Mahuang Tang) (Anonymous, 2009g; Bensky *et al.,* 2004; Chen *et* Chen, 2004; Flws, 1999d; Wu, 2005; Yanfu, 2002a) in order to enhance its effect of relieving the exterior of the body by inducing sweat (Ganzhong et al., 2003b).

### *2. Relieves Wheezing and Dyspnea, Stops Cough*

*Wind-cold constriction of the Lung leading to Lung qi reversal:* Mahuang disseminates and facilitates the Lung qi, calms wheezing, and stops coughing (Anonymous, 2009g; Bensky *et al.,* 2004; Chen *et* Chen, 2004; Yanfu, 2002a) and dyspnea and characterized by wind-cold attacking the exterior that leads to abnormal rising of Lung qi (Chen *et* Chen, 2004; Yanfu, 2002a). The herb both encourages the Lung qi to flow more easily, and directs it downward (Bensky *et al.,* 2004). It is important for treating either externally-contracted or internally-generated wheezing (Anonymous, 2009g; Bensky *et al.,* 2004).

- For treating asthmatic cough due to stagnation of the lung qi caused by exogenous wind-cold, mahuang is used together with *Semen Armeniacae Amarum* (Xingren, bitter apricot kernel) (Chen *et* Chen, 2004; Flws, 1999d; Ganzhong et al., 2003b; Wu, 2005; Yanfu, 2002a) and *Radix Glycyrrhizae* (Gancao, liquorice) in order to enhance its effect of halting asthmatic attacks, for example, the San-ao Decoction (Ganzhong et al., 2003b; Wu, 2005; Yanfu, 2002a) / Three Crude Drugs Decoction (Gongwang, 2002) / Three-Unbinding Decoction (Bensky *et al.,* 2004) / (Three Rough & Ready [Ingredients] Decoction) (Flws, 1999d). Mahuang and Xing Ren work synergistically to treat cough, as the former herb disperses Lung qi and relieves stagnation while the latter herb sends qi downward (Chen *et* Chen, 2004).
- For cough and asthma with profuse, thin, clear sputum that results from obstruction of the Lung by Cold Phlegm, it is used with *Herba Asari* (Xi Xin), *Zingiberi Officinalis* (Gan Jiang), and *Rhizoma Pinelliae* (Ban Xia) in "The Minor Green Dragon Decoction" (Xiao Qing Long Tang) (Flws, 1999d; Ganzhong et al., 2003b; Wu, 2005; Yanfu, 2002a). This formula is also used for wheezing or cough from wind-cold attack at the exterior and cold stagnation in the interior (Chen *et* Chen, 2004).
- Wheezing or cough caused by Lung heat: combine it with *Gypsum Fibrosum* (Shi Gao) and *Semen Armeniacae Amarum* (Xing Ren). Mahuang and Xing Ren have synergistic functions in treating wheezing and dyspnea. Shi Gao clears Lung heat and neutralizes the warm property of Mahuang to prevent the possible side effect of excess perspiration (Chen et Chen, 2004). Ma Xing Gan Shi Tang (Ephedra, Apricot Kernel, Licorice, and Gypsum Decoction) is an exemplar formula (Bensky *et al.,* 2004; Chen *et* Chen, 2004; Flws, 1999d; Ganzhong et al., 2003b; Wu, 2005; Yanfu, 2002a).
- Wheezing and dyspnea caused by stagnation of qi and phlegm: combine it with *Semen Armeniacae Amarum* (Xing Ren), *Pericarpium Citri Reticulatae* (Chen Pi) and *Cortex Magnoliae Officinalis* (Hou Po). Shen Mi Tang (Mysterious Decoction) is an exemplar formula (Chen et Chen, 2004).
- With *Ginseng Radix* (Renshen) for wind-cold where there is underlying primal qi deficiency (Bensky *et al.,* 2004).

### *3. Regulates Water Circulation and Relieves Edema*

*Edema with exterior syndrome:* Mahuang enters the Lung and Urinary Bladder channels to regulate water circulation and eliminate oedema. Excess water is generally eliminated through perspiration, increased urination, or both (Chen *et* Chen, 2004).

- Promotes urination and reduces oedema (Anonymous, 2009g; Anonymous, 2009l; Bensky *et al.,* 2004; Ganzhong et al., 2003b; Leite, 2005a; Liu et Tseng, 2005a): especially for oedema that accompanies an exterior condition (Anonymous, 2009g; Bensky *et al.,* 2004; Ganzhong et al., 2003b) by promoting water metabolism (Ganzhong et al., 2003b). Used to treat edema with obvious or wind-cold type external symptoms on the upper body (Anonymous, 2009l).
- Edema with exterior wind-cold signs or symptoms: use Mahuang with *Rhizoma Zingiberis Recens* (Sheng Jiang), *Rhizoma Atractylodis Macrocephalae* (Bai Zhu) and *Radix Glycyrrhizae* (Gan Cao), etc. to dispel the exterior condition and eliminate water accumulation. Yue Bi Jia Zhu Tang (Maidservant from Yue Decoction plus Atractylodes) is an exemplar formula (Bensky *et al.,* 2004; Chen *et* Chen, 2004; Ganzhong et al., 2003b; Yanfu, 2002a).
- For edema with fever, it is used with *Gypsum fibrosum* (Flws, 1999d; Gongwang, 2001a; Wu, 2005). The ratio of dosage of gypsum and ephedra is used with a ration of approximately 3 to 1 (Gongwang, 2001a).
- For edema with deep pulse and cold, it is used with *Radix Aconiti Carmichaeli Preparata* (Zhi Fu Zi) and *Radix Glycyrrhizae Uralensis* (Gan Cao) in "The Ephedra Aconiti Licorice Decoction" (Mahuang Fu Zi Gan Cao Tang) (Flws, 1999d; Wu, 2005).

### *4. Disperses Cold*

*Bi zheng (painful obstruction syndrome):* warm and dispersing in nature, *Mahuang* disperses and eliminates cold and damp from the exterior parts of the body (Chen *et* Chen, 2004). Also for wind-cold-damp painful obstruction (Bensky *et al.,* 2004).

- *Bi zheng* caused by wind-damp: use it with *Semen Coicis* (Yi Yi Ren), *Semen Armeniacae Amarum* (Xing Ren) and *Radix Glycyrrhizae* (Gan Cao) to treat muscle aches and pain of the extremities caused by wind-damp (Chen *et* Chen, 2004).
- Yin sores: use Mahuang with *Radix Rehmanniae Preparata* (Shu Di Huang), *Semen Sinapis* (Bai Jie Zi) or *Gelatinum Cornu Cervi* (Lu Jiao Jiao) (Chen *et* Chen, 2004). This condition is characterized by localized, painful swellings without heads that blend into the surrounding tissues. They often appear to be the same

color as the skin and are not hot to the touch. The underlying cause of this problem is blood deficiency with stagnation of cold and phlegm (Bensky *et al.,* 2004; Chen *et* Chen, 2004).

- Arthritis obliterans, obliterating phlebitis or *Raynaud*'s disease: use it with *Radix Rehmanniae Preparata* (Shu Di Huang), *Semen Sinapis* (Bai Jie Zi), *Gelatinum Cornu Cervi* (Lu Jiao Jiao), *Cortex Cinnamomi* (Rou Gui) and *Radix Glycyrrhizae* (Gan Cao) (Chen *et* Chen, 2004).
- With *Aconiti Radix lateralis preparata* (zhì fù zî) for wind-cold painful obstruction, or exterior cold conditions and edema associated with yang deficiency (Bensky *et al.,* 2004).
- With *Rehmanniae Radix preparata* (Shu Di Huang). This combination is also used for cough and wheezing associated with Kidney yin deficiency, as in Yang-Heartening Decoction (Yang He Tang) (Bensky *et al.,* 2004).

***Note:*** If heat is generated from the use of *Herba Ephedrae, Gypsum fibrosum* and *Radix Scutellariae* may be added for their cooling effect (Bensky *et al.,* 2004).

## Dosage and method of use

Decoction: 3-9g (Anonymous, 2009g; Greten, 2007; Leite, 2005a; Liu et Tseng, 2005a; Tierra, 1997; Yanfu, 2002a), 2-9g (Bensky et al., 2004; CP, 2005), 3-10g (Ni, 1991), 1.5 to 10 g (Anonymous, 2009l; Chen et Chen, 2004; Flaws, 1999d; Ganzhong et al., 2003b), 1.5-9 g (Gongwang, 2001a; Wu, 2005), 2.5 g to 6 g. Use of Mahuang in treating edema requires dosage between 10 and 15 grams (Chen et Chen, 2004) or 9-15g according to Gongwang (2001a). To relieve exterior, use fresh, to control asthma, the herb is fried with honey (Gongwang, 2001a).
The maximum dosage of Mahuang is 20 to 25 grams (Chen *et* Chen, 2004). According to Chu (2008) the large amount is up to 15 g.

When used properly, the warming dispersal of Mahuang can be a powerful and versatile agent, but its use requires familiarity with the qualities of the local environment and population. A dosage appropriate in one place may be excessive in another and Chinese physicians have been debating the relationship between locality and dosage of this herb for a long time (Bensky *et al.,* 2004).

The proper method for preparing Mahuang is to predecoct it (Anonymous, 2009g; Chen *et* Chen, 2004; Ganzhong et al., 2003b; Leite, 2005a) and remove the resultant foam from the solution prior to the addition of other herbs (Anonymous, 2009g; Chen *et* Chen, 2004). Classic texts state that the foam is the component more likely to cause irritability. To minimize diaphoresis and neutralize the warm nature of Mahuang, Shigao (*Gypsum Fibrosum*) is frequently used with Mahuang in a three-to-one ratio (Shigao 3: Mahuang 1). Different types of Mahuang have slightly different therapeutic functions: unprocessed Mahuang has a stronger function to induce perspiration and is commonly used to treat wind-cold conditions (Anonymous, 2009l; Chen et Chen, 2004; Leite, 2005a; Yanfu, 2002a); honey-fried Mahuang is weaker in inducing perspiration but more strongly moistens the Lung and relieves wheezing, dyspnea and cough (Anonymous, 2009l; Chen et Chen, 2004; Yanfu, 2002a) and asthma (Anonymous, 2009g; Anonymous, 2009l); and crushed Mahuang Rong is milder in inducing perspiration and is generally pediatric medicine to relieve exterior syndromes (Chen *et* Chen, 2004). To promote diaphoresis and induce diuresis, *Herba Ephedrae* is usually used unprepared; for relieving cough and dyspnea, it is stir-baked (Wu, 2005). According to Flaws (1999) decoct in water and administer internally. For effusing sweat and resolving the exterior, disinhibiting water and dispersing swelling, mostly use uncooked. For stopping cough and leveling panting use mix-fried (Flaws, 1999d).

### Nomenclature & Preparation

➢ Cleaned Ephedra *(淨麻黃 jìng má huáng)*

This has the nodes on the stalks removed, as well as the roots, as both are generally considered to reduce the herb's diaphoretic effect. The nodes can be left if the herb is not to be used to induce sweating. For example, the formula Three-Unbinding Decoction *(sän âo täng)* specifically calls for *Herba Ephedrae* without the nodes removed, since the desired effect is to disseminate the Lung qi and calm wheezing, rather than sweating (Bensky *et al.,* 2004).

➢ Ephedra Cotton *(麻黃絨 má huáng róng)*

Cleaned ephedra is brought to a boil until it 'rolls over' in the water ten times, or simply infused in boiling water until froth rises; it is then removed and dried. Once dried, it is ground until the fibbers become soft. It is then called ephedra cotton. Usually, when cleaned ephedra is used to promote sweating, the patient first boils it, and then removes the froth, as it can cause agitation. Ephedra cotton saves this trouble. The diaphoretic effect, however, is slightly less than cleaned ephedra, while stronger than prepared ephedra (Bensky *et al.,* 2004).

➢ Prepared Ephedra *(炙麻黃 zhì má huáng)*

Cleaned ephedra is stir-fried with water. This method of preparation reduces the herb's diaphoretic action, but strengthens its effect in calming the Lungs. *Discussion of Cold Damage* says to remove the froth after boiling. According to *Materia Medica of Combinations,* this is because the froth "makes one irritable"; however, "frying with honey before use will also work" (Bensky *et al.,* 2004).

➢ Honey-prepared Ephedra *(蜜炙麻黃 mì zhì má huáng)*

Honey is first brought to a boil slowly, and the froth and any residual wax or extraneous material scraped from the surface. The honey is then poured through a filter. It is returned to the wok, and again brought to a boil, which is maintained at 116-118°C until the whole wok bubbles and the honey no longer stretches between the fingers. Boiling water is then added to thin the honey, which is then poured slowly over cleaned ephedra and left covered briefly. The amount of cooked honey should be approximately one-fifth the amount of herb, while the amount of water should be approximately one-third the quantity of honey; too much water and the herb will become overly damp and difficult to dry after preparation. The herb is then dry-fried at a low temperature until deep yellow and no longer sticky to the touch. When ephedra is prepared with honey, the diaphoresis is modified by the sweetness of the honey. Not only is the intensity of its acrid, dispersing qualities moderated, but the duration of its action is lengthened in a kind of 'timerelease' manner. Sweetness pertains to the earth phase and thus brings harmony. Honey preparation also moistens the Lungs and protects it from the drying effects of the acrid, warm qualities of the unprepared herb (Bensky *et al.,* 2004).

### Precautions and Contraindications

Because Mahuang strongly functions to induce diaphoresis and ventilate the lungs, chronic or repetitive use is not recommended. Inappropriate use may damage qi, yin and body fluids (Bensky *et al.,* 2004; Chen *et* Chen, 2004). Also the dosage should not be too large (Bensky *et al.,* 2004; Flaws, 1999d; Wu, 2005). Other herbs can be added to harmonize its strong effects (Chen *et* Chen, 2004). It should be used with caution in patients with weak constitutions (Bensky *et al.,* 2004; Chen *et* Chen, 2004), or those with wheezing associated with the failure of the kidneys to accept qi (Wu, 2005; Bensky et al., 2004). Precaution in spontaneous perspiration arising from qi deficiency (Wu, 2005; Chen et Chen, 2004; Gongwang, 2001a), sweating due to exterior deficiency (Bensky et al., 2004; Ganzhong et al., 2003b), night perspiration due to yin deficiency (Wu, 2005; Bensky et al., 2004; Chen et Chen, 2004; Ganzhong et al., 2003b) or qi deficiency (Gongwang, 2001a), wheezing or dyspnea caused by kidney deficiency (manifesting in long exhalation and short inhalation), edema due to spleen deficiency (Chen et Chen, 2004). Ingesting Mahuang is not recommended in patients with *Liv*er yang rising or yin-deficient fire, as its use may lead to vertigo, epistaxis, or hematemesis (Chen *et* Chen, 2004). Mahuang has a stimulating effect on the sympathetic nervous system (Chen *et* Chen, 2004). Thus, it should be used with caution in patients with such medical conditions as convulsions, epilepsy and seizure disorders, diabetes mellitus (Chen *et* Chen, 2004), hypertension (Anonymous, 2009g; Chen *et* Chen, 2004; Gongwang, 2001a; Wu, 2005; Tierra, 1997; Yanfu, 2002a), tachycardia (Gongwang, 2001a), hyperthyroidism and prostatic enlargement (Chen *et* Chen, 2004). Use with caution during pregnancy because of its stimulating effect on the uterus (Chen *et* Chen, 2004). This herb should cease to be taken as soon as the sweat comes out and the disease is cured; it is not suitable for administration over a long period (Anonymous, 2009l).

## Overdosage

Overdose of *Mahuang* is characterized by stimulation of the sympathetic nervous system by the numerous ephedrine alkaloids in the herb (Chen *et* Chen, 2004). The toxic dose is approximately 30-45g (Bensky *et al.,* 2004). Symptoms of acute toxic reaction include insomnia, restlessness, perspiration, tremor (Bensky *et al.,* 2004; Chen *et* Chen, 2004), excitation, irritability, hypersensitivity, tinnitus, nausea, vomiting, red face, upper abdominal discomfort, poor appetite, thirst, increased blood pressure, dizziness, elevated blood glucose levels, chest pain (Chen *et* Chen, 2004), palpitations, chest pain, elevated temperature (Bensky *et al.,* 2004). Extreme overdoses can lead to blurred vision, dilated pupils, coma, dyspnea, dysuria, (Bensky *et al.,* 2004) convulsions, (Bensky *et al.,* 2004; Chen *et* Chen, 2004) respiratory arrest, cardiac failure, bradycardia, ventricular fibrillation (Bensky *et al.,* 2004), cardiac arrhythmia, increased blood pressure, and possibly epilepsy. Adverse reactions generally occur between one-half and two hours following ingestion of an excessive quantity of the herb (Chen *et* Chen, 2004).

### ***Chinese Treatment of Overdosage***

Overdose of *Mahuang* may be treated with either of two herbal formulas:

• Formula one contains *Radix et Rhizoma Rhei (Da Huang*) 9g, *Cortex Magnoliae Officinalis* (Hou Po) 9g, *Radix Aucklandiae* (Mu Xiang) 9g, *Natrii Sulfas* (Mang Xiao) 15g, and *Radix Glycyrrhizae* (Gan Cao) 6g. The decoction is to be taken once every four hours until toxic symptoms are alleviated.

• Formula two contains *Semen Phaseoli Radiati* (Lu Dou) 15g and *Radix Glycyrrhizae* (Gan Cao) 30g cooked in water to yield 300 ml of decoction. Patients are instructed to take 150 ml per dose, every two hours, for 3 to 5 doses (Chen *et* Chen, 2004).

## *7.2. Semen armeniacae*

### Introduction

By definition *Semen armeniacae* is the seed of *Prunus armeniaca* Linne var. *ansu* Maximowicz (Fig.17) (Chang *et al.,* 2005; Hwang *et al.,* 2008; Koo *et al.,* 2005; WHO, 1998a; WHO, 2001), which belongs to the Rosaceae Family (Anonymous, 2009d; Chang *et al.,* 2005; DerMarderosian *et* Beutler, 2002; Ganzhong et al., 2003a; Hwang *et al.,* 2008; Koo *et al.,* 2005; Newall *et al.,* 1996; WHO, 1998a; WHO, 2001; Wu, 2005a) or allied species (WHO, 2001). *Semen armeniacae* is a traditional drug with many benefits, including the provision of antipyretic, antitussive, thirst-quenching (Chang *et al.,* 2006 *et* 2005; Hwang *et al.,* 2008; Koo *et al.,* 2005) and anticancer effects (Hwang *et al.,* 2008). In traditional oriental medicine, *Semen armeniacae* has been used for the treatment of asthma (Chang *et al.,* 2006 *et* 2005; Hwang *et al.,* 2008; Koo *et al.,* 2005), bronchitis, emphysema (Chang *et al.,* 2006 *et* 2005; Hwang *et al.,* 2008), nausea, leprosy, leucoderma (Chang *et al.,* 2006 *et* 2005; Hwang *et al.,* 2008), constipation, nausea (Chang *et al.,* 2005; Hwang *et al.,* 2008), aplastic anemia, tumors (Koo *et al.,* 2005), pain (Chang *et al.,* 2005 *et* 2006) and inflammation (Chang *et al.,* 2005).

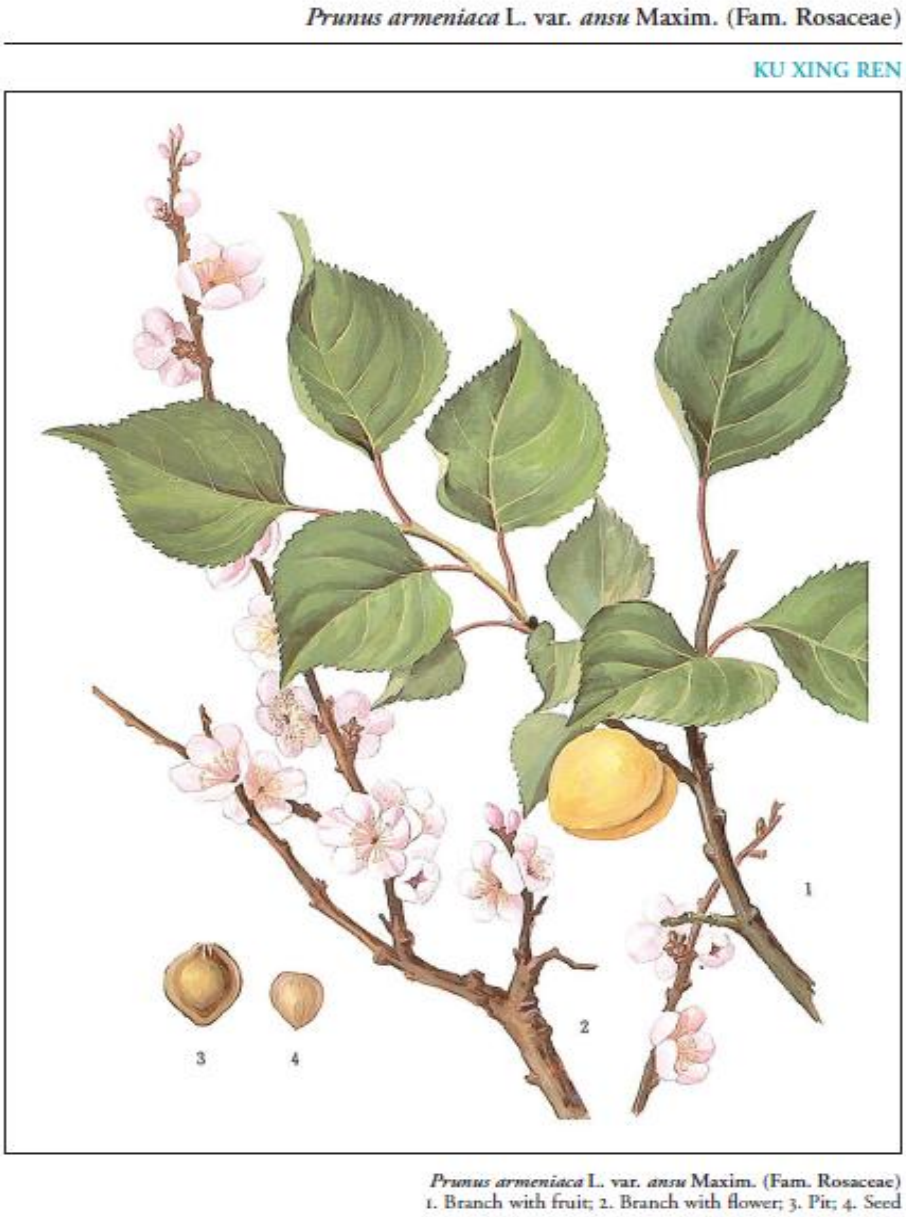



**Fig. 17.** *Prunus armeniaca* Linne var. *ansu* Maxim. (adapted from Wu, 2005a)

## Historical perspective

In India and China, the apricot has been used for over 2000 years. During the 2nd century AD, a physician, Dong Feng, is said to have received his payment in apricot trees. There are also biblical references to the plant. The Greeks wrongly assumed the apricot to have originated in Armenia, hence the botanical name *"Prunus armeniaca"*. The Romans termed the fruit "praecocium" meaning "precocious," referring to the fruit´s early ripenleg. From this, the name "apricot" evolved (DerMarderosian *et* Beutler, 2002). Amygdalin is considered the major constituent of *Semen armeniacae*, a cyanogenic glycoside (WHO, 2001). When apricot is ground up, the enzyme emulsin breaks down amygdalin, releasing benzaldehyde and hydrogen cyanide, HCN, which is a deadly poison. So, this preparation was used by the ancient Egyptians and Romans in making various poisons (Anonymous, 2009g).

## Synonyms

*Armeniaca vulgaris* Lam. (Barnes et al, 2007; WHO, 2001) var. vulgaris, Ku Xing Ren (seed/kernel), *Prunus armeniaca* L., *Prunus tiliifolia* Salisb (Barnes *et al.,* 2007).

## Selected vernacular names

Apricot (DerMarderosian *et* Beutler, 2002; WHO, 2001, 1998, 1997), abricotier, anzu, aprikose, aprikosenbaum, barqouq, bitter apricot, chuli, cuari, culu, elk mesmas, haeng-in, Himalayan wild apricot, hsing, ku-xinggren, kurbani, mao, michmich, mouchmouch, o mai, touffah armani, wild apricot, xing ren, zardalou, zardalu (WHO, 2001), sal-goo (WHO, 2001, 1998), Chinese almond (DerMarderosian *et* Beutler, 2002).

## Geographical distribution

*Semen armeniacae* is indigenous to the Korean peninsula and to China, India and Japan (WHO, 2001, 1997). Cultivated in Asia, North Africa and United States of America (WHO, 2001). Is produced mainly in the Chinese provinces of Inner Mongolia (Ganzhong et al., 2003a; WHO, 1997B), growing in Northeast, North and Northwest China, Inner Mongolia, Xiajiang and Chinese provinces along the Yangtzi River (Ganzhong et al., 2003a), Hebei, Shanxi, and Shandong (Wu, 2005a). Is mostly cultivated in Korea (WHO, 1998a, 1997). The apricot is native to China and Japan but is also cultivated in warmer temperate areas of the world, mainly the regions including Turkey through Iran, Southern Europe, South Africa, Australia and California (DerMarderosian *et* Beutler, 2002).

## Description

Apricots grow on trees up to 30 feet in height (DerMarderosian *et* Beutler, 2002). It is a medium-sized, deciduous tree (WHO, 2001, 1997), with reddish bark (WHO, 2001) and glabrous twigs (WHO, 2001, 1998, 1997). Leaves convoluted in bud, blade broadly ovate, 5–7 cm long, 4–5 cm wide, acuminate, crenate-glandular, hairy on the veins of the underside when young (WHO, 2001, 1997), glabrous when mature, except for the axils of the underside veins (WHO, 2001). Petiole approximately 2.5 cm long, glandular; stipules, lanceolate, glandular on the margins (WHO, 2001, 1997). Flowers appearing before the leaves, bisexual, pinkish to white (WHO, 2001, 1998, 1997), solitary or fascicled, pedicels very short; calyx-tube campanulate, puberulent, 5 mm long; surrounding lobes, pubescent, half the length of the tube (WHO, 2001, 1997).; petals suborbicular, 7–13 mm long (WHO, 2001).; stamens inserted with the petals at the mouth of the calyx-tube

(WHO, 2001, 1998, 1997); ovary and base of the style hairy (WHO, 2001, 1997). Fruit a downy or glabrous, yellow-tinged, red drupe (WHO, 2001, 1997) with a fleshy outer layer surrounding a hard stone containing the seed (WHO, 2001, 1998).
There are many varieties and species of apricot, differing in flavor, color and size. Fruits vary in color from yellows and oranges to deep purples. They ripen in late summer (DerMarderosian *et* Beutler, 2002). Then the seed is dried in sunlight, and crushed before use (Wu, 2005a).

## Plant material of interest

Kernel (seed) (Fig. 18) (Barnes *et al.*, 2007; WHO, 2001, 1998, 1997; Newall *et al.*, 1996), expressed oil (Barnes *et al.*, 2007; Newall *et al*., 1996; WHO, 2001).


**Fig. 18.** Apricot kernels (adapted from http://www.cancerchoices.com/Merchant2/merchant.mvc?Screen=PROD&Store_Code=001&Product_Code=ApricotKernels (visited 9-6-2009)

### *General appearance of the dried ripe seeds*

The apricot seeds are flattened, cordate, 1.1–1.9 cm long, 0.8–1.5 cm wide, 0.4–0.8 cm thick (WHO, 2001, 1997), acute at one end, plump, unsymmetrical, rounded at the other. Seed coat yellowish-brown to deep brown; short linear hilum situated at the acute end; chalaza at the rounded end, with numerous, deep-brown veins radiating upwards. Testa, thin (WHO, 2001); two cotyledons (WHO, 2001, 1997).

## Organoleptic properties

Odourless; taste: bitter (WHO, 2001, 1997).

### *Microscopic characteristics*

Epidermal surface has stone cells, 60–90 µm in diameter, on veins protruded by vascular bundles, which appear as angular circles–ellipses, approximately uniform in shape, with uniformly thickened walls. In lateral view, stone cells appear obtusely triangular, walls extremely thickened at the apex (WHO, 2001).

## General identity tests

Macroscopic and microscopic examinations and microchemical tests (WHO, 2001).

## Purity tests

### *Microbiological*

Tests for specific microorganisms and microbial contamination have different limits are set according to the use of the material and the material itself.

• For contamination of "crude" plant material intended for further processing (including additional decontamination by a physical or chemical process) the limits are given for untreated plant material harvested under acceptable hygienic conditions:

- *Escherichia coli*, maximum $10^4$ per gram;
- Mould propagules, maximum $10^5$ per gram.

• For plant materials that have been pretreated (e.g. with boiling water as used for herbal teas and infusions) or that are used as topical dosage forms:

- Aerobic bacteria, maximum $10^7$ per gram;
- Yeasts and moulds, maximum $10^4$ per gram;
- *Escherichia coli*, maximum $10^2$ per gram;
- Other enterobacteria, maximum $10^4$ per gram;
- *Salmonellae*, none.

• For other plant materials for internal use:

- Aerobic bacteria, maximum $10^5$ per gram;
- Yeasts and moulds, maximum $10^3$ per gram;
- *Escherichia coli*, maximum 10 per gram;

- Other enterobacteria, maximum $10^3$, per gram;
- *Salmonellae*, none (WHO, 1998b).

***Pesticide residues***

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (WHO, 2001).

***Heavy metals***

For maximum limits and analysis of heavy metals, according the WHO guidelines on quality control methods for medicinal plants the following maximum amounts in dried plant materials, are proposed:

- Lead, 10 mg/kg;
- Cadmium, 0.3 mg/kg (WHO, 1998b).

***Radioactive residues***

Even at maximum observed levels of radioactive contamination with the more dangerous radionuclides, significant risk is associated only with consumption of quantities of over 20 kg of plant material per year so that a risk to health is most unlikely to be encountered given the amount of medicinal plant materials that would need to be ingested. Additionally, the level of contamination might be reduced during the manufacturing process. Therefore, no limits for radioactive contamination are proposed (WHO, 1998b).

***Other purity tests***

Chemical, foreign organic matter, total ash, acid-insoluble ash, sulfated ash, alcohol-soluble extractive, water-soluble extractive and loss on drying tests to be established in accordance with national requirements (WHO, 2001).

***Chemical assays***

Contains not less than 3.0% amygdalin determined by titrimetric assay with silver nitrate. A high-performance liquid chromatography method is also available (WHO, 2001). Amygdalin also has been determined from seeds, using gas chromatography (DerMarderosian *et* Beutler, 2002).

The VIII Portuguese Pharmacopoeia (2005) doens´t inscribe the monography of *Semen armeniacae.*

## Chemical constituents

*Semen armeniacae* is divided into the outer husk and an inner part that contains glycoside, amygdaline, starch, and fatty acids (Chang *et al.,* 2005). Amygdalin occurs in the seeds of Rosaceae, principally in the fruit of *Semen Armeniacae* (bitter almonds) (Yang *et al.,* 2007; Du *et al.,* 2005) and *Semen Persicae* (sweet almond) (Yang *et al.,* 2007). Amygdalin (Fig. 19) is considered the major constituent of *Semen armeniacae* (up to 4.9%), a cyanogenic glycoside (a plant compound that contains sugar and produces cyanide) (WHO, 2001). According to DerMarderosian *et* Beutler (2002) kernels contain up to 8% amygdalin cyanide content in kernels varies from 2 to 200mg/100g (Barnes *et al.,* 2007; DerMarderosian *et* Beutler, 2002; Newall *et al.,* 1996). Other cyanogenic compounds present are prunasin and mandelonitrile (Fig. 20). Also present are the amygdalin-hydrolysing enzyme, emulsin, and fatty acids and sitosterols (WHO, 2001).

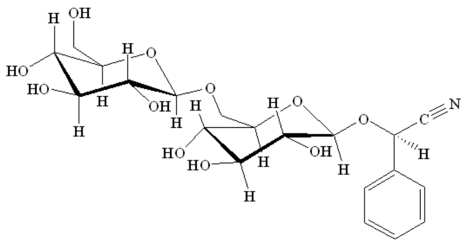


**Fig. 19.** Chemical structure of amygdalin (adapted from http://www.angelo.edu/faculty/kboudrea/molecule_gallery/04_aromatics/00_aromatics.htm) (visited 9-6-09)

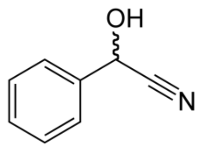


**Fig. 20.** Chemical structure of mandelonitrile (adapted from http://en.wikipedia.org/wiki/File:Racemic-mandelonitrile-2D-skeletal.png) (visited 9-6-09)

Amygdalin is a disaccharide consisting of two glucose molecules in which a carbon bearing a cyano (CN) group and a benzene ring is attached to one of the oxygen atoms on a glucose. The combination of a cyano group with a OH or OR group on a single carbon is called a cyanohydrin; cyanohydrins easily break down to release the cyanide ion, $CN^-$. When apricot are ground up, the enzyme emulsin breaks down amygdalin, releasing benzaldehyde and hydrogen cyanide, HCN, which is a deadly poison (Fig. 21) (Anonymous, 2009g).

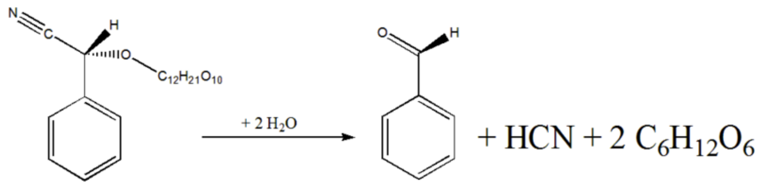



**Fig. 21.** Hydrolisis of amygdalin (adapted from http://commons.wikimedia.org/wiki/File:Amygdalin-benzaldehyd.png (visited 9-6-09)

***Amigdalin Epimerization***

*Semen armeniacae* contains not only amygdalin but also emulsin, which is an enzyme that hydrolyzes amygdalin. It was reported that d-amygdalin in S*emen armeniacae* undergoes hydrolytic reaction by emulsin when using water, and it is almost decomposed when extracting from powder type. In addition, it was reported that d-amygdalin in boiling water is epimerized to neoamygdalin (L-mandelonitrile-β-D-gentiobioside) (Fig. 22). Since amygdalin has been referred as an antitumor drug and neoamygdalin has no antitumor activity, it is important to prevent D-amygdalin from being converted into neoamygdalin by epimerization in water (Koo *et al.,* 2005). Therefore, the quantitative measurement of the amygdalin epimers in the crude drugs is a very important step to evaluate the quality of such drugs (Isozaki *et al.,* 2001).

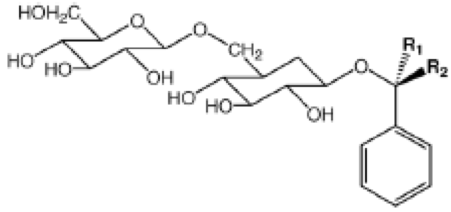



**Fig. 22.** Chemical structures of d-amygdalin and neoamygdalin (adapted from Koo *et al.,* 2005).

## Effects and uses

Among his traditional uses are cough (WHO, 1998a, 1997), phlegm and common cold (WHO, 1998a). Used internally as a decoction, after processing by dipping in boiling water and stir-frying until yellow, for symptomatic treatment of asthma, cough with profuse expectoration and fever. The seed oil is used for treatment of constipation (WHO, 2001).

Used in traditional medicine for the treatment of gynaecological disorders, skin hyperpigmentation, headache and rheumatic pain. The seed oil is used in the form of eardrops for inflammation and tinnitus, and for treatment of skin diseases (WHO, 2001).

In very small amounts, the toxic prussic acid (hydrogen cyanide) present in apricot kernels is prescribed in Chinese Medicine for asthma treatment, cough and constipation. Decoction of the plant´s bark serves as an astringent to soothe irritated skin. Other folk medicine uses of apricot include treatment of hemorrhage, infertility, eye inflammation and spasm. Apricot kernel paste may help eliminate vaginal infections (DerMarderosian *et* Beutler, 2002). *Semen armeniacae* is known to have antidiarroheic, antipyretic, antiemetic, and anthelmintic effects (Chang *et al.,* 2005).

***Food Use***

Apricots are usually eaten as a fruit, either fresh or dried, made into jams and jellies or alcoholic beverages. The seeds are used like almonds by Chinese and Afghan cultures. The oil (apricot kernel oil) (Fig. 23) is also used. Its used in food, flavorings, confection, juices, jams, etc. is common. Some cultures use certain varieties of apricot kernels as almonds (DerMarderosian *et* Beutler, 2002). Apricot is listed by the Council of Europe as a natural source of food flavourings (categories N1 and N2). These categories limit the total amount of hydrocyanic acid permitted in the final product to 1mg/kg. Exceptions to this are 25mg/kg for confectionery, 50mg/kg for marzipan and 5mg/kg for fruit juices. Previously, apricot kernel extract has been listed as GRAS (Generally Recognised As Safe) (Barnes *et al.,* 2007).

**Fig. 23.** Apricot kernel oil (adapted from http://www.apricotkerneloil.com/) visited (10/1/2010)

***Other Uses***

Traditionally, the oil has been incorporated into cosmetic and perfumery products such as soaps and creams (Fig. 24-26) (Barnes *et al.,* 2007). The oil is used in cosmetics or as a pharmaceutical vehicle (DerMarderosian *et* Beutler, 2002).


**Fig. 24.** Example of cosmetic containg apricot kernel oil (adapted from http://store.bluemountainorganics.com/index.php?cPath=21_22) visited (10/1/2010)


**Fig. 25.** Example of cosmetic containg apricot kernel oil (adapted from http://www.stendersshop.com/en/shop/Body/?id=2923) visited (10/1/2010)

**Fig. 26.** Example of cosmetic containing apricot kernel oil (adapted from http://www.akomaskincare.co.uk/product.php/71/apricot_kernel_oil_certified_organic) visited (10/1/2010)

## Pharmacological Effects

### *Antitumor effects*

Laetrile, a semi-synthetic derivative of the naturally occurring "amygdalin," has been used (during late ´70s, early ´80s) in a highly controversial treatment for cancer (Barnes *et al.,* 2007; DerMarderosian *et* Beutler, 2002; Newall *et al.,* 1996). Although it was advocated as a new cancer cure or preventative and examined clinically in the late 1970s and early 1980s, it was not approved by the FDA for cancer treatment due to insufficient clinical evidence of its efficacy and potential toxicity. Despite the failure of clinical tests to demonstrate the anticancer effects of amygdalin in the US and in Europe, amygdalin continues to be manufactured and administered as an anticancer therapy in northern Europe and Mexico, and few studies have examined other pharmacological activities of amygdalin (Hwang *et al.,* 2008). It has been reported that D-amygdalin selectively kills cancer cells at the tumor site without systemic toxicity, which is the usual problem when using general chemotherapeutic agents (Koo *et al.,* 2005). A theory claimed that laetrile, when metabolized by the enzyme β-glucosidase, released toxic cyanide. The enzyme was said to be most prevalent in tumor tissue (as opposed to normal tissue). As a result, this reaction was believed to destroy mainly cancer cells. It was later proven that both cancerous and normal cells contained only traces amounts of this enzyme. Although the treatment may have slight activity in some cases, it was not as valuable as once thought. A report in 1980 concluded laetrile to be ineffective in cancer treatment (DerMarderosian *et* Beutler, 2002). One suggestion is that amygdalin enhances the functions of pancreatic enzymes, which may prevent transformation of cancer primordial germ cells (Chang *et al.,* 2006). Other theory claimed that cancerous cells contained abundant quantities of β-glucosidases and high concentrations of rhodanese, an enzyme which converts cyanide to the less toxic thicyanate. However, this theory was disproved when it was shown that both cancerous and normal cells contain only traces amounts of β-glucosidases, and similar amounts of rhodanese. In addition, it was thought that amygdalin was not absorbed intact from the gastrointestinal tract (Barnes *et al.,* 2007; Newall *et al.,* 1996). Another theory proposed that following ingestion, amygdalin was hydrolysed to mandelonitrile, transported intact to the liver and converted to a β-glucuronide complex. This complex was then carried to the cancerous cells, hydrolysed by β-glucosidases to release mandelonitrile and subsequently hydrogen cyanide. This theory was considered to be untenable (Barnes *et al.,* 2007; Newall *et al.,* 1996). Another theory proposed that laetrile is vitamin $B_{17}$, (Barnes *et al.,* 2007; Yang *et al.,* 2007; Chang *et al.,* 2006 *et* 2005; Newall *et al.,* 1996) that cancer is a result of a deficiency of this vitamin, and that chronic administration of laetrile would prevent cancer (Barnes *et al.,* 2007; Newall *et al.,* 1996) and restores the vitamin deficiency that could lead to metabolic disorders in cancer patients (Chang *et al.,* 2006). Again this was not substantiated by any scientific evidence. Furthermore, it was claimed that patients taking laetrile reduced their life expectancy as a result of lack of proper medical care and chronic cyanide poisoning (Barnes *et al.,* 2007; Newall *et al.,* 1996). Taking apricot kernel or the amygdalin constituent orally is not effective for treating cancer (Anonymous, 2009d). A recent review concluded that there is no evidence from controlled clinical trials to support the alleged beneficial effects of laetrile as an anticancer agent, or as an adjunctive agent in cancer chemotherapy (Barnes *et al.,* 2007).

***Respiratory effects***

Amygdalin (D-mandelonitrile-b-D-gentiobioside) is a natural compound with the antitussive activitie. It is decomposed by the action of b-D-glucosidase to yield hydrocyanic highacid (Isozaki *et al.,* 2001) which stimulates the respiratory center reflexively and produces a kind of antitussive and antiasthmatic effects (Ganzhong et al., 2003a; Isozaki *et al.,* 2001).

***Antiinflammatory and analgesic activities***

Recently, it was reported that *Semen armeniacae* containing abundant amygdalin exhibits analgesic and anti-inflammatory effects, showing that low doses of amygdalin may relieve pain (Yang *et al.,* 2007; Chang *et al.,* 2006, Chang *et al.,* 2005).

Amygdalin extract inhibited the LPS-stimulated enhancement of the COX-1 mRNA expression, the COX-2 mRNA expression and the $PGE_2$ synthesis in the mouse BV2 microglial cells. Amygdalin suppressed the COX-2 mRNA expression more potently compared to the COX-1 mRNA expression. The elevation of COX-2 activity was suggested to be closely associated with the occurrence of cancers, arthritis and several types of neurodegenerative disorders. $PGE_2$ is a major metabolite of the COX-2 pathway, and it has emerged as an important lipid mediator of the inflammatory and immunoregulatory processes. $PGE_2$ has been implicated in the pathogenesis of acute and chronic inflammatory disease states, and specific COX-2 inhibitors are known to attenuate the symptoms of inflammation. In a recent study, amygdalin extract inhibited the LPS-stimulated enhancement of iNOS mRNA expression and NO production in the mouse BV2 microglial cells. The COX activity and the subsequent production of $PGE_2$ are closely related to the generation of the NO. It has been reported that NO modulates the activity of COX-2 in a cGMP-independent manner, and NO plays a critical role in the release of $PGE_2$ by the direct activation of COX-2. NO production has been shown to be a key regulator of homeostasis and an important mediator of inflammation in several animal models. Especially, the generation of NO by iNOS plays an important role in inflammation, in the host-defense responses and for tissue repair. After cells are exposed to endogenous and exogenous stimulators such as LPS and viral infections, iNOS is quantitatively induced in a variety of cells, and it triggers several deleterious cellular responses inducing inflammation, sepsis and stroke. Inhibition of the iNOS expression in murine macrophages has been suggested as another possible underlying mechanism of the non-steroidal anti-inflammatory drugs (Yang *et al.,* 2007).

***Actions on the gastrointestinal tract***

Fatty oil in apricot kernel can lubrificate the intestines and promote defecation. Amygdalin can be dissociated by enzymes to produce benzaldeyde, which can inhibit the activity of pepsine and prevent the development of peptic ulcers (Ganzhong et al., 2003a).

***Antihelmintic action***

Fatty oil of apricot kernel can inhibit and kill ascaris, ancylostomi (Anonymous, 2009f; Ganzhong et al., 2003a) and pinworm, and it can also produce a bactericidal effect to inhibit some pathogenic bacteria (Ganzhong et al., 2003a) including typhoid bacillus and paratyphoid bacillus (Anonymous, 2009f).

## Pharmacokinetics

After ingestion, amygdalin is metabolized in the gastrointestinal tract to produce prunasin and mandelonitrile, which are further broken down to benzaldehyde and hydrocyanic acid, the latter of which is highly toxic (WHO, 2001).

After intragastric administration of 30.0 mg of amygdalin or prunasin to rats, capacity for hydrolysing these compounds was greatest in the organs of 15-day-old animals, most of the activity being concentrated in the tissues of the small and large intestines. The activity decreased with age. In adult rats, hydrolysis of prunasin was greater than that of amygdalin and was concentrated in the spleen, large intestine and kidney (35.0 µg, 15.0 µg and 8.9 µg of prunasin hydrolysed per hour per gram of tissue, respectively). Minced liver, spleen, kidney and stomach tissue had a greater hydrolytic capability than the homogenate of these organs, while the reverse was the case with the small and large intestines. Following oral administration of 30.0 mg of amygdalin to adult rats, distribution after the first hour was as follows: stomach 0.89 mg, small intestine 0.78 mg, spleen 0.36 mg, large intestine 0.30 mg, kidney 0.19 mg, liver 0.10 mg and serum 5.6 µg/ml. At the end of the second hour, the highest amygdalin content, 0.79 mg, was found in the large intestine (WHO, 2001).

## Toxicology

***Acute poisoning***

Apricot kernel ingestion is a common source of cyanide poisoning (Fig. 27) (Barnes *et al.,* 2007; DerMarderosian *et* Beutler, 2002; Newall *et al.,* 1996). The lethal dose is reported to be 7–10 kernels in children and 50–60 kernels (approximately 30 g) in adults (WHO, 2001) but deaths are reported from as little as ingesting two kernels (DerMarderosian *et* Beutler, 2002). There may be considerable variation in the number of kernels required to be toxic, depending on the concentration of amygdalin and β-glucosidases present in the kernels, the timespan of ingestion, the degree of maceration of the kernels, individual variation in hydrolysing, and detoxifying abilities (Barnes *et al.,* 2007; Newall *et al.,* 1996). Apricot kernels are toxic because of their amydaline content. Hydrolysis of the amygdaline molecule by β-glucosidases, heat, mineral acids or high doses of ascorbic acid (vitamin C) yields hydrogen cyanide (HCN), benzaldehyde, and glucose. β-glucosidases are not generally abundant in the gastro-intestinal tract, but they are present in the kernels themselves as well certain foods including beansprots, carrots, celery, green peppers, lettuce, mushrooms, and sweet almonds (Newall *et al.,* 1996).


**Fig. 27.** Typical illustration of cyanide = poison in http://northerndoctor.com/2009/03/08/apricot-kernels-theyve-still-got-cyanide-in-them/) (visited in 23-6-2009)

Extract of amygdalin and water extract of apricot kernel produced sedation, convulsion, hyperventilation and death in mice. Amygdalin content in apricot pits varies and can be up to 8%. Wild varieties may contain 20 times the amount of cultivated apricot varieties (DerMarderosian *et* Beutler, 2002). Hydrolysis of amygdalin yielding the toxic hydrogen cyanide (HCN) is more rapid in alkaline pH (than acidic, in the GI tract), which can delay symptoms of poisoning (Barnes *et al.,* 2007; DerMarderosian *et* Beutler, 2002; Newall *et al.,* 1996). Symptoms of cyanide toxicity include: dizziness, headheache, nausea/vomiting; and quickly progress to palpitations, hypotension, convulsion, paralysis, coma and death, from 1 to 15 minutes after ingestion (Barnes *et al.,* 2007; DerMarderosian et Beutler, 2002; Newall *et al.,* 1996). Cyanide is rapidly absorbed from the upper gastrointestinal tract, diffuses readily throughout the body and promptly causes respiratory failures if untreated (Barnes *et al.,* 2007; Newall *et al.,* 1996).

***Chronic poisoning***

Principal symptoms include increased blood thyocyanate, goitre, thyroid cancer, lesions of the optic nerve, blindness, ataxia, hypertonia, cretinism and mental retardation. These symptoms may develop as a result of ingesting significant amounts of cyanide, cyanogenetic precursors in the diet, or cyanogenetic drugs such laetrile. Demyelinating lesions and other neuromyophaties reportedly occur secondary to choric cyanide exposure, including long-term therapy with laetrile. Agranulocytosis has also been attributed to long-term laetrile therapy (Barnes *et al.,* 2007; Newall *et al.,* 1996).

Normally, low concentrations of ingested cyanide are controlled naturally by exhalation or by rapid conversion to the less toxic thiocyanate by the enzyme rhodanese. Oral doses of 50mg of hydrogen cyanide (HCN) can be fatal. This is equivalent to approximately 30g kernels which represents about 50-60 kernels, and approximately 2mg HCN/g kernel. Apricot seed has also been reported to contain 2.92mg HCN/g. A 500-mg laetrile tablet was found to contain 5-51mg HCN/g (Barnes *et al.,* 2007; Newall *et al.,* 1996).

Systemic concentrations of β-glucosidases are low and therefore toxicity following parenteral absorption of amygdalin is low. However, cyanide poisoning has been reported in rats following intraperitoneal administration of laetrile, suggesting another mechanism of hydrolysis has ocorred (Barnes et al, 2007; Newall *et al.,* 1996).

It is thought that cyanogenetic glycosides may possess carcinogenic properties. Mandelonitrile (amygdalin= mandelonitrile diglucoside) is mutagenic and stimulates guanylate cyclase (Barnes et al, 2007; Newall *et al.,* 1996).

Antidotes to cyanide poisoning include nitrite, thiosulfate, hydroxocobalamin and aminophenol (Barnes *et al.,* 2007; DerMarderosian et Beutler, 2002; Newall *et al.,* 1996) and cobalt edetate (Newall *et al.,* 1996).

## Adverse reactions

The side-effects associated with amygdalin treatment are the same as the symptoms of cyanide poisoning (WHO, 2001). Cyanide is a neurotoxin that initially causes nausea and vomiting headache and dizziness (Anonymous, 2009d; WHO, 2001), rapidly progressing to cyanosis (bluish discoloration of the skin due to oxygen-deprived haemoglobin in the blood) (WHO, 2001), drowsiness, dyspnea, palpitations (Anonymous, 2009d), liver damage, ptosis (droopy upper eyelid), ataxic neuropathies (difficulty in walking due to damaged nerves), fever, mental confusion (WHO, 2001), marked hypotension, convulsions, coma and death (Anonymous, 2009d; WHO, 2001). These side-effects can be potentiated by the concurrent administration of raw almonds or crushed fruit pits, eating fruits and vegetables that contain β-glucosidase, such as celery, peaches, bean sprouts and carrots, or high doses of vitamin C. Overdose causes dizziness, nausea, vomiting and headache, which may progress to dyspnoea, spasms, dilated pupils, arrhythmias and coma (WHO, 2001). Apricot can also cause chronic poisoning, with symptoms of increased blood thiocyanate, goiter, thyroid cancer, optic nerve lesions, blindness, ataxia, hypertonia, cretinism, and mental retardation. Demyelinating lesions and neuromyopathies reportedly occur secondary to chronic exposure, including long-term therapy (Anonymous, 2009d). Contact dermatitis has been reported from apricot kernels (DerMarderosian *et* Beutler, 2002; Newall *et al.,* 1996). Kernel ingestion may be teratogenic as well (DerMarderosian *et* Beutler, 2002). Contact dermatitis has been reported following contact with apricot kernels (Barnes *et al.,* 2007; Newall *et al.,* 1996).

## Precautions and contraindications

### *Carcinogenesis, mutagenesis, impairment of fertility*

No effects on fertility were observed in rats fed a diet containing 10% *Semen armeniacae* for 5 weeks. An aqueous extract of the seeds was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100, or in the *Bacillus subtilis* H-17 recombinant assay at concentrations of up to 100.0 mg/ml. However, a hot aqueous extract of the seeds was mutagenic in the *Salmonella*/microsome assay in *S. typhimurium* strains TA98 and TA100 at a concentration of 12.5 mg/plate (WHO, 2001).

### *Pregnancy and Breastfeeding*

Intragastric administration of amygdalin (dose not specified) to pregnant hamsters induced skeletal malformations in the offspring, and intravenous administration resulted in embryopathic effects (WHO, 2001). The ingestion of cyanogenetic substances may result in teratogenic effects (Barnes *et al.,* 2007).

*Semen armeniacae* should not be administered during pregnancy or nursing, or to children (WHO, 2001).

## Interactions

No information available concerning drug interactions (Barnes *et al.,* 2007; Werneke *et al.,* 2004; WHO, 2001) or drug and laboratory test interactions (WHO, 2001).

## Storage

This dosage forms should be store in a cool, dry place, protected from moths (CP, 2005a; WHO, 2001).

## Posology

Average daily dose: 3–9g (Greten, 2007; WHO, 2001) of dried ripe seeds processed by breaking into pieces, rinsing in boiling water and stir-frying until yellow, then adding to a decoction when nearly finished (WHO, 2001). According to Chinese Pharmacopoeia (2005a): 4.5-9g, decocted later.

### Safety and regulatory actions in the United States

In 1984, amygdalin was classified as POM (prescription-only medicine) in an effort to protect the general public (Anonymous, 2009d; Newall *et al.,* 1996). In 1987, it was ruled to be an unapproved drug and its importation into the USA under an affidavit system created in 1977 ended. The FDA has sought a permanent injunction against three corporations for unlawfully promoting and marketing laetrile and apricot seeds or kernels for treating cancer on their Internet websites (Anonymous, 2009d).

## 7.2.1. *Semen armeniacae* (杏仁) according to Traditional Chinese Medicine

The source is from the mature seed of *Prunus armeniacae* L., or *P. armeniacae* L. var. ansu Maxim, family Rosasea. The medicinal material is produced in the areas of Northeast, North and Northwest China, Xinjiang, and the reaches of the Yangtze River of China (Yanfu, 2002b). The seeds are collected after the fruits ripen in summer, and they are then dried in the sun (CP., 2005a; Ganzhong et al., 2003a; Yanfu, 2002b). The raw kernels are also pounded to prepare a paste for clinical application (Ganzhong et al., 2003a).

### Common name

(Bitter) apricot seed (Chu, 2009; Gongwang, 2001d; Greten, 2007; Wu, 2005a), apricot seed or kernel (Anonymous, 2009e).

### Pharmaceutical name

*Semen Pruni Armeniacae* (Chu, 2009; Flaws, 1999db; Gongwang, 2001d; Greten, 2007;

Wu, 2005a), *Semen Armeniacae Amarum* (Anonymous, 2009h; Yanfu, 2002b), *Semen Armeniacae Amarae* (Greten, 2007).

### Botanical name

*Prunus armeniaca* L.var. ansu Maxim. or *P. armeniaca* L. (Gongwang, 2001d).

### Pinyin name

*Xing Ren* (Anonymous, 2009e; Flaws, 1999db; Ganzhong et al., 2003a; Greten, 2007; Liu et Tseng, 2005b; Ni, 1991a) (Ku XingRen) (Bei Xing Ren) (Liu et Tseng, 2005b), Xingren (Gongwang, 2001d; Yanfu, 2002b).

## Other names

Xing ren (杏仁) (Chu, 2009), ku xing ren (苦杏仁) (Anonymous, 2009e; Chu, 2009), kuang xing ren (光杏仁), ku he ren (杏核仁，炒杏仁), jian xing ren (尖杏仁), xing ren xiang (杏仁霜) (Chu, 2009).

## Part used

Seed (Greten, 2007; Liu et Tseng, 2005b; Tierra, 1997a; Wu, 2005a), dried ripe seed (Fig. 28) (Wu, 2005a)

**Fig. 28.** Dried ripe seed (adapted from http://tcm.health-info.org/Herbology.Materia.Medica/xingren-properties.htm) (visited 9-6-2009)

## Classification

In cough, pieira and for moistoring. Belongs to the group *"Tussostatica- XIII c)"* (Greten, 2007) i.e. "Herbs that Relieve Coughing and Wheezing" (Anonymous, 2009e).

## Sapor & Temperature

Neutral (Greten, 2007), slightly warm (Anonymous, 2009f; Chu, 2009; Flaws, 1999db; Ganzhong et al., 2003a; Gongwang, 2001d; Greten, 2007; Leite, 2005d; Liu et Tseng, 2005b; Ni, 1991a; Tierra, 1997a; Yanfu, 2002b), bitter, (Anonymous, 2009f; Chu, 2009; Flaws, 1999db; Ganzhong et al., 2003a; Gongwang, 2001d; Greten, 2007; Leite, 2005d; Liu et Tseng, 2005b; Ni, 1991a; Tierra, 1997a; Wu, 2005a; Yanfu, 2002b), acrid (Flaws, 1999db), slightly toxic (Anonymous, 2009f; Anonymous, 2009h; Chu, 2009; Wu, 2005a; Ganzhong et al., 2003a; Gongwang, 2001d; Leite, 2005d; Ni, 1991a; Tierra, 1997a; Yanfu, 2002b), (sweet) (Greten, 2007).

## Orbs

Crass intestinal, pulmonar (Anonymous, 2009f; Anonymous, 2009h; Chu, 2009; Flaws, 1999db; Ganzhong et al., 2003a; Gongwang, 2001d; Greten, 2007; Wu, 2005a; Leite, 2005d; Liu et Tseng, 2005b; Ni, 1991a; Tierra, 1997a; Yanfu, 2002b).

## Functions

Its bitterness can send down rebellious qi to relieve cough and asthma (Anonymous, 2009h; Wu, 2005a); moisturizes the lung (Anonymous, 2009f). The warmness can disperse algor venti in the lung channel. Its action is rather slow and uniform. It is applicable in compound prescriptions for treatment of cough and asthma caused by exopathogen and internal injury, cold and heat, depletio and repletio. It is especially effective in treatment of cough with abundant expectoration due to algor venti invasion of lung (Anonymous, 2009h).

It is rich in oil, which acts on the large intestine channel to lubricate the bowel to relieve constipation (Anonymous, 2009h, Wu, 2005a), moistens intestine (Flaws, 1999db; Gongwang, 2001d; Leite, 2005d; Liu et Tseng, 2005b; Yanfu, 2002b), relax the bowels (CP, 2005a; Yanfu, 2002b), helping bowel movements (Chu, 2009; Gongwang, 2001d; Leite, 2005d) and promoting defecation (Ganzhong et al., 2003a; Gongwang, 2001d; Tierra, 1997a).

## Indications

Against coughing (Anonymous, 2009f; Chu, 2009; Ganzhong et al., 2003a; Gongwang, 2001d; Leite, 2005d; Liu et Tseng, 2005b; Tierra, 1997a; Yanfu, 2002b), and wheezing (Liu et Tseng, 2005b; Tierra, 1997a), for arresting asthma (Anonymous, 2009f; Chu, 2009; Ganzhong et al., 2003a; Gongwang, 2001d; Tierra, 1997a), bronchitis (Tierra, 1997a), expelling phlegm (Chu, 2009). It is particularly effective in counteracting dry coughs (Tierra, 1997a). Used in chronic bronchitis manifesting coughing, profuse sputum and short breath (Anonymous, 2009f). Chronic coughing due to deficient lungs and kidneys (Anonymous, 2009f). For short breath and edema (abnormally large amounts of fluid in the intercellular tissue spaces of the body) (Anonymous, 2009f).

Used to treat constipation due to dryness in the intestines (Anonymous, 2009h; Ganzhong et al., 2003a), dry stools (Gongwang, 2001d; Leite, 2005d; Liu et Tseng, 2005b).

## Chinese therapeutic actions and examples of major combinations

1-Treats coughs and dyspnea (shortness of breath): entering the lung channel, being so bitter as to be lowering and with its dredging, lubricating, opening and clearing properties, almond can ventilate the lungs while sending down adversely rising lung-qi to such an extent as to arrest coughing and relieve dyspnea, so it is a major herb for the treatment of coughs and dyspnea. It can be used for a large variety of ailments with coughs and dyspnea when it is used in combination with other herbs according to each case (Anonymous, 2009f).

- for coughs and dyspnea due to algor venti, it can be used in combination with *Herba Ephedrae* (Mahuang) and *Radix Glycyrrhizae* (Gancao), i.e., San Ao Tang (Anonymous, 2009f; Ganzhong et al., 2003a; Gongwang, 2001d; Yanfu, 2002b), in order to dispel pathogenic wind-cold, ventilate the lungs and relieve dyspnea (Anonymous, 2009f).
- For algor venti common cold with cough and qi panting, mostly it is combined with *Folium Perillae Frutescentis* (Su Ye) as in Xing Su San (Armeniaca & Perilla Powder) (Flaws, 1999db).
- For coughs and dyspnea due to wind-heat, it can be used in combination with *Folium Mori* (Sangye) (mulberry leaves) and *Flos Chrysanthemi* (Juhua) (chrysanthemum) (Anonymous, 2009f; Flaws, 1999db; Ganzhong et al., 2003a; Gongwang, 2001d; Wu, 2005a; Yanfu, 2002b), e.g., Sang Ju Yin, in order to dispel pathogenic wind-heat, ventilate the lungs and arrest coughing (Anonymous, 2009f). This decoction is also called "The Decoction of Folium Mori and Flos Chrysanthemi" (Morus & Chrysanthemum Drink) (Flaws, 1999db; Wu, 2005a).
- For treatment of cough due to exopathogenic wind-heat, it can be used together with *Fructus Arctti, Folium Mori, Bulbus Fritillariae, Radix Platycodi, Radix Glycyrrhizae* (Ganzhong et al., 2003a).
- Coughs due to dryness-heat, it can be used in combination with *Folium Mori* (Sangye), *Bulbus Fritillariae* (Beimu) (thunberg fritillary bulb) and *Radix Adenophorae Strictae* (straight ladybell) (Anonymous, 2009f; Flaws, 1999db; Ganzhong et al., 2003a; Gongwang, 2001d; Wu, 2005a; Yanfu, 2002b), e.g., Sang Xing Tang, in order to clear heat away from the lungs, remove dampness by moistening and arrest coughing (Anonymous, 2009f; Ganzhong et al., 2003a). This decoction is also called "The Decoction of Folium Mori and Semen Pruni Armeniacae" (Wu, 2005a) or Morus & Armeniaca Decoction (Flaws, 1999db).
- Coughs due to the lung-heat it is used in combination with *Herba Ephedrae* (Mahuang), *Gypsum Fibrosum* (Shegshigao) and *Radix Glycyrrhizae*, e.g., Ma Xing Shi Gan Tang (Anonymous, 2009f; Anonymous, 2009h; Flaws, 1999db;

Ganzhong et al., 2003a; Gongwang, 2001d; Yanfu, 2002b), in order to clear heat away from the lungs, purge away heat, ventilate the lungs and relieve dyspnea (Anonymous, 2009f; Anonymous, 2009h). This decoction is also called Ephedra, Armeniaca, Gypsum & Licorice Decoction (Flaws, 1999db).

2. Treats constipation due to dryness in the intestines (Anonymous, 2009f; Yanfu, 2002b): containing oil and grease, almond is lubricating in quality, and being so bitter in taste to keep adverse qi flowing downward, this herb can relax the bowels to relieve constipation (Anonymous, 2009f).

- For treatment of constipation due to bowel dryness, it is commonly used in combination with *Radix Angelicae Sinensis, Radix Paeoniae Alba, Fructus Cannabis,* and so on to nourish *Yin* and supplement *blood*, lubricate the bowel to relieve constipation (Anonymous, 2009h).
- For constipation due to dryness of the intestine, it is used with *Semen Cannabis Sativae* (Huo Ma Ren) (Flaws, 1999db; Wu, 2005a), *Radix Angelicae Sinensis* (Dang Gui), and *Fructus Aurantii* (Zhi Qiao) (Wu, 2005a) and *Semen Pruni Persicae* (Tao Ren) in “The Intestine-Moistening Pill” (Run Chang Wan) (Flaws, 1999db; Wu, 2005a; Yanfu, 2002b).

## Dosage and method of use

Decoct in water and administer internally (Flaws, 1999db). Decoct almond for oral administration and it should be pounded finely for decoction. It could also be eaten raw (Anonymous, 2009f). The dosage varies according to different authors: 3-10 g (Anonymous, 2009f; Wu, 2005a; Ganzhong et al., 2003a; Ni, 1991a; Yanfu, 2002b), decocted in water for an oral dose (Wu, 2005a). According to Flaws (1999b) the referred dosage is 6-10g. It should be decocted after other herbs (Wu, 2005a; Ganzhong et al., 2003a). Fried apricot kernel is used to treat coughing and asthma in weak patients with deficiency of the spleen; and apricot kernel frost (de-oiled apricot kernel) is used for patients with diarrhea (Ganzhong et al., 2003a).Use 3 to 9g (Gongwang, 2001d; Greten, 2007; Leite, 2005d; Liu et Tseng, 2005b; Tierra, 1997a). Should be coarsely crushed for cooking (Liu et Tseng, 2005b) and decoct for 10 minutes only (Tierra, 1997a).

## Precautions and contraindications

Use with caution in children due to its toxicity (Flaws, 1999db; Wu, 2005a; Ganzhong et al., 2003a; Gongwang, 2001d; Tierra, 1997a; Yanfu, 2002b). This drug is contraindicated for treatment for coughing due to yin deficiency (Ganzhong et al., 2003a). Should not be prescribed for patients with diarrhea (Ganzhong et al., 2003a; Tierra, 1997a). Should not be prescribed in a large dose, because of its toxicity (Flaws, 1999db; Ganzhong et al., 2003a; Gongwang, 2001d).

### Herb interactions

Do not use this herb with astragalus (Huang Qi - *Radix Astragali membranacei*), pueraria (Ge Gen – *Radix Pueraria)* or scutelaria (Huang Qin – *Radix Scutellaria baicalensis*) (Leite, 2005d; Tierra, 1997a).

### Sweet and bitter apricot kernel

There are differences in the functions between bitter apricot seed (Kuxingren) and sweet apricot seed (Tianxingren) (Gongwang, 2001d). Bitter apricot seed, also called Bei xin ren (northern xing ren, *Prunus armeniaca*) (Chu, 2009) is characterized by bitterness in its flavor and tends to lower the flow of adverse qi, which is good for treating cough and asthma (Gongwang, 2001d); while sweet apricot seed, also called Nan xin (southern xin ren, *Prunus dulcis*) (Chu, 2009), tends to moisten and treats mostly chronic cough due to lung qi deficiency. Both of them can treat constipation due to loss of body fluid (Gongwang, 2001d). Sweet apricot seed is milder and is suitable for older people with weaker bodies and with cough and asthma. Bitter apricot seed is stronger in property and it is suitable for stronger and younger people and in strong syndromes (Chu, 2009).

For treatment of cough due to exopathogen, bitter *Semen armeniacae* is mostly used, while of cough due to consumption, the sweet one is mostly used (Anonymous, 2009h).

Sweet apricot kernel (*Semen Armeniacae Dulce*) is the sweet seed of some species of apricot trees cultivated in Hebei and Shandong provinces, and Beijing. It is also called large apricot kernel because its size is bigger than that of the bitter apricot kernel. Sweet apricot kernel is sweet is taste and neutral in nature, with a similar therapeutic effect to bitter apricot kernel, but it is less drastic in nature. Sweet apricot kernel can produce a better nourishing and moistening effect to enrich lung *qi*, but is does not have any effect on dispersing qi. Therefore, it is useful to treat chronic coughing due to deficiency of the lungs and constipation due to exhaustion of jin (body fluid) (Ganzhong et al., 2003a).

## *7.3. Ramuli Cinnamomi / Cortex Cinnamomi*

### Introduction

In western literature, including monographs and scientific papers, most references to cinnamon are related to the bark, not the twigs. Would not expect too many difference in the ingredients, as bark is part of stems and twigs. This is pertinent for this study, because *Ramuli Cinnamomi* "Guizi" (twigs) and *Cortex Cinnamomi* "*Rougui"* (bark) have different uses in Traditional Chinese Medicine (TCM).

Yet whereas in the Chinese Pharmacopoeia (CP) Guizhi is defined as the Cinnamomi Ramulus (the whole twig), in the Japanese Pharmacopoeia (JP) it is defined as the Cinnamomi Cortex (the bark). Until the Han period, the drug name Gui was commonly used for products made from the bark (the cork from the bark being removed) of cinnamomic plant. Such products have been excavated from a tomb where they were interred in the second century B.C., and the drug name Guixin was commonly used for them until the Tang period. The terms Gui, Qin, Mugui, Guirou, Rougui, Guixin, and Guizhi found in medical texts up to the tenth century were all used for the products made from the bark. The Tang government's pharmacopoeia of 659, the Xinxiu Bencao, designates their material plant as either *C. cassia* or *C. obtusifolium*. This product primarily corresponds to Cinnamomi cortex, being Keihi in JP or Rougui in CP. The term Jungui was used from the third century B.C. for products in the shape of a bamboo pipe which was made from the bark of cinnamomic plant twig that had been repeatedly rolled up, and which were used as dietary foods or spices. The Xinxiu Bencao designates the material plant as *C. burmanni*, and the product corresponds to the cinnamon sticks now in use (Mayanagi, 1995). In *Ephedra* Decoction (mahuang tang), cinnamon twigs are used. Mahuang tang is correspondent to the Japanese mao-to, equal to the Chinese formula, except that uses the cinnamon bark (Kainuma *et al.,* 2004; Shijie *et al.,* 2008). Although the Chinese Pharmacopoeia refers to the twigs and bark of cinnamon, the Japanese Pharmacopoeia only refers to the cortex. Based on these findings, the author decided to refer in this master thesis both parts of the plant (*Ramuli Cinnamomi* and *Cortex Cinnamomi*).

## 7.3.a. *Cortex Cinnamomi*

According to Barnes *et al.* (2007a) the sources of *Cortex Cinnamomi* include *Cinnamomum cassia* (cassia) and *Cinnamomum verum* (cinnamon). The systematic classifications and correct taxonomic names of species and/or related sub-species to the officinal specie are currently being discussed, because there are various commercial varieties, which differ by their quantitative and qualitative composition of essential oil (Wichtl *et* Anton, 1999).

By definition, cinnamon is the bark of the *Cinnamomi cassiae* (Fig. 29) (Kim *et al.*, 2006; Tabak et al, 1999; Newall et al., 1996a), Family Lauraceae (Anonymous, 2009m; Barnes et al, 2007a; Duke, 2003; Ganzhong et al., 2003c; Kim *et al.*, 2006; Newall et al., 1996a; WHO, 1999, 1997) or according to WHO (1999) *Cortex Cinnamomi* consists of the dried inner bark of the shoots grown on cut stock of *Cinnamomum verum* J.S. Presl. or of the trunk bark, freed of cork, of *Cinnamomum cassia* Blume. The Chinese cinnamon is obtained from the bark of the branches of *Cinnamomum cassia* Blume (*C. cassia* Nees) with similar smell to the *Ceylon cinnamon* (*C. verum*), with characteristics of a fineness less appreciated (Wichtl *et* Anton, 1999), less attractive, and therefore more for local consumption or for the acquisition of essential oil (Cunha, 2005). Cassia from China is less aromatic than that from Vietnam and Indonesia. Cassia from all three countries has a sweet, aromatic, and pungent flavor. Vietnamese, or Saigon, cassia is particularly highly esteemed. Cassia buds, the dried, unripe fruits of *Cinnamomum cassia* and *Cinnamomum loureirii*, have a cinnamon-like aroma and a warm, sweet, pungent taste akin to that of cassia bark. The whole buds are added to foods for flavouring (Anonymous, 2009f).

Other species of cinnamon include: *Cinnamomum loureirii* Nees (*Cinnamomum obtusifolium* Nees var. loureirii Perr. & Eb., Saigon Cassia, Saigon Cinnamon), *Cinnamomum burmanii* (Ness) Bl. (Batavia Cassia, Batavia Cinnamon, Padang-Cassia, Panang Cinnamon) (Barnes et al., 2007b). Falsifications occur occasionally with Saigon cinnamon bark (*Cinnamomum loureirii* Ness) (Wichtl *et* Anton, 1999).


**Fig. 29.** *Cinnamomum cassia* Blume (adapted from Wu, 2005b)

## Other names for Chinese cinnamon

Cassia Bark (Barnes *et al.,* 2007a; Duke, 2003; WHO, 1999a; Newall et al., 1996a; PDR, 1998)*, Cinnamomum aromaticum* Nees (Barnes *et al.,* 2007a; WHO, 1999a; Newall et al., 1996a; PDR, 1998), Cassia Lignea (Barnes *et al.,* 2007a; Duke, 2003; Newall et al., 1996a; PDR, 1998), False Cinnamon (Barnes *et al.,* 2007a; Newall et al., 1996a; PDR, 1998), Cassia (Duke, 2003; PDR, 1998), Bastard Cinnamon, *Cassia aromaticum*, Canton Cassia (PDR, 1998), China Junk Cassia, Chinese Cassia, Saigon Cinnamon (Duke, 2003), *Cinnamomum pseudomelastoma* auct. Non Liao (Barnes *et al.,* 2007a) and *Cinnamomum cassia* Blume (Newall et al., 1996a; WHO, 1999a; Wu, 2005b).

## Other names for Ceylon Cinnamon

*Cinnamomum zeylanicum* Bl. (Barnes et al., 2007b; Duke, 2003; Cunha et al., 2003a; WHO, 1999a), *Cinnamomum verum* J.S. Presl. (Barnes et al., 2007b; Cunha et al., 2003a; WHO, 1999a), True Cinnamon (Barnes et al., 2007b), *Laurus cinnamomum* L. (Duke, 2003; Ooi *et al.,* 2006; WHO, 1999a), *C. zeylanicum* Nees (Ooi *et al.,* 2006). *Cinnamomum verum* J.S. Presl. is the correct botanical name according to the International Rules of Botanical Nomenclature (WHO, 1999a).

## Selected vernacular names

***Cinnamomum verum J.S. Presl.***

Abdalasini, blood-giving drops, canela, canela en raja, cannalavanga pattai, cannelle de ceylan, cannelle dite de Ceylan, cannelier, Ceylon celonzimi cinnamon, Ceylon cinnamon, cinnamon, cinnamon bark, cinnamon tree, cortex cinnamomi ceylanici, dalchini, dalochini, dar sini quirfa, darchini, daruchini, darusila, ecorce de cannelier de Ceylan, echter Kanel, gujerati-dalchini, kannel, kuei-pi, kurundu, kurundu-potu, kulit kayumanis, ob choei, tamalpatra, wild cinnamon, zimtrinde (WHO, 1999a).

***Cinnamomum cassia Blume***

Annan cinnamon, cassia, cassia bark, cassia bark tree, cassia lignea, chinazimt, Chinese cassia, Chinese cinnamon, ching hua yu-kuei, cinnamomi cassiae cortex, cinnamon, cinnamon bark, dalchini, guipi, guizhi, kannan keihi, keihi, keishi, kuei-chíí, lavanga-pattai, lavanga-patti, lurundu, macrophyllos cassia bark tree, rou gui, róugì, Saigon cinnamon, saleekha, taj, toko keihi, Viet Nam cinnamon (WHO, 1999a).

## Description

***Cinnamomum verum J.S. Presl.***

A moderate-sized evergreen tree (Fig. 30-32); bark rather thick, smooth, pale; twigs often compressed; young parts glabrous except the buds which are finely silky. Leaves opposite or subopposite (rarely alternate), hard and coriaceous, 7.5–20 by 3.8–7.5 cm, ovate or ovate-lanceolate, subacute or shortly acuminate, glabrous and shining above, slightly paler beneath, base acute or rounded; main nerves 3–5 from the base or nearly so, strong, with fine reticulate venation between; petioles 1.3–2.5 cm long, flattened above. Flowers numerous, in silky pubescent, lax panicles usually longer than the leaves; peduncles long, often clustered, glabrous or pubescent; pedicels long. Perianth 5–6mm long; tube 2.5 mm long; segments pubescent on both sides, oblong or somewhat obovate, usually obtuse. Fruit 1.3–1.7 cm long, oblong or ovoid-oblong, minutely apiculate, dry or slightly fleshy, dark purple, surrounded by the enlarged campanulate perianth that is 8 mm in diameter (WHO, 1999a).

**Fig. 30.** *Cinnamomum zeylanicum*. Ceylon Cinnamon twig, showing leaf venation (adapted from http://chestofbooks.com/health/materia-medica-drugs/Manual-Pharmacology/Cinnamomum-Cinnamon.html) (visited on 8/5/2009).

**Fig. 31.** *Cinnamomum zeylanicum* (adapted from http://www.gaiaherbs.com/herb_of_the_week.php?id=1 (visited on 8/5/2009).

**Fig. 32.** *Cinnamomum verum*, from Koehler's *Medicinal-Plants* (1887) (adapted from http://en.wikipedia.org/wiki/Cinnamon) (visited on 6/12/2009).

### *Cinnamomum cassia Blume*

An evergreen tree, up to 10 m high (Fig. 33). Leaves alternate, coriaceous, petiolate, oblong, elliptical-oval or oblong-lanceolate, 8–15cm long by 3–4cm wide, tip acuminate, base rounded, entire, 3-nerved; glabrous or underside lightly pubescent; petiole 10 mm long, lightly pubescent. Inflorescence a densely hairy panicle as long as the leaves; panicles cymose, terminal and axillary. Flowers yellowish white, small, in cymes of 2–5. Perianth 6-lobed. No petals. Stamens 6, pubescent. Ovary free, 1-celled. Fruit a globular drupe, 8mm long, red. The bark is used in either channelled pieces or simple quills, 30–40cm long by 3–10cm wide and 0.2–0.8 cm in thickness. The surface is grayish brown, slightly coarse, with irregularly fine wrinkles and transverse lenticels. There are found scars of holes, indicating the insertion of leaves or lateral shoots; the inner surface is rather darker than the outer, with fine longitudinal striate. The fracture is short, the section of the thicker pieces showing a faint white line (pericyclic sclerenchyma) sometimes near the centre, sometimes near and parallel to the outer margin (WHO, 1999a).

**Fig. 33.** Cassia tree (adapted from http://acupuntura.blogas-pt.com/gui-zhi-ramulus-cinnamomi/ ) (visited on 14/9/9)

***General appearance of the bark***

***Cinnamomum verum* J.S. Presl.**

The bark (Fig. 34) is about 0.2–0.8 mm thick and occurs in closely packed compound quills made up of single or double quills. The outer surface is smooth, yellowish brown with faint scars marking the positions of leaves and axillaries buds and has fine, whitish, and wavy longitudinal striations. The inner surface is slightly darker and longitudinally striated. The fracture is short and fibrous (WHO, 1999a).

**Fig. 34.** Cinnamon bark (adapted from http://www.ancientway.com/Pages/MartialArtsHerbs.html ) (visited on 8/5/2009).

***Cinnamomum cassia* Blume**

The drug is channeled or quilted, 30–40cm long, 3–10cm in diameter, 2–8mm thick. Outer surface grayish brown, slightly rough, with irregular fine wrinkles and transverse raised lenticels, some showing grayish white streaks; inner surface reddish brown, with fine longitudinal striations and exhibiting oily trace on scratching. Texture hard and fragile, easily broken, fracture uneven, outer layer brown and relatively rough, inner layer reddish brown and oily and showing a yellowish brown line between two layers (WHO, 1999a). Chinese cinnamon consists of the completely or partly peeled, dried stem bark from the above ground axis. The drug comes from 2 to 3 cm thick branches; it is peeled with horn knives and freed from cork and outer rind and dried in the sun within 24 hours (PDR, 1998). Cassia bark is peeled from stems and branches and set aside to dry. Some varieties are scraped. While drying, the bark curls into quills. The color varies from light reddish brown for the thin, scraped bark to gray for the thick, unscraped bark. Ground cassia is reddish brown in color (Anonymous, 2009f).

## Geographical distribution

***Cinnamomum verum J.S. Presl.***

The tree of *Cinnamomum zeylanicum* originates in India (Cunha et al., 2003a; Dugoua *et al.,* 2007; Ooi *et al.,* 2006; WHO, 1999a) and Ceylon (Cunha et al., 2003a). Also is native to Sri Lanka (Dugoua *et al.,* 2007; WHO, 1999a) and cultivated in parts of Africa, the Seychelles, Indonesia, South America, and the West Indies (WHO, 1999a). It was introduced in the islands of the Pacific Ocean and the southwest of India and Asia. Sri Lanka remains the largest exporter (Cunha et al., 2003a).

***Cinnamomum cassia Blume***

The bark of Chinese cinnamon is mainly cultivated in China (Ooi *et al.,* 2006; PDR, 1998; WHO, 1999a; WHO, 1997C; Wichtl *et* Anton, 1999) (provinces of Guangxi, Guangdong, Yunnan (Chu, 2009; Ganzhong et al., 2003c), Fujian (Chu, 2009) and Malabar (Wichtl *et* Anton, 1999). Also found in Indonesia, the Lao People's Democratic Republic (Ooi *et al.,* 2006; WHO, 1999a; WHO, 1997C), Burna (PDR, 1998) and Viet Nam (Ooi *et al.,* 2006; PDR, 1998; WHO, 1999a; WHO, 1997C).

## Historical perspective

Cinnamon is among the world's oldest and most frequently consumed spices and is often used as an herbal remedy (Qin *et al.,* 2008). There are reports of cinnamon being imported to Egypt from China as early as 2000 BC (Dugoua *et al.*, 2007). Cinnamon is mentioned in the Bible (Exodus and Proverbs) (Dugoua *et al.*, 2007; Ravindran *et al.,*

2004) and in Chinese texts written 4000 years ago (Dugoua *et al.*, 2007; Qin *et al.,* 2008). The name cinnamon comes from the Greek *kinnámōmon*, ultimately from the Malaysian and Indonesian *kayu manis*, which means ‘‘sweet wood’’ (Anonymous, 2009f; Ravindran *et al.*, 2004). Common cinnamon correctly refers to ‘‘true cinnamon,’’ or its synonym Ceylon cinnamon (*Cinnamomum verum*, *C. zeylanicum*). In addition, the related species cassia cinnamon (*C. aromaticum*), also known as Chinese cinnamon, is sometimes sold labeled as cinnamon (Dugoua *et al.*, 2007). Cinnamon was once more valuable than gold (Anonymous, 2009f). In Egypt it was sought for embalming (Anonymous, 2009f; Ravindran *et al.,* 2004) and witchcraft; in medieval Europe for religious rites and as a flavoring (Anonymous, 2009f).

The south Arabians held a virtual monopoly on the spice trade for a very long time, but historical evidence is quite insufficient to come to a conclusion on the relative roles played by the Arabians and Phoenicians in the ancient spice trade. The Arab domination of the spice trade was broken by the rise of the Roman Empire. By the thirteenth century, the East Indies became a busy trading centre in spices. China emerged as a major trader of spices during this period, trading in cassia and ginger and procuring large quantities of pepper and other spices from the Malabar Coast and the East Indies. At this time cassia and cassia buds became popular spices in Europe and England. Of course, spices were beyond the reach of common folk, as they were so costly, mainly because no direct trade links existed between Europe and the eastern spice-producing countries. The Arabs monopolized the trade in the east, and Venice controlled the trade in the Mediterranean. The modern chapter in the saga of spices begins with the discovery of the sea route to India and the landing of Vasco da Gama on the Malabar Coast. This indeed was the beginning of the history of modern India too. The West European countries were compelled to establish a sea route to the eastern spice lands following the conquest of the Roman Empire and the closure of Constantinople for trade by the Ottoman Turks in 1453. The quest for spices opened up the era of great expeditions; Columbus discovered America and Vasco da Gama sailed eastwards round the Cape of Good Hope and arrived in India. In the decades that followed the Portuguese gradually established their hold on spice trading (Ravindran *et al.,* 2004). Later it was the most profitable spice in the Dutch East India Company trade (Anonymous, 2009f; Ravindran et al., 2004). The seventeenth century saw the rise of British naval supremacy. Yet another chapter in the saga of cinnamon starts with the British occupation of Ceylon in 1796, and the monopoly of cinnamon trade changed hands once more. Even today, cinnamon is associated with the lives of people of Sri Lanka, emotionally, socially and economically. For them it is the spice of life (Ravindran *et al.,* 2004). In modern times, cinnamon is used to flavor a variety of foods, from confections to curries; in Europe and the United States it is especially popular in bakery goods. In China, it is used as a decongestant herb to relieve exterior syndromes (Anonymous, 2009f).

## Organoleptic properties

Odour, characteristic and aromatic; taste, characteristic, slightly sweet and fragrant (WHO, 1999a).

## General identity tests

Macroscopic and microscopic examinations; and thin-layer chromatographic analysis for the presence of cinnamaldehyde (WHO, 1999a).

## Purity tests

### *Microbiology*

The test for *Salmonella* spp. in *Cortex cinnamomi* products should be negative. The maximum acceptable limits of other microorganisms are as follows. For preparation of decoction: aerobic bacteria—not more than $10^7$/g; fungi—not more than $10^5$/g; *Escherichia coli*—not more than $10^2$/g. Preparations for internal use: aerobic bacteria—not more than $10^5$/g or ml; fungi—not more than $10^4$/g or ml; enterobacteria and certain Gram-negative bacteria—not more than $10^3$/g or ml; *Escherichia coli*—0/g or ml (WHO, 1999a).

### *Foreign organic matter*

*C. verum*: not more than 2%. *C. cassia*: not more than 1% (WHO, 1999a).

### *Total ash*

*C. verum*: not more than 6% (WHO, 1999a). *C. cassia*: not more than 5% (CP, 2005b; WHO, 1999a).

### *Acid-insoluble ash*

*C. verum*: not more than 4%. *C. cassia*: not more than 2% (WHO, 1999a).

### *Sulfated ash*

*C. verum*: not more than 6%. *C. cassia*: to be established in accordance with national requirements (WHO, 1999a).

### *Moisture*

Not more than 15% (CP, 2005b).

### *Volatile oil*

It contains not less than 1.2% (ml/g) (CP, 2005b).

### *Alcohol (90%)-soluble extractive*

*C. verum*: 14–16%. *C. cassia*: to be established in accordance with national requirements (WHO, 1999a).

### *Pesticide residues*

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for *Cortex Cinnamomi* is not more than 0.05 mg/kg (WHO, 1999a).

***Arsenic and heavy metals***

Recommended lead and cadmium levels are not more than 10mg/kg and 0.3 mg/kg, respectively, in the final dosage form of the plant material (WHO, 1999a).

***Radioactive residues***

Analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239 (WHO, 1999a).

***Other tests***

Chemical tests to be established in accordance with national requirements (WHO, 1999a).

***Chemical assays***

Not less than 1.2% v/w of volatile oil derived from C. *verum* or C. *cassia*, containing 60–80% w/w aldehydes calculated as cinnamaldehyde. Assay for cinnamaldehyde content by means of thin-layer or highperformance liquid chromatographic methods (WHO, 1999a).

## Chemical constituents

According to Dugoua *et al.* (2007) common and cassia cinnamon contain 1%–4% of volatile oils and the major constituent is cinnamaldehyde (Fig. 35-36), at concentrations of 60-80%, or 65–80% (Anonymous, 2002; WHO, 1999a) or 67% to 83% (Anonymous, 2009m).

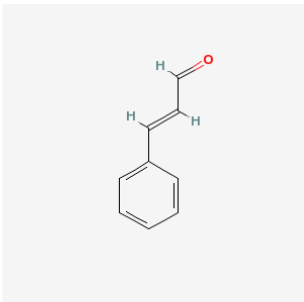



**Fig. 35.** Chemical structure of cinnamaldehyde (adapted from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=637511&loc=ec_rcs) (visited on 6/12/09).

**Fig. 36.** Cinnamaldehyde (adapted from http://www.made-in-china.com/showroom/queena689/product-detailAoqQvsWPfLcZ/China-Cinnamaldehyde.html) (visited on 20/5/09)

Also contains *trans*-cinnamic acid (5-10%); phenolic compounds (4-10%) such as catechins and proanthocyanidins (Fig. 37); monoterpenes and sesquiterpenes; calcium-monoterpenes oxalate; gum; mucilage; resin; starch; sugars; and coumarin (Dugoua *et al.,* 2007).

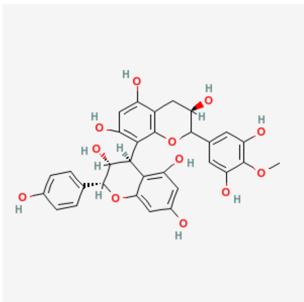


**Fig. 37.** Chemical structure of proanthocyanidin (adapted from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=108065&loc=ec_rcs) (visited on 6/12/09)

*C. verum* differs considerably from *C. cassia* in its eugenol (phenolic compound) (Fig. 38) and coumarin (Fig. 39) contents. Coumarin is present in *C. cassia*, but not in *C. verum* (WHO, 1999a). According to Anonymous (2009), *Cassia cinnamon* contains a wide range of coumarin concentrations from 0.004% to 1.2%. So, the presence of coumarin and other compounds can be used to distinguish *C. cassia* from *C. verum*.

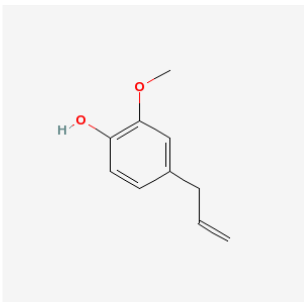


**Fig. 38.** Chemical structure of eugenol (adapted from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3314&loc=ec_rcs) (visited on 6/12/09)

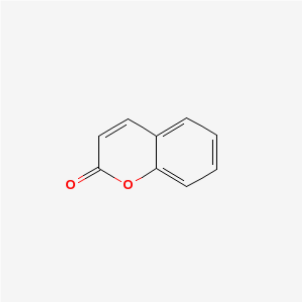


**Fig. 39.** Chemical structure of coumarin (adapted from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=323&loc=ec_rcs) (visited on 6/12/09).

Of the various types of cinnamon bark the oil of *C. verum* is stated to contain the highest amount of eugenol (Barnes et al., 2007b), 10% according to WHO (1999) whereas in *C. cassia*, only a trace quantity of this compound is found (Barnes et al., 2007b; WHO, 1999a). Cinnamon oil also differs from the closely related cassia oil in that the latter is reported to be devoid of monoterpenoids and sesquiterpenoids (Barnes et al., 2007b).

### ***Cinnamomum cassia* bark**

The main components are cinnamaldehyde (Kim *et al.*, 2006), cinnamic acid (Fig. 40) (Kim *et al.*, 2006; PDR, 1998), tannin and methylhydroxychalcone polymer (Kim *et al.*, 2006). Cinnamic acid has preservative properties (Sweetman, 2009a).

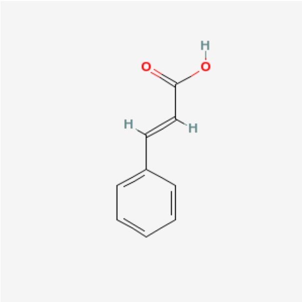


**Fig. 40.** Chemical structure of cinnamic acid (adapted from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=444539&loc=ec_rcs) (visited on 6/12/09).

Contains 1-2 % of volatile oils (Barnes *et al.,* 2007a; Newall et al., 1996a; Ooi *et al.,* 2006; Van Hellemont, 1986a.). The main constituents of *C. cassia* bark oil are cinnamaldehyde (Kim *et al.*, 2006; Chang *et al.*, 2001; Ooi *et al.,* 2006; PDR, 1998), about 75-90% (Barnes *et al.*, 2007a; Sweetman, 2009b; Van Hellemont, 1986a), 60–80% (Ooi *et al.,* 2006) and coumarin (Barnes *et al.,* 2007a; Chang *et al.*, 2001; Ooi *et al.,* 2006; PDR, 1998; Newall et al., 1996a). Other major components include salylaldehyde, methylsalicyladehyde, methyleugenol (Barnes *et al.,* 2007a; Newall et al., 1996a), cinnamylacetate, cinnamyl alcohol, *o*-methoxycinnamaldehyde (Fig. 41), diterpenes, tannins, oligomere proanthocyanidins (PDR, 1998), mucilages (Barnes *et al.,* 2007a; PDR, 1998; Newall et al., 1996a) (higher content compared to cinnamon) (Barnes *et al.,* 2007a; Newall et al., 1996a), about 11.5% according to Van Hellemont (1986a). Eugenol is reported to be absent. Although cassia oil contains no monoterpenoids or sesquiterpenoids, complex diterpenoids have been isolated (Barnes *et al.,* 2007a; Newall et al., 1996a). Also contains calcium oxalate (Barnes *et al.,* 2007a; Newall et al., 1996a), resins, sugars, condensed tannins (Barnes *et al.,* 2007a; Newall et al., 1996a), about 2-3% (Van Hellemont, 1986b).

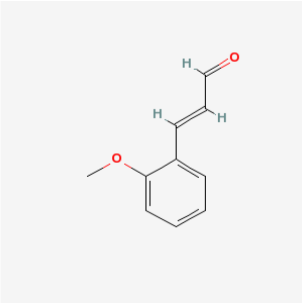



**Fig. 41.** Chemical structure of *o*-methoxycinnamaldehyde (adapted from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=641298&loc=ec_rcs) (visited on 28/11/09).

***Cinnamomum verum* bark**

The cinnamon bark contains volatile oils up to 4% (Barnes et al., 2007b; Van Hellemont, 1986), 0.5 to 2.5% according to Wichtl *et* Anton (1999), 1.2-2.5% according to Cunha *et al.,* (2003a) or 1.2-2% according to Fitoterapia (1998). The dry plant has to contain at least 12ml/kg of essential oil (Fitoterapia, 1998). The bark also contains condensed tannins (Anonymous, 2002; Barnes et al, 2007; Wichtl et Anton, 1999) and according to Van Hellemont (1986) also contains starch, and methylamilketone that gives finesse to the essence. Other constituents are calcium oxalate (Barnes et al, 2007; Van Hellemont, 1986), cinnzeylanin, cinnzeylanol (Barnes et al, 2007), mannitol, L-arabino-D-xylan, β-sitosterol (Wichtl *et* Anton, 1999), coumarin (Anonymous, 2002; Barnes et al, 2007; Fitoterapia, 1998), gum (Barnes et al, 2007), mucilages (Barnes et al, 2007; Cunha *et al.,* 2003a; Wichtl *et* Anton, 1999; Fitoterapia, 1998), resins and sugars (Barnes et al, 2007).

Cinnamaldehyde was the predominant active compound found in cinnamon oil (Prabuseenivasan *et al.,* 2006), 60-75% according to Barnes *et al.* (2007), 65-75% according to Wichtl *et* Anton (1999), 65-80% according to Cunha *et al.* (2003a), WHO (1999) and Ooi *et al.* (2006) and 50-75% according to Fitoterapia (1998). Contains benzaldehyde and cuminaldehyde; phenols (4-10%) including eugenol (Anonymous, 2002; Barnes et al., 2007b; Ooi *et al.,* 2006) (about 5% according to Wichtl *et* Anton (1999), 4-10% according to Cunha *et al.* (2003a), Fitoterapia (1998) and Van Hellemont

(1986) and *trans*-cinnamic acid (Anonymous, 2002; Ooi *et al.,* 2006), about 5–10% (Ooi *et al.,* 2006). Also contains methyleugenol, α-pinene, phellandrene, cymeme and caryophyllene (hydrocarbons), cinnamyl acetate and benzyl benzoate (esters), linalool (Barnes et al., 2007b). The essential oil also contains procyanidic oligomers (Anonymous, 2002; Cunha *et al.,* 2003a; Wichtl *et* Anton, 1999) (less than 2%, otherwise too much primary bark is present) (Wichtl *et* Anton, 1999) and *o*-methoxycinnamaldehyde (Anonymous, 2002; WHO, 1999a; Wichtl *et* Anton, 1999). Also contains cinnamic alcohol (Fig. 42) (Anonymous, 2002; Wichtl *et* Anton, 1999) and its acetate (Anonymous, 2002; Cunha *et al.,* 2003a; Wichtl *et* Anton, 1999); mono- and sesquiterpenes in small quantities, pentacyclic diterpenes with insecticidal activity (cincassiols, cinnzeylanine), phenolic acids (protocatechic acid, hydroxycinnamic acids...) (Wichtl *et* Anton, 1999), cineol, linalool, β-caryophyllene (about 2% each), limonene, α-terpineol (Anonymous, 2002), carbohydrates, tannins (Anonymous, 2002; Cunha *et al.,* 2003a; Fitoterapia, 1998; Van Hellemont, 1986). The cinnamon oil also contains traces of terpenic compounds (α-pineno, cineol, phellandrene, linalool) and methylketone (Fitoterapia, 1998).

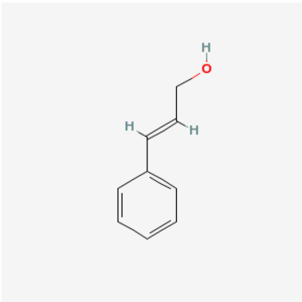



**Fig. 42.** Chemical structure of cinnamic alcohol (adapted from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=5315892&loc=ec_rcs) (visited on 6/12/09)

### *Essential Oil*

According to the Portuguese Pharmacopoeia (2005) and Sweetman (2009b) by definition *C. cassia* essential oil (*Cinnamomi cassiae aetheroleum*) is the essential oil obtained by the steam distillation of leaves and young branches of *Cinnamomum cassia* Blume (*C. aromaticum* Nees.) and *C. verum* essential oil (*Cinnamomi zeylanicii corticis aetheroleum*) is the essential oil obtained by the steam distillation of the bark of young branches of *Cinnamomum zeylanicum* Nees (*C. verum* JS Presl). In some countries cassia oil is known as cinnamon oil (Sweetman, 2009b).

### *Oil Appearance*

The cassia and cinnamon essential oil should be: liquid fluid, clear, the characteristic odor resembling that of cinnamaldehyde (FP, 2005). The color of cassia essential oil should be yellow to brown – reddish and the color of cinnamon essential oil should be light yellow, becoming reddish with age (FP, 2005, Sweetman, 2009b, 2009c).

***Oil Identification***

*C. cassia* and *C. verum*: Thin-layer chromatography. Chromatographic profile. Gas chromatography.

Relative density: *C. cassia*: 1.052 to 1.070. *C. verum*: 1.000 to 1.030.

Refractive index: *C. cassia*: 1.600 to 1.614. *C. verum*: 1.572 to 1.591.

Angle of optical rotation: *C. cassia*:-1 ° to +1 °. *C. verum*: -2 ° to +1 °.

The levels are between the following values:

- *trans*-cinnamaldehyde: *C. cassia*: 70.0 - 90.0 %,
- Cinnamyl acetate: *C. cassia*: 1.0- 6.0 %,
- Eugenol: *C. cassia*: less than 0.5 %, *C. verum*: less than 7.5 %,
- Coumarin: *C. cassia*: 1.5-4.0 %, *C. verum*: less than 0.5 %,
- *trans*-2-methoxy cinnamaldehyde: *C. cassia*: 0.3-1.5 % *C. verum*: 0.1 - 1.0%,
- Cineole: *C. verum*: less than 3.0 %,
- Linalool: *C. verum*: 1.0-6.0 %,
- β-Caryophyllene: *C. verum*: 1.0-4.0 %,
- Safrole: *C. verum*: less than 0.5 %,
- Aldehyde *trans*-cinnamic: *C. cassia*: 70.0-90.0 % *C. verum*: 55.0-75.0 %,
- Benzyl benzoate: less than 1.0 % (FP, 2005).

## Effects and uses

*Cortex Cinnamomi* is used in the symptomatic treatment of gastrointestinal disorders (PDR, 1998), including the treatment of dyspeptic conditions such as mild spastic conditions (PDR, 1998; WHO, 1999a). *Cortex Cinnamomi* is stated to possess antispasmodic properties (Barnes *et al.,* 2007b; Barnes *et al.,* 2007a; Cunha *et al.,* 2003a; Fitoterapia, 1998 Newall et al., 1996a) and is used in intestinal spasms (Barnes et al., 2007b; Cunha *et al.,* 2003a; Fitoterapia, 1998; Wichtl *et* Anton, 1999), stomachache (Van Hellemont, 1986b; WHO, 1997C) and possess orexigenic (Barnes *et al.,* 2007b; Cunha *et al.,* 2003a; Fitoterapia, 1998), antidiarrheic, antimicrobial (Barnes *et al.,* 2007b; Barnes et al, 2007a; Cunha et al., 2003a; Fitoterapia, 1998; Lirussi *et al.,* 2004; Newall *et al.,* 1996a) and antihelmintic properties. It has been used for anorexia (Barnes *et al.,* 2007b; Barnes *et al.,* 2007a; Cunha *et al.,* 2003a; Fitoterapia, 1998; Newall *et al.,* 1996a), as appetite stimulating (Cunha *et al.,* 2003a; Fitoterapia, 1998; PDR, 1998; WHO, 1999a; Wichtl *et*

Anton, 1999), for diarrhea (Barnes *et al.,* 2007a; Newall *et al.,* 1996a) including infantile diarrhea (Barnes et al., 2007b; Cunha *et al.,* 2003a), flatulence (Cunha *et al.,* 2003a; PDR, 1998; Wichtl *et* Anton, 1999; WHO, 1999a) and bloating (Cunha *et al.,* 2003a; PDR, 1998; Wichtl *et* Anton, 1999). The plant is occasionally used as an eupeptic (Cunha *et al.,* 2003a; Fitoterapia, 1998; Van Hellemont, 1986; Wichtl *et* Anton, 1999), carminative (Barnes *et al.,* 2007b; Barnes *et al.,* 2007a; Cunha *et al.,* 2003a; Fitoterapia, 1998; Newall *et al.,* 1996a; Van Hellemont, 1986; Wichtl *et* Anton, 1999) and antiemetic (Barnes *et al.,* 2007a; Newall *et al.,* 1996a). Used for hiposecretic dispepsys, meteorism (Fitoterapia, 1998), gastritis (Fitoterapia, 1998), stimulant of digestive secretions (Cunha *et al.,* 2003a), flatulent colic (Barnes *et al.,* 2007b; Barnes *et al.,* 2007a; Newall *et al.,* 1996a) and dyspepsia with nausea (Barnes *et al.,* 2007b). The German Commission E indicates its use for loss of appetite, flatulence and bloating (Cunha *et al.,* 2003a). It has antibacterial, fungistatic properties, improves immunity in animal tests, promotes motility and inhibits ulcers (PDR, 1998). Also used to treat abdominal pain (WHO, 1999a), with diarrhea and pain associated with amenorrhoea and dysmenorrhoea (WHO, 1999a; WHO, 1997C). Used in shock, clammy extremities, cough and wheezing, pain in the lower part of the body a knees, low blood pressure, frost bite (WHO, 1997C). Cinnamon is used as a tonic on convalescence state consecutively on infectious diseases (Van Hellemont, 1986b), in temporary states of exhaustion and to increase weight (PDR, 1998). Used to treat common cold (Barnes et al., 2007b; Barnes et al, 2007a; Fitoterapia, 1998; Newall et al., 1996a; PDR, 1998; WHO, 1997C), influenza (Cunha *et al.,* 2003a; Barnes *et al.,* 2007b), coryza accompanied by inflammation of the oropharynx (Cunha *et al.,* 2003a; Fitoterapia, 1998) and respiratory tract (Cunha *et al.,* 2003a). Used to treat cough and bronchitis, emphysema, bronquiectasias, fevers (Fitoterapia, 1998), asthma (Cunha et al., 2003a; Fitoterapia, 1998) as a respiratory stimulant (Cunha *et al.,* 2003a). *Cortex cinnamomi* is also stated to be astringent (Barnes *et al.,* 2007b; Barnes *et al.,* 2007a; Newall *et al.,* 1996a) due to tannins (Barnes *et al.,* 2007b). Used in the treatment of amenorrhea (Fitoterapia, 1998) and dysmenorrhoea (Cunha *et al.,* 2003, Fitoterapia, 1998). Possesses emenagogue (Fitoterapia, 1998; Van Hellemont, 1986), even abortive properties (Van Hellemont, 1986b). In animals shows estrogen action (Cunha *et al.,* 2003a). *C. cassia* is anticarcinogenic, insecticide, antipyretic, and stimulant of human linfocitary activity *in vitro* (Lirussi *et al.,* 2004). The cinnamon oil is a muscletropic of papaverine type which has a cardiac positive inotropic and chronotropic effects (Wichtl *et* Anton, 1999).

*C. cassia* is one of the traditional folk herbs used in Korea, China and Russia for *diabetes mellitus* (Kim *et al.*, 2006). Used in Chinese medicine for impotence, diarrhea, enuresis, rheumatic conditions, testicle hernia, menopause syndrome, amenorrhoea, abortion and to stabilize immunity (PDR, 1998). In TCM is prescribed in decoction alone or together with the other herbs to relieve stomachache, and to improve general blood circulation, especially in the lower part of the body, such as loin, knee joints, legs and extremities. It is also used to promote sweating and expel the "weakness" inside the internal organs of the body, thus, to reach the balance of "Yin and Yang" in Chinese traditional medical terms. All these actions are due to the Yang quality of the volatile aroma and the medicinal characteristics of this bark (Ooi, *et al.,* 2006).

According to the WHO (1999), *Cortex Cinnamomi* is used for the treatment of impotence, frigidity, dyspnea, inflammation of the eye, leucorrhoea, vaginitis, rheumatism, neuralgia, wounds, and toothache, but this uses are described in folk medicine and not supported by experimental or clinical data (WHO, 1999a).

In folk medicine, the cinnamon essential oil is used in dysmenorrhoea (Wichtl *et* Anton, 1999). The cinnamon oil is used externally in stomatitis, cutaneous mycosis (Cunha *et al.,* 2003a), parodontophathys, dermatomicosis, otitis and vulvovaginitis (Fitoterapia, 1998), possesses tonic and antihelmintic properties (Van Hellemont, 1986a) and it´s slight astringent and rubefacient (Fitoterapia, 1998).

***Food use of the bark***

Cinnamon has a certain value as a flavoring agent (Van Hellemont, 1986a), also the correspondent oil (Barnes *et al.,* 2007a; Newall *et al.,* 1996a). Cinnamaldehyde and coumarin from *C. cassia* oil have been used as food additives (Chang *et al*., 2001). Cinnamon is listed by the Council of Europe as a natural source of food flavoring (category N2). This category indicates that cinnamon can be added to foodstuffs in small quantities (Barnes et al., 2007b; Barnes *et al.,* 2007a; Newall *et al.,* 1996a). In the food industry and home cookery, when cinnamon is added to bakery items or food preparations, it functions as an additive flavor and aroma with the bonus of microbial inhibition (Ooi *et al.,* 2006). According to the United States Food and Drug Administration (USFDA), *Cinnamomum* spp., including common and cassia cinnamon, are generally recognized as safe (GRAS) (Anonymous, 2009m; Barnes *et al.,* 2007b; Barnes *et al.,* 2007a; Dugoua *et al.,* 2007; Newall *et al.,* 1996a; Ziengefuss *et al.,* 2006) when used in amounts commonly found in food (Dugoua *et al.,* 2007). Cinnamon is commonly used as a spice in cooking (Barnes *et al.,* 2007b; Barnes *et al.,* 2007a; Newall *et al.,* 1996a; Wichtl *et* Anton, 1999; Van Hellemont, 1986), sometimes also in liquor preparation (Anonymous, 2009f; Wichtl *et* Anton, 1999; Van Hellemont, 1986), although at levels much less than the stated therapeutic doses. The acceptable daily intake of cinnamaldehyde has been temporarily estimated as 700µg/kg body weight (Barnes *et al.,* 2007b; Barnes *et al.,* 2007a; Newall *et al.,* 1996a) and the accepted daily intake of eugenol is up to 2.5mg/kg (Barnes *et al.,* 2007b).

***Other uses***

The oil is used also in perfumes (Anonymous, 2009f).

## Pharmacological Activities

Activities documented for cinnamaldehyde include CNS stimulation (low dose), sedation (high dose) (Barnes *et al.,* 2007a; Duke, 2003), hypothermic and antipyretic actions (Anonymous, 2009f; Barnes *et al.,* 2007a); antibacterial and antifungal activity, acceleration of catecholamine (mainly adrenaline) release from the adrenal glands, weak papaverine-like action, increase in peripheral blood flow, hypotension and bradycardia have also been reported (Barnes *et al.,* 2007a) Cinnamaldehyde has the analgesic effect (Anonymous, 2009f; Shen *et al.,* 2002), has the effect for sedation, relieve fever, is used against eclampsia, stimulates peristalsis of stomach and intestine, has cholagogue (Shen *et al.,* 2002) and antitumor properties (Anonymous, 2009m; Shen *et al.,* 2002). Also has convulsion-resistant properties and injecting cinnamaldehyde into the abdominal cavity of a mouse can alleviate the body sprain reaction caused by acetic acid. The use of the dosage of 500 mg/kg can resist tonic convulsions caused by strychnine. Also relieves coughing and induces diuresis (Anonymous, 2009f). Cinnamaldehyde may also have immunomodulating activity (Anonymous, 2009m).

Much of the cinnamaldehyde content of cassia is thought to be lost by evaporation and auto-oxidation during decoction of the crude drug, so the contribution of cinnamaldehyde to the overall therapeutic efficacy of cassia has, therefore, been questioned (Barnes *et al.,* 2007a). That`s why it´s so important to add the drug at the end of the decoction preparation.

***Anti-infectious effects***

Antifungal, antiviral, bactericidal (Dugoua *et al.,* 2007) and larvicidal actions have been reported for the volatile oil (Barnes et al., 2007b; Dugoua *et al.,* 2007). The essential oil is active *in vitro* against the following bacteria: *Escherichia coli*, *Staphylococcus aureus* (Barnes et al., 2007b; WHO, 1999a), *Salmonella typhimurium*, *Bacillus subtilis* and *Pseudomonas aeruginosa* (WHO, 1999a). The essential oil, *per os*, at a dose of 0.1ml, is active in cystitis caused by *E. coli* (Cunha *et al.,* 2003a). It was also active *in vitro* against the following fungi: *Aspergillus* spp., *Cladosporium werneckii*, *Geotrichum candidum*, *Kloeckera apivulata*, *Candida lipolytica* (WHO, 1999a) and *C. albicans* (WHO, 1999a; Barnes *et al.,* 2007b). The antibacterial and fungicidal effects have been attributed to *o*-methoxycinnamaldehyde (Ooi *et al.,* 2006; WHO, 1999a), but according to Tabak *et al*. (1999) cinnamaldehyde seems to be the main inhibitory component of cinnamon.

According to Senhaji *et al.* (2007) the major antimicrobial components of cinnamon and the essential oil are cinnamaldehyde and eugenol. Cinnamaldehyde has broad spectrum gram-positive and gram-negative antibacterial activity (Dugoua *et al.,* 2007; Liu *et al.,* 2007) in which it was shown to inhibit the growth of *Clostridium perfringens*, *Bacteroides fragilis*, *Bifidobacterium bifidum*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Escherichia coli*, *Enterobacter aerogenes*, *Proteus vulgaris* (Dugoua *et al.,* 2007), *Vibrio cholerae*, *V. parahaemolyticus*, and *Salmonella typhimurium* as well as broad-spectrum vaginal microflora. One mechanism that has been explored for this antibacterial activity is that cinnamaldehyde destroys the cytoplasmic membrane of both gram-positive and gram-negative bacteria and induces depletion of the intracellular ATP concentration (Dugoua *et al.,* 2007). Cinnamaldehyde also exhibits antibacterial activity against clinical *P. aeruginosa* (Dugoua *et al.,* 2007; Liu *et al.,* 2007) and has a synergistic effect with tetracycline, gentamycin, and streptomycin (Liu *et al.,* 2007). In addition, (–)-epicatechin; 1,8-cineole; α-pinene; α-terpineol; benzaldehyde; benzoic acid; cinnamic acid; cuminaldehyde; eugenol; geranial; guaiacol; limonene; linalool; methyleugenol; OPC; *p*-cymene; procyanidins; safrole; salicylic acid; terpinen-4-ol are referred to have antibacterial effects (Duke, 2003).

Cinnamaldehyde was previously found inhibited the *Mycobacterium tuberculosis* and influenza virus effectively, and could regulate the immunological function (Ma *et al.,* 2008). A low concentration of *trans*-cinnamaldehyde elevates the antimicrobial action of clindamycin, and suggests a possible clinical benefit for utilizing these natural products for combination therapy against *C. difficile* (Shahverdi *et al.,* 2006). Cinnamaldehyde has also been shown to inhibit growth of fungi (Dugoua *et al.,* 2007) including yeasts (4 species of *Candida*: *C. albicans*, *C. tropicalis*, *C. glabrata*, and *C. krusei*), filamentous molds (3 *Aspergillus* spp. and 1 *Fusarium* sp.), and dermatophytes (*Microsporum gypseum*, *Trichophyton rubrum*, and *T. mentagrophytes*), as well as the eggs and adult females of human head louse *Pediculus humanus capitis* (Dugoua et al., 2007). The mechanism of antimicrobial activity has been partially revealed in a study on yeast cells (*Saccharomyces cerevisiae*). The inhibitory effect of *trans*-cinnamaldehyde was due to its ability to inhibit yeast cell wall-synthesizing enzymes, β-(1,3)-glucan synthase and chitin synthase I (Ooi *et al.,* 2006). *o*-Methoxycinnamaldehyde was shown to inhibit the growth and toxin production of mycotoxinproducing fungi. Inhibits the growth of *Aspergillus parasiticus, A. flavus, A. ochraceus* and *A. versicolor*. It also inhibits the production of aflatoxin, ochratoxin A and sterigmatocystin. *o*-Methoxycinnamaldehyde is also effective against *S. aureus* and *C. botulinum* (Morozumi, 1978). In addition, 2-methoxycinnamaldehyde has been reported to inhibit the growth of *Aspergillus parasiticus* and *A*. *sterigmatocystin* (Guo *et al.,* 2006b). Aqueous and alcohol extracts of cinnamon have demonstrated antibacterial effects against *H. pylori* (Dugoua *et al.,* 2007). A recent study indicates that *trans*-cinnamaldehyde could potentially be used to kill *Enterobacter sakazakii* in reconstituted infant formula (Amalaradjou *et al.,* 2008). *C. cassia* bark also shows activity against *Tryponosoma cruzi* (Lirussi *et al.,* 2004) and *Salmonella enteritidis* (Dugoua *et al.,* 2007). The use of commercial cinnamon preparation produced an improvement of oral candidiasis of HIV infected patients. Cinnamon bark essential oil exhibited high activity against Listeria *monocytogenes* at low doses and might be useful as a food preservative because of its possible low sensory impact (Cava *et al.,* 2007). It can be incorporated into creams, lotions, drops, etc. which are applied externally on the body to treat diseases caused by *Aspergillus niger*. In a recent study comparing different antibacterial oils (cinnamon, clove, geranium, lemon, lime, orange and rosemary) cinnamon oil has the most potential bactericidal properties. It can be used as antibacterial supplement in the developing countries towards the development of new therapeutic agents. Additional *in vivo* studies and clinical trials would be needed to justify and further evaluate the potential of this oil as an antibacterial agent in topical or oral applications (Prabuseenivasan *et al.,* 2006). Antiviral properties has been attributed to several constituents of cinnamon, including: (–)-epicatechin; $\alpha$-pinene; cinnamaldehyde; geranial; limonene; linalool; oligomeric procyanidin (OPC); p-cymene; procyanidins. In addition: $\alpha$-pinene; limonene; *p*-cymene are referred to have antiflu effects (Duke, 2003).

***Gastrointestinal effects***

The essential oil of *C. verum* has carminative activity and decreases smooth muscle contractions in guinea-pig trachea and ileum, and in dog ileum, colon and stomach. The active antispasmodic constituent of the drug is cinnamaldehyde. A reduction of stomach motility in rats and dogs and intestinal motility in mice and a decrease in the number of stress- and serotonin induced ulcers in mice have been described. An ethanol extract of the drug inhibits histamine- and barium-induced contractions in guinea-pig ileum but the hot-water extract was not active (WHO, 1999a). Animal studies suggest that an extract of cinnamon bark taken orally may help prevent stomach ulcer. Cinnamaldehyde was completely inhibiting both sensitive and resistant strain of *Helicobacter pylori* (Prabuseenivasan *et al.,* 2006). Eugenol and cavracol also exert varying inhibitory effects on *H. pylori* (Tabak *et al*., 1999). Anti-ulcerogenic properties have been described for two propionic derivatives identified as 3-(2-hydroxyphenyl)-propanoic acid and its *O*-glucoside isolated from cassia (Tanaka et al., 1989). An *in vivo* study using rats reported activity against a variety of ulcerogens including serotonin, phenylbutazone, ethanol, water immersion, and stress. The compounds where thought to act by improving gastric blood flow rather than by inhibiting gastric secretion (Barnes *et al.,* 2007a; Newall et al., 1996a;

Tanaka *et al.,* 1989). These results suggest that the antiulcerogenic effect is probably attributable to the potentiation of defensive factors through the improvement of the circulatory disorder and gastric cytoprotection (Tanaka *et al.,* 1989). Several constituents has been referred has antiulcer compounds such as (+)-catechin, cinnamaldehyde and eugenol. Also procyanidins have reported to be antigastritic compounds (Duke, 2003). Water and ether extract of *C. cassia* bark have shown antidiarrheic effects in laboratory mice. Choleretic and analgesic effects have been seen in anesthetized laboratory rats. The effects are due to the "warming" and analgesic effects of the stomach and spleen (Anonymous, 2002). In addition, its constituent's eugenol, eugenol acetate, and methyl eugenol have been reported to enhance trypsin activity in vitro (Dugoua et al., 2007). The mucilage present in cinnamon has demulcent properties and 1,8-cineole is secretagogue. Eugenol; methyl-salicylate and safrole possess carminative effects (Duke, 2003).

***Cytotoxic effects***

Antitumor activity has been described to cinnamon and the activity depends on the plant source used (Barnes et al., 2007a). Weak tumor-promoting activity on the mouse skin and weak cytotoxic activity against HeLa cells has been documented for eugenol (Barnes et al., 2007b). Anti-tumor properties has been attributed to several constituents of cinnamon, including: (+)-catechin; (–)-epicatechin; $\alpha$-pinene; $\alpha$-terpineol; benzaldehyde; cinnamaldehyde; cinnamic acid; coumarin; eugenol; isoeugenol; limonene; linalool; methyl-eugenol; methyl-salicylate; mucilage; OPC; safrole; salicylic acid; *trans*-cinnamaldehyde (Duke, 2003).

***Anti-inflammatory effects***

Previous studies have found that C. *cassia* has anti-inflammatory effects on various soft tissue conditions. Some recent studies have suggested that the anti-inflammatory effects of *C. cassia* were attributed to the scavenging of nitric oxide free radicals by this herb in the tissues (Fung *et* Ng, 2005). Cinnamaldeyde is also a potent anti-inflammatory compound through its inhibitory action on nuclear factor *k*B (NF-*k*B), nitric oxide (NO) synthase or cicloxigenase 2 (COX2) activities (Boudry *et* Perrier, 2008).

*In vivo* inhibitory activity against complement formation has been documented and attributed to the diterpenoid and condensed tannin constituents. Anti-inflammatory activity exhibited by the Japanese plant *Cinnamomum sieboldii* Meisn (also used as a source of cassia bark), has been attributed to a series of condensed tannins constituents (Barnes *et al.,* 2007a). 2-methoxycinnamaldehyde can affect the PGE2 release in rat cerebral microvascular endothelial cells (rCMEC) induced by IL-1, which might be related with its inhibition on the activity of COX-2 (Guo *et al.,* 2006c). Anti-inflammatory properties has been attributed to several constituents of cinnamon, including: (+)-catechin; (–)-epicatechin; alpha-pinene; beta-pinene; cinnamaldehyde; cinnamic acid; coumarin; eugenol; methyl-salicylate; OPC; salicylic-acid. In addition, (+)-catechin; eugenol; salicylic-acid are referred as COX-2-inhibitors (Duke, 2003).

***Antipyretical and analgesic effects***

Prostaglandin E2 (PGE2), a COX-derived metabolite of arachidonic acid, is a well-defined mediator of fever. IL-1b is a principle component of endogenous pyrogens, and it has been generally recognized that IL-1b released from cells peripherally produces fever by signaling the brain *via* various routes (Guo *et al.,* 2006b). Recently, Guo *et al.* (2006b) showed that 2-methoxycinnamaldehyde dose-dependently inhibits IL-1b -induced PGE2 production through the inhibition of COX-2 protein and COX-2 activity in rat cerebral endothelial cells (CECs), while 2-methoxycinnamic acid (Fig. 43) does not influence the PGE2 production in CECs with IL-1b inducement. Cinnamaldehyde was previously found that relieved fever and pain and could regulate the immunological function. Recent research also showed that it could reduce the amount of cyclooxygenase (COX)-1, COX-2 and prostaglandin E2 (PGE2) and perhaps this is the mechanism of its relieving-fever effect (Ma *et al.,* 2008). In addition, analgesic effects are attributed to: coumarin; eugenol; methyl-salicylate; p-cymene; salicylic-acid (Duke, 2003).

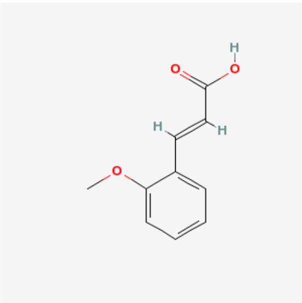


**Fig. 43.** Chemical structure of 2-methoxycinnamic acid (adapted from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=734154&loc=ec_rcs) (visited on 28/11/09).

***Antithrombotic effects***

Antiplatelet aggregation and antithrombotic actions have also been reported for *C.cassia*. These actions, together with the documented anti-inflammatory activity, are thought to contribute to the suppression of thrombus formation in certain diseases (Barnes *et al.,* 2007a).

***Anti-diabetic and anti-dislipidemic effects***

Recently was reported that cinnamon extract (*C. cassia*) decreases blood glucose in *Wistar* rats. It was shown that cinnamon increases the insulin sensitivity and glucose uptake in adipocytes. Cinnamon extract has a regulatory role in blood glucose level and lipids and it may also exert a blood glucose-suppressing effect by improving insulin sensitivity or slowing absorption of carbohydrates in the small intestine, in *db/db* mice. The cassia extract does not have any role in the alteration of the body weight, food intake and food efficiency ratio (FER); However, it was observed that cinnamon extract significantly reduces blood glucose levels in *db/db* mice after 2 weeks of treatment, which also demonstrates that there is significantly higher rate of glucose disposal. There was also a significant increase in the levels of serum insulin after administration of a cinnamon extract to *db/db*. So, the possible mechanism by which cinnamon extract brings about its hypoglycemic action in diabetic mice may be by potentiating the effect of insulin in serum or by increasing either the pancreatic secretion of insulin from the existing beta cells or its release from the bound form. There was significant decrease in triglyceride and total cholesterol level whereas increase in HDL–cholesterol and HTR (total cholesterol ratio) (%) levels in cinnamon-treated mice. It was reported that triglyceride and total cholesterol were decreased by administration of cinnamon extract in rats treated with streptozotocin for 3 weeks. The mechanism is explained by the AMPK-enhanced triacylglycerol lipase activity that increases glycogen synthesis in the liver and enhances glucose uptake in skeletal muscle and adipocytes. However, in insulin-deficient diabetics, free fatty acid concentration in the serum is elevated as a result of increased free fatty acid outflow from fat depots, where the balance of the free fatty acid esterification–triglyceride lipolysis cycle is displaced in favor of lipolysis. Another possible mechanism of cinnamon extract in anti-hyperglycemic effect may be due to decreased activity of small intestinal α-glycosidase activity that converts carbohydrates into glucose preventing the rapid upward swing of PB2 (postprandial 2h blood glucose levels) level and slow absorption of carbohydrate in the small intestine (Kim *et al.*, 2006). Polyphenolic polymers such as hydroxychalcone found in cassia cinnamon seem to potentiate insulin action. These compounds seem to increase phosphorylation of the insulin receptor, which increases insulin sensitivity. Increased insulin sensitivity may improve blood glucose control and lipid levels (Anonymous, 2009m). *In vitro* studies have shown that cinnamon enhances glucose uptake by activating insulin receptor (IR) kinase activity, autophosphorylation of IR, glycogen synthesis and glycogen synthase activity (Baker *et al.,* 2008; Mang *et al.,* 2006a). According to Baker *et al.,* 2008 these activities have been also seen *in vivo* studies. *In vivo*, cinnamon extract enhances glucose utilization in rats in a dose dependent fashion by potentiating insulin-stimulated tyrosine phosphorylation of (IR)- β, IR substrate

(IRS)-1 and the IRS-1 association with phosphatidylinositol (PI) 3-kinase (Mang *et al.,* 2006a). It has been assumed that the methylhydroxychalcone polymer (MHCP) (Fig. 44) is the active substance (Mang *et al.,* 2006a) and it was found to be an effective mimetic of insulin (Dugoua et al., 2007; Jarvill- Taylor *et al.,* 2001; Pham *et al.,* 2007).

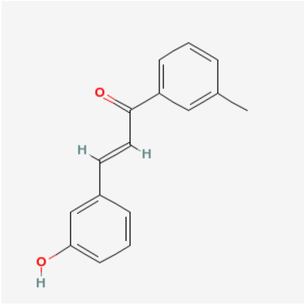



**Fig. 44.** Chemical structure of 3'-methyl-3-hydroxychalcone (adapted from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6440383&loc=ec_rcs) (visited on 7/12/09).

Combining MHCP and insulin provided synergistic effects on both glucose uptake and glycogen production *in vitro* (Jarvill- Taylor *et al.,* 2001; Pham *et al.,* 2007). However, other findings suggested that the previously identified MHCP in cinnamon may have actually been water-soluble polyphenolic type-A polymers. Thus, the biologically active insulin-like substance in cinnamon remains unidentified. *In vivo*, oral administration of cinnamon extract has enhanced glucose utilization in rats by increasing the glucose infusion rate into skeletal muscle (Pham *et al.,* 2007). In addition to improving cellular glucose metabolism, cinnamon may provide additional benefits for persons with diabetes through its antioxidant activity (Anderson *et al.,* 2004). The polyphenolic polymers have antioxidant effects, which may provide synergistic benefits for the treatment of diabetes. Botanical antioxidants may play a role in helping maintain the integrity of cell membranes by preventing polyunsaturated fatty acid peroxidation. The lipid composition of muscle membrane phospholipids reflects the combined influences of diet and desaturase/elongase activity, and in turn, the phospholipid composition affects the binding and action of insulin. In general, the more unsaturated the membrane, the better glucose is utilized. The more saturated the membrane, the more deleterious the effects on insulin efficiency. Lipid peroxidation and damage by reactive oxygen metabolites are also major problems in terms of diabetic complications. Clinical studies have shown that supplementation of both nutrient and phytochemical antioxidants can reduce or slow the progression of various complications of diabetes. It was reported that the major procyanidin oligomers in the ethanolic and aqueous extracts of cinnamon are doubly linked type-A (Anderson *et al.,* 2004). It was demonstrated that water-soluble polymeric compounds isolated from cinnamon have insulin-enhancing biological activity in the *in vitro* assay measuring the insulindependent effects on glucose metabolism and also function as antioxidants. These same compounds have been shown to inhibit phosphotyrosine phosphatase in the insulin-receptor domain and to activate insulin receptor kinase and function as a mimetic for insulin in 3T3-L1 adipocytes (Anderson *et al.,* 2004). It was suggested that used various aqueous cinnamon extracts and showed insulin-enhancing properties *in vitro* in adipocytes, suggesting that isolated A-type doubly linked procyanidin oligomers of the catechins and/or epicatechins from cinnamon may be responsible for the observed effect (Mang *et al.,* 2006a). In a recent study made by Khan *et al.* (2003) supplementation of 1, 3, or 6 g of cinnamon for 40 days caused positive effects on fasting serum glucose and blood lipids. However, the results of this study, which was performed in Pakistan, may not be valid for Western populations (Mang *et al.,* 2006a). Mang *et al.* (2006a) evaluated the effect of an aqueous cinnamon extract on fasting plasma glucose, HbA1c and serum lipids in Western type 2 diabetics. This study showed that in Western type 2 diabetics treated in accordance with the current guidelines, the intake of an aqueous cinnamon extract leads to a moderate effect on fasting plasma glucose, but not on HbA1c, serum lipids or blood coagulation parameters (Mang *et al.,* 2006a). Another recent study showed that ingestion cinnamon reduces postprandial blood glucose concentrations and gastric emptying rate (GER) in healthy subjects. This finding could indicate that the reduction in the postprandial blood glucose response seen after the ingestion of cinnamon could be partly explained by an accompanying reduction in gastric emptying, because the rate of gastric emptying acts as a major factor in blood glucose homeostasis in normal subjects by controlling the delivery of carbohydrate to the small intestine. However, the reduction in the blood glucose concentrations, unexpectedly, was much more noticeable and pronounced in the present study than was the lowering of the GER. Therefore, it should be assumed that the change in GER itself could not be the only reason for the lower blood glucose response after the addition of cinnamon to the meal. In fact, cinnamon has been shown to improve insulin receptor function by activating insulin receptor phosphoinositide 3-kinase (PI 3-kinase) and inhibiting tyrosine phosphates. Cinnamon has also been shown to stimulate the insulin receptor activity by increasing the concentrations of the phosphorylated intracellular protein insulin receptor substrate-1 (IRS-1) and increasing the binding to PI 3-kinase, which leads to enhanced cellular glucose uptake. It has been shown that cinnamon prevents the development of insulin resistance in rats fed a high-fructose diet by enhancing the insulin signaling, possibly via the nitric oxide pathway in skeletal muscle. A new study shows that rats given cinnamon and then administered a glucose tolerance test had decreased blood glucose concentrations. The same study shows that cinnamon has a direct antidiabetic effect by increasing insulin concentrations in plasma. A recent study shows that the presence of cinnamon in a semisolid meal reduces postprandial glucose responses in healthy subjects and that the cause of this reduction could at least partly be a delayed GER (Hlebowicz *et al.,* 2007). However, studies show that cinnamon might also have a direct role in lipid metabolism. For example, cinnamon bark powder at different doses 1, 3 and 6 g/day prevents hypercholesterolaemia and hypertriglyceridaemia and lowers the levels of free fatty acids and triglycerides in plasma of type 2 diabetic subjects by its strong lipolytic activity. Cinnamate, a phenolic compound found in cinnamon bark and other plant materials, lowers cholesterol levels in high fat-fed rats by inhibiting hepatic 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity. Research findings clearly show that cinnamon triggers the insulin cascade system (Kannappan *et al.,* 2006). Although the physiological basis of metabolic dyslipidaemia appears to be hepatic overproduction of apolipoprotein (apo)B-containing very low-density lipoprotein (VLDL) particles, emerging evidence suggests that intestinal overproduction of apoB-containing lipoproteins, in insulin- resistant states, may be an important contributor to the elevation of circulating triglyceride (TG)-rich lipoproteins (TRLs). ApoB-48 is an essential structural component of intestinally derived chylomicrons and its remnants, and a marker of TRLs of intestinal origin. Recent studies suggest that the accumulation of postprandial apoB48-TRLs not only leads to the enhanced delivery of exogenous lipids to liver, which will result in an increased production of hepatic lipoproteins, but also delays in the clearance of hepatic-derived TRLs. Consequently, apoB-48 TRL and remnants may play a disproportionally more important role in postprandial lipoprotein metabolism, even if the absolute plasma concentrations of chylomicrons are low compared with levels of hepatic-derived VLDL particles. Recent results suggest that acute oral aqueous cinnamon extracts treatment inhibits the increase in postprandial triglycerides and the overproduction of apoB48-containing lipoproteins in fructose-fed, insulin-resistant rats (Qin *et al.,* 2008).

Peroxisome proliferator-activated receptors (PPARs) are transcriptional factors involved in the regulation of insulin resistance and adipogenesis. Cinnamon is found to activate PPAR$\gamma$ and $\alpha$, resulting in improved insulin resistance, reduced fasted glucose, free fatty acids (FFA), LDL-c, and AST levels in high-caloric diet-induced obesity (DIO) and *db/db* mice in its water extract form. *In vitro* studies demonstrate that cinnamon increases the expression of peroxisome proliferator-activated receptors $\gamma$ and $\alpha$ (PPAR$\gamma/\alpha$) and their target genes such as Lipoprotein lipase (LPL), fatty acid transporter (CD36), glucose transporting protein 4 (GLUT4), and Acyl-CoA oxidase (ACO) in 3T3-L1 adipocyte. The transactivities of both full length and ligand-binding domain (LBD) of PPAR$\gamma$ and PPAR$\alpha$ are activated by cinnamon as evidenced by reporter gene assays. These data suggest that cinnamon in its water extract form can act as a dual activator of PPAR$\gamma$ and $\alpha$, and may be an alternative to PPARγ activator in managing obesity-related diabetes and hyperlipidemia (Shen *et al.,* 2008).

It was showed that cinnamon oils can improve insulin sensitivity and cinnamon water extract (CE) increases glucose uptake in 3T3-L1 adipocyte. However, the separated compounds derived from cinnamon displayed little insulinlike or insulin-enhancing activity. In a recent report, it was demonstrated that cinnamon water extract can elevate the expression of both PPARγ, *α* and their target genes in 3T3-L1 adipocyte possibly through stimulation of the transactivities of both full length and LBD of PPARγ and PPARα. *In vivo* study reveals that cinnamon water extract improves insulin resistance and lipid metabolism in both high-calorie dietinduced obesity (DIO) mice and *db/db* mice. This study demonstrated that CE had several beneficial effects on type 2 diabetes possibly through the activation of both PPARγ and PPARα resulting in improved insulin resistance, lowered blood glucose, and serum lipid level without weight gain and the structure change of the white adipose tissue. In addition, CE improved the liver function of obese mice. CE may have potential use in management of obesity-related type 2 diabetes and hyperlipidemia (Shen *et al.,* 2008).

Furthermore, cinnamon may inhibit hepatic 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase activity and lower blood lipids in animals and humans. However, a cholesterol-increasing effect has also been shown in rats in a previous study (Mang *et al.,* 2006a). A recent study made by Altshuler *et al.* (2007) evaluates the effect of cinnamon on glycemic control in type 1 diabetic adolescents. The results did not demonstrate any benefit of cinnamon in this patient population. There were no significant differences in final A1C, change in A1C, total daily insulin intake, or number of hypoglycemic episodes between the cinnamon and placebo arms (Altshuler *et al.,* 2007). Recently, Baker *et al.* (2008) performed a meta-analysis of five randomized placebo controlled trials with patients with type 1 or type 2 diabetes receiving cinnamon. It was not demonstrated statistically or clinically significant changes in A1C, FBG, or lipid parameters in comparison with subjects receiving placebo. Concerning this matter, human studies are needed, of better methodological quality, referring to exercise control or patients' diet, drug therapy diabetes control or other metabolic factors, as blood pressure or lipid values (Luis *et* Haler, 2008). However, it seems promising that if these data will be validated in the future clinical trials.

***Antioxidant effects***

The polyphenolic polymers found in *C. verum* and *C. aromaticum* have antioxidant activity and have been shown to reduce oxidative stress in a dose-dependant manner through inhibition of 5-lipooxygenase enzyme (Dugoua *et al.,* 2007). Specific antioxidant phytochemicals that have been identified in cinnamon include epicatechin, camphene, eugenol, γ-terpinene, phenol, salicylic acid, and tannins (Anderson *et al.,* 2004). A water-soluble polyphenol typ-A polymer from cinnamon showed *in vitro* to have an antioxidant effect (Hlebowicz *et al.,* 2007). The beneficial effect of these compounds has been approached in the "Anti-diabetic and anti-dislipidemic effects" concerning the insulin-mimetic activity.

Antioxidant properties has been attributed to several constituents of cinnamon, including: (+)-catechin; (–)-epicatechin; camphene; eugenol; γ-terpinene; isoeugenol;methyl-eugenol; OPC; procyanidins; salicylic acid (Duke, 2003). Also cinnamaldehyde reveals antioxidant properties (Anonymous, 2009m; Prabuseenivasan *et al.,* 2006).

***Respiratory effects***

According to Duke (2003) expectorant properties has been attributed to several constituents of cinnamon, including: 1,8-cineole; α-pinene; benzoic-acid; camphene; guaiacol; limonene; linalool. Antitussive effects are attributed to: 1,8-cineole; terpinen-4-ol. Antibronchitic effects to1,8-cineole. Also linalool is referred as bronchorelaxant (Duke, 2003).

***Neurological and neuroprotective effects***

As for the effect of cinnamaldehyde on the CNS, it is known that an action is concentration dependent: the administration of low doses stimulates this system, while high doses cause sedation (Barnes et al., 2007a, Duke, 2003). The cinnamaldehyde accelerates the release of catecholamines, primarily adrenaline, from adrenergic glands into the bloodstream (Duke, 2003). Increases peripheral blood flow, slows heart rate, reduces blood pressure, and has antipyretic and hypothermic effects (Dugoua *et al.,* 2007). Cinnamaldehyde is a circulostimulant and it accelerates release of catecholamines (mainly adrenaline) from the adrenal glands into the blood (Duke, 2003). Common cinnamon bark reduces the amplitude of penile somatosensory-evoked potentials in a mechanism that is not clearly understood, but may be useful in the treatment of premature ejaculation (Dugoua *et al.,* 2007). Several constituents such as 1,8-cineole, α-pinene, α-terpineol, benzaldehyde, cinnamaldehyde, coumarin, eugenol, farnesol, isoeugenol, limonene, linalool, methyl-eugenol and *p*-cymene have been referred to have sedative properties (Duke, 2003).

In traditional Japanese Oriental (Kampo) medicine, the bark of *C. cassia* Blume, *Cinnamomi cortex*, is one of the medicinal plants that have been used for improving various diseases caused by insufficient blood microcirculation. This medicinal plant has also been often administered to patients suffering from ischemic brain diseases. It was found that a water extract from the bark of *C. cassia* (CC) provided a marked protective effect against glutamate-induced neuronal death and also an inhibitory effect on $Ca^{2+}$

influx *in vitro.* Antithrombotic and endothelium-dependent vasodilator actions of CC have been reported. These actions may contribute to improvement of cerebral blood flow. Further, these findings suggest that CC may be a potential medicinal plant with protective activity against ischemic brain injury (Shimada *et al.,* 2000).

***Activation of the olfactory cortex of the brain***

A recent study conducted an observational study on 23 human subjects to determine the effect of abstract linking of linguistic and odor information in the brain using functional magnetic resonance imaging (fMRI). Odour-related terms, such as reading the word ‘‘cinnamon’’, elicited activation in the primary olfactory cortex, which include the piriform cortex and the amygdale (Dugoua *et al.,* 2007).

***Other effects***

Cinnamon oil is locally applied with much benefit in neuralgia and headache (Prabuseenivasan *et al.,* 2006). Antiseptic and anesthetic properties have been documented for eugenol (Barnes et al., 2007b).

There is a lack of clinical research assessing the effects of cinnamon and cassia rigorous randomized controlled clinical trials are required (Barnes et al., 2007b; Barnes *et al.,* 2007a).

***Non Medical Effects***

Constituents of the *Cinnamomum* bark, as *trans*-cinnamaldehyde, eugenol and salicylaldehyde revealed insecticidal activity (Park *et al.,* 2000). Other two insecticidal compounds, cinnzeylanin and cinnzeylanol, have been isolated (Barnes et al., 2007b).

## Adverse reactions

Cinnamon bark absorbed in large quantities (as well as cinnamon oil at moderate doses) leads to tachycardia, intestinal peristaltisme stimulation an increase in respiratory rate and sweating, and this phase of the vasomotor centers excitation is followed by a state of sedation with drowsiness and depression (Anonymous, 2002; Wichtl *et* Anton, 1999). Allergic reactions, mainly contact sensitivity, to cassia oil and bark have been reported (Barnes *et al.,* 2007a; WHO, 1999a). The irritant and sensitizing properties of cassia oil have been attributed to cinnamaldehyde (Barnes *et al.,* 2007a; Newall et al., 1996a). The dermal $LD_{50}$ of the *C.verum* oil is reported to be 690mg/kg body weight (Barnes et al., 2007b) and for cassia oil is stated as 320mg/kg body weight (Barnes *et al.,* 2007a; Newall et al., 1996a). The consumption of flavored gum with cinnamon causes perioral dermatitis

(Cunha et al., 2003a; Fitoterapia, 1998) and stomatitis (Tremblay *et* Avon, 2007). Topically, allergic skin reactions and stomatitis from toothpaste flavored with cassia cinnamon have been reported (Anonymous, 2009m). Cassia oil is stated to be one of the most hazardous oils and should not be used on the skin in concentrations of more than 0.2% (Barnes *et al.,* 2007a; Newall et al., 1996a). The essential oil of *C. verum* can cause contact dermatitis, irritation of mucous membranes or allergic reactions (bronchospasm). Internally, in high doses, it can produce nervous changes (Cunha et al., 2003a). Cinnamaldehyde in toothpastes and perfumes has also been reported to cause contact sensitivity (Barnes *et al.,* 2007a; Newall et al., 1996a). Examples of adverse reactions include the following: contact dermatitis, stomatitis, oral lichen planus, oral leukoplakia, mouth-burning syndrome, sunscreen dermatitis, urticaria, perioral dermatitis, oral erythema multiform-like sensitivity reaction (Dugoua *et al.,* 2007). There is one case wherein squamous cell carcinoma was reported after long-term cinnamon-gum chewing. Although cinnamon has not been specifically implicated as a carcinogenic agent given that its ethanolic extract was shown to be no mutagenic, caustic chemical irritants acting through cytotoxic mechanisms can have carcinogenic activity when excessive doses exceed threshold levels. Of some concern is the case in which first- and second-degree burns were convincingly linked to cinnamon oil exposure (Dugoua et al., 2007). No health hazards or side effects are known as conjunction the proper administration of designated therapeutic dosages (Wichtl *et* Anton, 1999; PDR, 1998; Van Hellemont, 1986). Orally, cassia cinnamon appears to be well-tolerated. No significant side effects have been reported in clinical trials (Anonymous, 2009m; Barnes et al., 2007b; PDR, 1998). Additionally, there is some concern about the safety of ingesting large amounts of cassia cinnamon due to its coumarin content. Coumarin can cause hepatotoxicity in animal models. In humans, very high doses of coumarin from 50-7000 mg/day can result in hepatotoxicity that resolves when coumarin is discontinued. In most cases, ingestion of cassia cinnamon won't provide a high enough amount of coumarin to cause significant toxicity; however, in especially sensitive people, such as those with liver disease, prolonged ingestion of large amounts of cassia cinnamon might exacerbate the condition (Anonymous, 2009m).

## Contraindications and warnings

Do not administer orally or topically, the essential oil (*C. verum)* to people with respiratory allergies or with known hypersensitivity to this or other aromatic products. Do not use with vanilla (Cunha et al., 2003a; Fitoterapia, 1998) neither Peru balsam (Cunha et al., 2003a; Fitoterapia, 1998; WHO, 1999a) because they may have cross-reaction (Fitoterapia, 1998). Preparations with cinnamon should not use it in case of gastric ulcer or intestinal ulcer (Cunha et al., 2003a; Fitoterapia, 1998; WHO, 1999a; Wichtl *et* Anton, 1999). Do not use in case of gastritis, syndrome bowel disease, ulcerous, colitis, *Crohn* disease, hepatopathys, epilepsy, *Parkinson* and other neurologic diseases (Fitoterapia, 1998). The drug is contraindicated in cases of fever of unknown origin (Ooi *et al.,* 2006; WHO, 1999a) and in patients with an allergy to cinnamon (WHO, 1999a). However, clinical safety data and toxicity data for cinnamon and cassia are limited and further investigation of these aspects is required (Barnes et al., 2007b; Barnes *et al.,* 2007a; PDR, 1998).

Beware of the alcohol content in fluid extract, tincture and syrup (Fitoterapia, 1998).

***Pregnancy and lactation***

Available data are not sufficient for an adequate benefit/risk assessment (Anonymous, 2009m; WHO, 1999a; PDR, 1998). Therefore, *Cortex Cinnamomi* should not be used during pregnancy (Anonymous, 2009m; Cunha et al., 2003a; Fitoterapia, 1998; Ooi, *et al.,* 2006; WHO, 1999a; Wichtl *et* Anton, 1999; PDR, 1998). According to Barnes (2007) there are no known problems with the use of cinnamon during pregnancy and lactation, provided that doses do not greatly exceed the amounts used in foods (Newall et al., 1996a; WHO, 1999a). There is one report of teratogenicity of cinnamaldehyde in chick embryos, but studies of teratogenicity in chick embryos are of limited usefulness when evaluating the teratogenic potential for humans. A methanol extract of the drug given by gastric intubation was not teratogenic in rats. Concerning nursing mothers available data are not sufficient for an adequate benefit/risk assessment (WHO, 1999a). It is not known whether the constituents of cassia are secreted into breast milk (Barnes *et al.,* 2007a). Therefore, *Cortex Cinnamomi* should not be used during lactation (WHO, 1999a).

***Pediatric use***

The safety and efficacy of *Cortex cinnamomi* in children have not been established (WHO, 1999a). Do not administer orally or topically, the essential oil (*C. verum)* to children under 6 years-old (Cunha et al., 2003a; Fitoterapia, 1998).

## Interactions with Diseases or Conditions

***Diabetes****:* Cassia cinnamon might lower blood glucose in patients with type 2 diabetes. Tell patients with diabetes to use cassia cinnamon products cautiously and monitor blood glucose levels very closely (Anonymous, 2009m).

***Liver disease****:* There is some concern that ingesting large amounts of cassia cinnamon might cause hepatotoxicity in susceptible people. Cassia cinnamon contains coumarin which can cause hepatotoxicity in animal models. In otherwise healthy humans, very high doses of coumarin from 50-7000 mg/day can result in hepatotoxicity that resolves when coumarin is discontinued. Lower amounts cassia cinnamon might exacerbate liver function in people with existing liver disease (Anonymous, 2009m).

***Surgery**:* Cassia cinnamon might affect blood glucose levels. Theoretically, cassia cinnamon might interfere with blood glucose control during and after surgical procedures. Tell patients to discontinue cassia cinnamon at least 2 weeks before elective surgical procedures (Anonymous, 2009m).

## Drug interactions

### *Antidiabetic drugs*

Although theoretical, the antidiabetic effect of common and cassia cinnamon may have an additive effect with antidiabetic medication and insulin (Dugoua *et al.,* 2007). Patients taking antidiabetic medication or insulin should be monitored by their health care provider when taking common or cassia cinnamon (Anonymous, 2009m; Dugoua *et al.,* 2007). Some antidiabetic drugs include glimepiride, glyburide, insulin, metformin, pioglitazone, rosiglitazone and others (Anonymous, 2009m).

### *Tetracycline*

*C. cassia* bark extract (2 g in 100 ml) markedly decreased the *in vitro* dissolution of tetracycline hydrochloride. In the presence of *C. cassia* bark, only 20% of tetracycline was in solution after 30 minutes, in contrast to 97% when only water was used. However, the clinical significance of this interaction has not been established (WHO, 1999a).

## Interactions with Herbs & Supplements

***Hepatotoxic herbs and supplements**:* There is some concern that ingesting large amounts of cassia cinnamon might cause hepatotoxicity in some people. Theoretically, concomitant use with other potentially hepatotoxic products might increase the risk of developing liver damage. Some of these products include androstenedione, chaparral, comfrey, dehydroepiandrosterone (DHEA), germander, kava, niacin, pennyroyal oil, red yeast and others (Anonymous, 2009m).

***Herbs and supplements with hypoglycemic potential***: Cassia cinnamon might lower blood glucose levels. Theoretically, it might have additive effects when used with other herbs and supplements that also lower glucose levels. This might increase the risk of hypoglycemia in some patients. Some herbs and supplements with hypoglycemic effects include alpha-lipoic acid, bitter melon, chromium, devil's claw, fenugreek, garlic, guar gum, horse chestnut, *Panax ginseng*, psyllium, Siberian ginseng and others (Anonymous, 2009m).

***Other interactions***

Cortex *Cinnamomi Cassiae* (Rou Gui) antagonizes *Halloysirum Rubrum* (Chi Shi Zhi) (CP, 2005b; WHO, 1999a; Wu, 2005b). Chinese cassia bark is averse to red kaoline (Anonymous, 2009f).

## Interactions with Laboratory Tests

***Blood glucose***

Cassia cinnamon might lower blood glucose levels and test results in some patients (Anonymous, 2009m).

***Liver function tests***

There is some concern that ingesting large amounts of cassia cinnamon might increase liver enzymes and cause hepatotoxicity in some people due to coumarin content (Anonymous, 2009m).

## Dosage forms

Crude plant material, powder, volatile oil and other galenic preparations (WHO, 1999a). Mode of administration: comminuted bark for infusions, essential oil, as well as other galenic preparations for internal use (PDR, 1998).

## Posology

***Crude drug***

Average daily dose: 2-4g (Cunha et al., 2003a; PDR, 1998; WHO, 1999a).

***Infusion***

1-3g per cup, boil for 2 minutes and infusion for 10 min. (Fitoterapia, 1998) 3 cups a day, before meals (Cunha et al., 2003a; Fitoterapia, 1998) or 0.5-1.0g as an infusion three times daily (Barnes *et al.,* 2007a; Cunha et al, 2003; Newall et al., 1996a; Van Hellemont, 1986).

***Fluid extract***

30-50 drops, 1-3 times/day (Fitoterapia, 1998).

***Essential oil***

2 or 3 drops, on a lump of sugar, or in capsules with 25-50mg, 1-2 times/day (Cunha et al., 2003a) or 3 times/day (Fitoterapia, 1998), before meals (Cunha et al., 2003a; Fitoterapia, 1998). 0.05-0.2mL three times daily (Barnes et al, 2007a; Newall et al., 1996a). Average daily dose, 0.05–0.2g (Cunha et al., 2003a; WHO, 1999a; PDR, 1998).

***Syrup (10% of tincture***

1-3 tablespoon/day (Fitoterapia, 1998).

***Tincture* (1:5)**

Produced from 1 part of the drug and 5 parts of ethanol (70 per cent *V/V*) by an appropriate procedure (EP, 2005), 50-100 drops, 1-2 times/day (Cunha et al., 2003a) or XX to XL drops several times a day (Van Hellemont, 1986b), 2-4ml (Barnes et al., 2007b).

***Pulvis cinnamomi***

500mg to 1g (Van Hellemont, 1986a), or 250-500mg per capsule (Cunha et al., 2003a), 3-5 times/day (Van Hellemont, 1986a), 1-2 times/day (Cunha et al., 2003a) or 1-3 times/day (Fitoterapia, 1998).

***Infusion for external use***

5g/cup (Cunha et al., 2003a). Boil 10 min, applied with compressing pad, collutory, irrigation or instillation (Fitoterapia, 1998).

***Tincture for external use* (1:10)**

Apply locally (Cunha et al., 2003a; Fitoterapia, 1998).

***Essential oil for external use***

Diluted to 5% in almond oil: 2-3 applications per day (Cunha et al., 2003a; Fitoterapia, 1998).

***Aqua cinnamomi***

1 tablespoon per shot (Van Hellemont, 1986b).

### Storage

Cool, dry conditions in well-sealed (PDR, 1998), well-filled airtight containers (Sweetman, 2009b). Use glass or metal container (do not use plastic). Keep away from light (FP, 2005; Sweetman, 2009b; WHO, 1999a; Wichtl *et* Anton, 1999), humidity (FP, 2005; WHO, 1999a; Wichtl *et* Anton, 1999) and heat (Sweetman, 2009b). According to Chinese Pharmacopoeia (2005b) should be preserved in a cool and dry place.

## 7.3.b. *Ramuli Cinnamomi cassia*

Cinnamon twig (Guizhi) is the tender twigs of the bushy evergreen tree *Cinnamomum cassia* Presl. (Fig. 45) (Anonymous, 2009f; Ganzhong et al., 2003d), of the Lauraceae family. Native to Sri Lanka (Ceylon cinnamon--Cinnamomum zeylanicum Bl.), the neighboring Malabar Coast of India and Myanmar (Burma), it is also cultivated in South America and the West Indies for the spice consisting of its dried inner bark. The Chinese herb cinnamon twigs are mainly produced in the Chinese provinces Guangdong, Guangxi and Yunnan (Anonymous, 2009f; Yanfu, 2002c). The spice is light brown in color and has a delicately fragrant aroma and warm, sweet flavor (Anonymous, 2009f).

The medicinal parts of the plant are collected in spring and summer, and dried in the sun (Anonymous, 2009f; Ganzhong et al., 2003d; Yanfu, 2002) or in the shade after the leaves have been removed. Before clinical use, they are further processed into slices or small pieces by soaking, softening, cutting, and drying in the shade or in the sun (Fig. 46) (Ganzhong et al., 2003d; Yanfu, 2002).

**Fig. 45.** Cinnamon twigs

(adapted from http://www.asante-academy.com/ke-explains/medicinesa-z/cassiatwig.htm) (visited on 8/5/2009).

**Fig. 46.** Cinnamon processed twigs

(adapted from http://www.nmbm.com.cn/www/nmbm/en/cp/productDetail.jsp?productId=1470 (visited on 8/5/09)

## Chemical constituents

Cinnamic oil is the active component of guizhi. It consists of cinnamaldehyde, cinnamic acid, and a small amount of cinnamyl acetate and phenylpropyl acetate (Ganzhong et al., 2003d). In a recent study performed by Kaul *et al.* (2003) different parts of the *C. verum* plant were analyzed by gas chromatography (GC) and GC/mass spectrometry (GC/MS). The essential oil yield was 0.40% for the tender twigs. This oil was richer in α-phellandrene, limonene and (E)-cinnamaldehyde comparing to the oil of other different parts of the plant as pedicels of buds and flowers, from buds and flowers, from pedicels of fruits and from fruits.

In 2001, Xu *et al.* performed a gas chromatography on an essential oil from cinnamon cassia twigs prepared in accordance with to the standard method of extraction in the Chinese Pharmacopoeia. All the qualitative results are shown in Table 3. The components identified account for 89.55% of the total content of the sample. Unfortunately, 31 components remain unidentified, because of the low signal-to-noise ratio or the absence of the compound from the mass spectra database. The compound present in largest amount is *E*- 3-Phenyl-2-propenal (cinnamaldehyde) (50.43%). Other referring compounds are: benzaldehyde (Fig. 47) (2.90%), 1-ethenyl-4-methoxybenzene (Fig. 48) (3.77%), 3-(2-methoxyphenyl) 2-propenal (2-methoxycinnamaldehyde) (4.72%), hexadecanoic acid (Fig. 49) (4.31%) (Xu *et al.,* 2001).

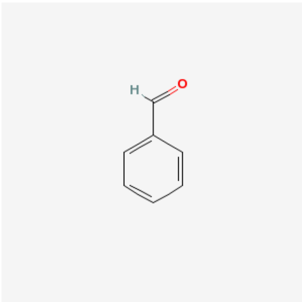


**Fig. 47.** Chemical structure of benzaldehyde (adapted from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?sid=11528246&loc=es_rss) (visited on 7/12/09)

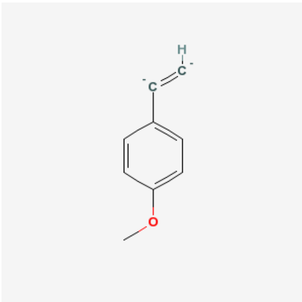


**Fig. 48.** Chemical structure of 1-ethenyl-4-methoxybenzene (adapted from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?sid=80512878&loc=es_rss) (visited on 7/12/09)

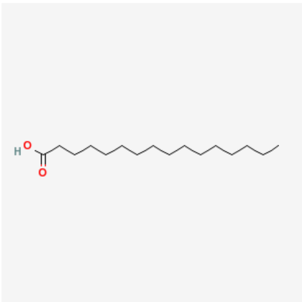


**Fig. 49.** Chemical structure of hexadecanoic acid (palmitic acid) (adapted from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?sid=85088443&loc=es_rss) (visited on 7/12/09)

**Table 3.** Composition of the essential oil from *Ramulus cinnamomi* (adapted from Xu *et al.*, 2001)

| Retention time (min) | Compound name | Formula | Content (%) |
|---|---|---|---|
| 8.288 | 1-Methylheptane | $C_8H_{18}$ | 0.04 |
| 8.310 | 1-Methylethylbenzene | $C_9H_{12}$ | 0.62 |
| 8.345 | 2,4-Dimethylhexane | $C_8H_{18}$ | 0.06 |
| 8.616 | 3,7-Dimethyl-*E*-1,3,6-octatriene | $C_{10}H_{16}$ | 0.49 |
| 8.754 | Benzaldehyde | $C_7H_6O$ | 2.90 |
| 8.918 | Camphene | $C_{10}H_{16}$ | 0.28 |
| 9.445 | Methylheptenone | $C_8H_{14}O$ | 0.14 |
| 9.525 | β-Myrcene | $C_{10}H_{16}$ | 0.07 |
| 9.842 | Octanal | $C_8H_{16}O$ | 0.09 |
| 10.695 | 1,3,8-*p*-Menthatriene | $C_{10}H_{14}$ | 0.16 |
| 10.769 | 4-Hydroxybenzaldehyde | $C_7H_6O_2$ | 0.09 |
| 10.973 | Limonene | $C_{10}H_{16}$ | 0.20 |
| 11.593 | Acetophenone | $C_8H_8O$ | 0.46 |
| 11.667 | 2-Methylbenzaldehyde | $C_8H_8O$ | 0.19 |
| 12.027 | 3-Methylbenzaldehyde | $C_8H_8O$ | 0.10 |
| 13.040 | 2-Octen-l-ol | $C_8H_{16}O$ | 0.21 |
| 13.416 | Phenylethyl alcohol | $C_8H_{10}O$ | 0.01 |
| 14.156 | 1-Ethenyl-4-methoxybenzene | $C_9H_{10}O$ | 3.77 |
| 14.700 | Benzenepropanal | $C_9H_{10}O$ | 0.85 |
| 14.891 | 1-Phenyl-1,2-propanedione | $C_9H_8O_2$ | 0.18 |
| 15.565 | Linderol | $C_{10}H_{16}O$ | 0.77 |
| 16.259 | Terpineol | $C_{10}H_{18}O$ | 0.23 |
| 16.758 | 3-Phenyl-2-propenal | $C_9H_8O$ | 1.52 |
| 20.508 | *E*- 3-Phenyl-2-propenal | $C_9H_8O$ | 50.43 |
| 23.383 | α-Copaene | $C_{15}H_{24}$ | 0.89 |
| 23.741 | β-Elemene | $C_{15}H_{24}$ | 0.13 |
| 24.562 | Coumarin | $C_9H_6O_2$ | 0.43 |
| 24.687 | 7,11-Dimethyl-3-methylene-1,6,10-dodecatriene | $C_{15}H_{24}$ | 0.62 |
| 26.385 | (–)-α-Neoclovene | $C_{15}H_{24}$ | 0.62 |
| 26.505 | Curcumene | $C_{15}H_{24}$ | 0.98 |
| 27.164 | Naphthalene | $C_{15}H_{24}$ | 0.79 |
| 27.779 | 3-(2-Methoxyphenyl)2-propenal | $C_{10}H_{10}O_2$ | 4.72 |
| 29.185 | Nerolidol | $C_{15}H_{26}O$ | 0.36 |
| 29.495 | Palustrol | $C_{15}H_{26}O$ | 0.48 |
| 29.699 | 1-Naphthalenol | $C_{15}H_{26}O$ | 1.26 |
| 29.899 | (*E*)-Spathulenol | $C_{15}H_{24}O$ | 0.44 |
| 30.305 | Hexamethyl-1,3,5-cyclononatriene | $C_{15}H_{24}$ | 0.71 |
| 30.523 | Tetradecanal | $C_{14}H_{28}O$ | 2.15 |
| 32.814 | α-Bisabolol | $C_{15}H_{26}O$ | 1.61 |
| 32.962 | 2-Tetradecanal | $C_{14}H_{28}O$ | 0.22 |
| 35.158 | Tetradecanoic acid | $C_{14}H_8O_2$ | 1.50 |
| 35.434 | 9-Octadecenal | $C_{18}H_{34}O$ | 0.84 |
| 36.096 | Hexadecanol | $C_{16}H_{34}O$ | 0.62 |
| 36.580 | 2-Phenylethyl ester benzoic acid | $C_{15}H_{14}O_2$ | 0.18 |
| 37.662 | Pentadecanoic acid | $C_{15}H_{30}O_2$ | 0.75 |
| 40.530 | Hexadecanoic acid | $C_{16}H_{32}O_2$ | 4.31 |
| 44.404 | Oleic acid | $C_{18}H_{34}O_2$ | 1.08 |

Total content=89.55%

## Pharmacological actions

### *Vasodilator and diaphoretic effects*

Guizhi itself only has a weak diaphoretic effect (Ganzhong et al., 2003d). Cinnamic oil can expand blood vessels, regulate blood circulation, and make the blood flow toward the superficial part of the body (Ganzhong et al., 2003d).

### *Anti-infectious effects*

Tests *in vitro* have shown that water decoction of Guizhi and alcohol extract solution of *guizhi* can inhibit certain kinds of pathogenic bacteria; cinnamic oil and cinnamaldehyde can inhibit *Mycobacterium tuberculosis*. In addition, Guizhi has been proven to have an inhibitory effect on influenza virus and orphan virus (Ganzhong et al., 2003d).

### *Antipyretic and analgesic effects*

The active components cinnamaldehyde and cinnamic acid of Guizhi, and the Guizhi Decoction can lower increased body temperature of animals. This is related to the effects of expanding blood vessels in the skin, and promoting diaphoresis and heat dispersal. Guizhi can also increase the pain threshold, and the drug may produce a better analgesic effect when is included in a recipe (Ganzhong et al., 2003d).

### *Sedative and anticonvulsive effects*

The active component cinnamaldehyde can reduce the autonomic activities of mice and prolong the survival time of mice with titanic convulsions caused by strychnine (Ganzhong et al., 2003d).

### *Antiallergic effect*

Guizhi may inhibit the release of sensitizer from mastocytes caused by IgE (Ganzhong et al., 2003d).

## Storage

According to Chinese Pharmacopoeia (2005c) cinnamon twigs should be preserved in a cool and dry place.

## Ramuli *versus* Cortex

Many pharmacological investigations have been carried out on *Cinnamomi Cortex.* These studies have either looked at the volatile oil, in particular the major constituent cinnamaldehyde, or at parts excluding the oil (Newall et al., 1996a). Actions observed for essential oil-free aquous extracts have been reported to be weak (Barnes et al, 2007a; Newall et al., 1996a). This is suggestive that essential oil contributes to the pharmacological effects (Barnes et al, 2007a). Shen *et al.* (2002) performed a comparison study on the two different essential oils. Essential oil from *Ramulus Cinnamomi* and *Cortex Cinnamomi* (*Cinammomum cassia* Prels.) were obtained by steam distillation. The chemical components of the oil were examined and compared by means of gas chromatography- mass spectrometry (Table 4).

**Table 4.** Chemical components of the oil (GC- MS) (adapted from Shen *et al.*, 2002)

| | | | **Relative amount of %** | **Relative amount of %** |
|---|---|---|---|---|
| **Number** | **Compound name** | **Retention time** | ***Ramuli cinnamomi cassiae* oil** | ***Cortex cinnamomi* oil** |
| 1 | α-pinene | 2.5 | - | 0.07 |
| 2 | phenylethylene | 2.81 | - | 0.1 |
| 3 | β-pinene | 3.1 | - | 0.03 |
| 4 | limonene | 3.62 | - | 0.06 |
| 5 | *p*-cymene | 3.99 | - | 0.07 |
| 6 | **benzaldehyde** | 4.37 | **1.1** | **0.59** |
| 7 | 2-hydroxy-phenylaldehyde | 5.87 | 0.17 | - |
| 8 | phenylacetaldehyde | 6.05 | 0.06 | 0.02 |
| 9 | acetophenone | 6.47 | 0.21 | 0.04 |
| 10 | 2-methoxyphenol | 6.81 | 0.03 | - |
| 11 | 4-acetyl-1-methylcyclohexene | 6.91 | 0.04 | 0.04 |
| 12 | camphol | 7.26 | 0.62 | 0.66 |
| 13 | phenethyl alcohol | 7.52 | 0.24 | - |
| 14 | α-terpineol | 7.63 | 0.21 | 0.27 |
| 15 | 2-methyl-benzofuran | 8.02 | - | 0.03 |
| 16 | 2'-hydroxy-acetophenone | 8.82 | 0.03 | - |
| 17 | phenylpropyl aldehyde | 9.05 | 1.7 | 1.23 |
| 18 | 3-methyl acetophenone | 9.16 | 0.09 | 0.04 |
| 19 | citral | 10.01 | 0.06 | - |
| 20 | phenylpropanol | 10.55 | 0.41 | - |
| 21 | Not translated | 10.58 | - | 0.48 |
| 22 | *trans*-cinnamaldehyde | 10.8 | 3.19 | 3.44 |
| 23 | 2-methoxybenzaldehyde | 11.53 | 0.48 | - |
| 24 | α-cedrene | 12.23 | 0.03 | - |
| 25 | **cinnamaldehyde** | 13.33 | **64.57** | **83.1** |
| 26 | cinnamyl alcohol | 13.66 | 0.82 | 1.04 |
| 27 | caryophyllic acid (eugenol) | 14.14 | 0.54 | - |
| 28 | γ-cadinene | 14.62 | 0.29 | 0.16 |
| 29 | β-bisabolene | 15.07 | 0.22 | 0.11 |
| 30 | curcumene | 15.31 | 0.24 | 0.09 |
| 31 | α-muurolene | 15.54 | 0.21 | 0.29 |
| 32 | 1,5-dimethyl-naphthalene | 16.69 | 0.11 | - |
| 33 | δ-cadinene | 16.86 | 0.21 | 0.3 |

| | | | | |
|---|---|---|---|---|
| 34 | cadinene | 17.25 | - | 0.08 |
| 35 | cinnamic acid | 17.71 | 0.1 | 0.08 |
| 36 | *trans*-cinnamyl acetate | 18.37 | 1.31 | 0.92 |
| 37 | myristic aldehyde | 19.67 | 0.05 | - |
| 38 | paeonol | 20.03 | - | 0.63 |
| 39 | calacorene | 20.29 | 0.11 | 0.09 |
| 40 | methoxy cinnamaldehyde | 21.19 | 0.4 | 0.13 |
| 41 | spathulenol | 22.2 | 1.12 | 0.15 |
| 42 | oxy-caryophyllene | 22.62 | 0.38 | - |
| 43 | benzofuran | 23.48 | - | 0.32 |
| 44 | coumarin | 23.54 | 0.94 | - |
| 45 | aromadendrene | 23.93 | 0.1 | - |
| 46 | 1,2,3,4,4a,7-hexahydro-1,6-dimethyl-naphthaline | 24.54 | 0.22 | 0.32 |
| 47 | calamene;calarene | 24.97 | 0.37 | 0.06 |
| 48 | cadinol | 26.48 | 0.3 | 0.5 |
| 49 | bisabolol | 26.86 | 0.23 | - |
| 50 | **2-methoxy-cinnamaldehyde** | 28.28 | **12.72** | **2.61** |
| 51 | *cis*-farnesol | 31.81 | 0.16 | - |
| 52 | 1,4-dimethyl-7-(1-Methylethyl)-anthracene | 32.36 | 0.38 | 0.24 |
| 53 | hexadecanoic acid | 39.73 | 0.15 | 0.12 |
| 54 | benzyl benzenecarboxylate | 40.03 | 0.27 | 0.1 |

Fifty four of the separated constituents were identified. Ten components of these were not observed in the oil of *Ramulus Cinnamomi*, and sixteen components of these were not observed in the oil *Cortex Cinnamomi.* Cinnamaldehyde was the main component for both herbs, followed by benzaldehyde, trans-camphol, phenylpropyl aldehyde, trans-cinnamaldehyde, 2-methoxy-cinnamaldehyde, trans-cinnamyl acetate, and others (Shen *et al.,* 2002). The minor different components found in both of oils have no significant expression, as they commonly exist in nature, and they relative amount (%) is not relevant. What is interesting is the difference between the content of cinnamaldehyde 64.57 % for *Ramuli cinnamomi cassiae* oil and 83.1% for the *Cortex*. Also relevant is the difference between the content of 2-methoxy-cinnamaldehyde (12.72 % for *Ramuli cinnamomi cassiae* oil and 2.61 % for the *Cortex cinnamomi* oil).

## 7.3.1. *Cortex cinnamomi cassiae* (肉桂) according to Traditional Chinese Medicine

The source is from the bark of *C. cassia* Presl., family Lauraceae. In China, the medicinal material is mainly produced in the areas of Guangdong, Guangxi, and Yunnan, etc. (Yanfu, 2002d). The bark is cut *in situ* before mid-summer, and peeled in early autumn.

After the cork is removed, the bark is dried in the shade, and sliced or ground to prepare a powder as a raw product for clinical application. The dry bark with the cuticle removed is called *Rouguixin*, and the bark peeled from a thick branch of an old tree or from the thin stem of a young tree is called *Guangui* (Ganzhong et al., 2003c).

### Common name

Cassia bark (CP, 2005b; Gongwang, 2001b).

### Pharmaceutical name

*Cortex cinnamomi cassiae* (Gongwang, 2001b).

### Botanical name

Cinnamomum cassia Presl. (Gongwang, 2001b).

### Pynin name

Rou Gui (Chu, 2009; Flaws, 1999e; Leite, 2005b), Rougui (Ganzhong et al., 2003c; Gongwang, 2001b; Greten, 2007; Yanfu, 2002d).

### Part used

Inner bark of the tree (Tierra, 1997b). Rougui is the thick bark of the trees (Chu, 2009), or the bark of the trunk or thick branches of *C. cassia* (Ganzhong et al., 2003c).

### Classification

Warms the kidney and conduits. Belongs to the group "*Tepefacientia intimae*-IX)" (Greten, 2007), i.e. "Herbs that Warm the Interior and Expel Cold" (Anonymous, 2009n).

### Sapor & Temperature

Pungent (Anonymous, 2009f; Chu, 2009; Flaws, 1999d; Ganzhong et al., 2003c; Gongwang, 2001b; Leite, 2005b; Greten, 2007; Tierra, 1997b; Yanfu, 2002d), sweet (Anonymous, 2009f; Chu, 2009; Flaws, 1999d; Ganzhong et al., 2003c; Gongwang, 2001b; Greten, 2007; Leite, 2005b; Tierra, 1997b; Yanfu, 2002d) warm (Flaws, 1999d; Ganzhong et al., 2003c; Leite, 2005b; Tierra, 1997b), hot (Anonymous, 2009f; Chu, 2009; Flaws, 1999d; Ganzhong et al., 2003c; Gongwang, 2001b; Greten, 2007; Yanfu, 2002d).

### Orbs

Cardial, lienal, renal, hepatic (Anonymous, 2009f; Flaws, 1999d; Ganzhong et al., 2003c; Gongwang, 2001b; Greten, 2007; Leite, 2005b; Tierra, 1997b).

## Functions

Supplements fire and restores yang (Anonymous, 2009f; CP., 2005b; Gongwang, 2001b; Yanfu, 2002d), dispels cold and kills pain (Anonymous, 2009f; CP., 2005b; Gongwang, 2001b; Yanfu, 2002d)as well as warms the channels (Anonymous, 2009f; Gongwang, 2001b; Yanfu, 2002d) and removes obstruction in the collaterals. The addition of cassia bark into a recipe to nourish qi and replenish xue, can stimulate the growth of qi and xue (Anonymous, 2009f) and promotes the xue circulation (Yanfu, 2002d).

## Indications

Cinnamon bark alleviates an aversion to cold, cold limbs (CP, 2005b; Gongwang, 2001b; Tierra, 1997b); weak back; impotence; frequent urination; abdominal pain and spasms caused by algor; weak appetite, diarrhea, wheezing, and rheumatism caused by algor. Also improves digestion and warms the interior (Tierra, 1997b). Used in arthralgia due to cold and dampness pathogens, and lumbago (Ganzhong et al., 2003c). Used for sores and welling abcesses in the external medicine department categorized as qi and blood vacuity cold (Flaws, 1999d). Can be used to treat all pains due to accumulation of cold and stagnation of qi or xue stasis (Yanfu, 2002d). It´s used to treat impotence and retention of cold in the uterus due to the deficiency of spleen-yang, palpitations with asthma of the insufficiency type, etc. (Anonymous, 2009f), to treat cold pain in the chest and abdomen and cold hernia with pain, in cold pain in the abdomen due to invasion of cold into the interior or deficiency-cold in the spleen and stomach, vomiting with abdominal pain, cold limbs and loose stools (Anonymous, 2009f), cold pain in the epigastrium, poor appetite (Gongwang, 2001b) due to yang deficiency of the spleen and kidneys, cold hernia (Anonymous, 2009f). To treat lumbago with arthralgia due to cold, obstruction of qi in the chest and deep-rooted carbuncles, lumbago with arthralgia due to cold, epigastric pain due to obstruction of qi in the chest as a result of suppression of chest yang and invasion of pathogenic cold into the interior, deep-rooted carbuncles due to deficiency of yang and stagnation of cold (Anonymous, 2009f). To treat xue stasis due to accumulation of cold (Gongwang, 2001b), amenorrhea and dysmenorrhea (Anonymous, 2009f; Gongwang, 2001b). To treat weakness due to prolonged illness and insufficiency of qi and blood (Anonymous, 2009f).

## Chinese therapeutic actions and examples of major combinations

- Cassia bark can replenish fire and yang, expel cold pathogens, relieve pain and warm channels and blood vessels to treat deficiency of kidney yang and declination of fire in the life gate when the drug is prescribed with aconite side root, prepared rehmannia root and dogwood fruit (*Fructus Corni*) (Shanzhuyu) in the Pill of Eight Drugs Including Cassia Bark and Aconite Root (Gulf Bowie Wan) (Ganzhong et al., 2003c).

- In the Pill of Cassia Bark and Aconite Root for Adjusting the Middle Energizer (Guifi Lizhong Wan), cassia bark is prescribed with aconite side root, dry ginger, and bighead atractylodes tuber to treat deficiency of spleen and kidney yang (Ganzhong et al., 2003c).
- For insufficiency of kidney-yang with impotence, chilliness, soreness and coldness of loins and knees, frequent micturition, seminal emission, and enuresis, etc., it is usually used in combination with *Radix Aconiti Lateralis Praeparata* (Fuzi), *Rhizoma Rehmanniae Preaparatae* (Shoudihuang) (Gongwang, 2001b; Yanfu, 2002d), and *Fructus Corni* (Shanzhuyu), etc., such as Shenqi Wan (Pill) (Yanfu, 2002d).
- For syndrome with deficiency and weakness of kidney-yang and up-floating of deficiency-yang, the herbal medicine can be used in combination with *Radix Aconiti Lateralis Praeparata* (Fuzi) so as to direct fire to its source (Yanfu, 2002d).
- With *Radix Aconiti Lateralis Praeparata* (Fuzi), Lagerhead Atractylodes Rhizome (Baizhu) for deficiency of spleen and kidney yang (Gongwang, 2001b).
- With Prepared Rhizome of Adhesive Rehmania (Shoudihuang), Chinese Angelica Root (Danggui) for xue stasis due to accumulation of cold, abdominal pain of amenorrhea (Gongwang, 2001b).
- With Argy Wormwood Leaf (Aiye), Chinese Angelica Root (Danggui) for deficiency cold of qi and xue, dysmenorrhea (Gongwang, 2001b).
- With Chinese Taxillus Twig (Sangjisheng), Eucommia Bark (Duzhong) for pain in the loins due to cold arthralgia (Gongwang, 2001b).
- With Mulberry Leaf (Sangye), Doubleteeth Pulbescent Angelica Root (Duhuo) for arthralgia (Gongwang, 2001b).
- With Common Anemarrhea Rhizome (Zhimu), Chinese Corktree Bark (Huangbai) for diabetes and urine retention, uroschesis due to deficiency of the kidney (Gongwang, 2001b).
- With Prepared Rhizome of Adhesive Rehmania (Shoudihuang), Ginseng (Renshen) for palpitation, shortness of breath due to deficiency of both qi and blood (Gongwang, 2001b).
- With Prepared Rhizome of Adhesive Rehmania (Shoudihuang), Antler Glue (Lujiaijiao) for chronic carbuncle of yin type, un-rupted swelling abcess or slow-healing carbuncles (Gongwang, 2001b).

- With Tuber Fleeceflower Root (Heshouwu), Ass-hide Glue (Ejiao) for anemia (Gongwang, 2001b).
- Add Yanhusuo, Chinese Angelica Root (Danggui) for cold pain of the lower abdomen (Gongwang, 2001b).
- Add Coptidis Rhizome (Huanglian) for irritability, insomnia, soreness of loin and knees due to failure of the heart and kidney to integrate, and it is also used to treat choric diarrhea (Gongwang, 2001b).
- With White Peony Root (Baishaoyao) to suppress the liver yang (Gongwang, 2001b).
- For deficiency and coldness of the spleen and stomach marked by cold pain in epigastric abdomen, it can be used alone or together with *Rhizoma Zinziberis* (Ganjiang) and *Rhizoma Alpiniae Officinarum* (Gaoliagjiang) (Yanfu, 2002d).
- For colic of cold type with abdominal pain, usually combined *Radix Angelicae Sinensis* (Danggui) and *Rhizoma Chuanxiong* (Chuanxiong), etc. (Yanfu, 2002d).
- Powder of cassia bark or combined Chinese angelica root (*Radix Angelica Sinensis*, Danggui) and Sichuan lovage (*Rhizoma Ligustici*, Chuanxiong) can be taken by mouth to treat algor and pain in the epigastric region (Ganzhong et al., 2003c).
- In the Yang Activating Decoction (Yanghe Tang), cassia bark is combined with prepared rehmannia root, deer horn glue and ephedra to treat cellulitis of yin type (Ganzhong et al., 2003c).
- Cassia bark can be prescribed with milk vetch root (*Radix Astragali seu Hedysari*, Huangqui) and angelica root to treat deficiency of qi (Ganzhong et al., 2003c).
- For yin flat abscesses and chronic swellings with no head which are not red or hot, *Cortex Cinnamomi Cassiae* is commonly combined with uncooked *Radix Rehmanniae* (Shu Di), *Gelatinum Cornu Cervi* (Lu Jiao Jiao), and *Herba Ephedrae* (Mahuang) as in Yang He Tang (Yang Harmonizing Decoction) (Flaws, 1999d).
- For pudendal carbuncle and pyocutaneous disease of deficient-cold type that has not been healed for a long time, it is combined with *Colla Cornus Cervi* (Lujiaojiao), *Rhizoma Zinziberis Preparata* (Paojiang), and *Herba Ephedrae* (Mahuang), etc. Such as Yanghe Tang (Yanfu, 2002d).
- Combined with *Radix Astragali* (Huangqi), *Radix Angelicae Sinensis* (Danggui), etc., such as Tuoli Huagqi San (Powder) (Yanfu, 2002d).
- For welling abscesses and swellings which have produced pus but have not ruptured or, if after rupturing, endure without restraining and constraining, *i.e.*, closing, *Cortex Cinnamomi Cassiae* is commonly combined with *Radix Astragali*

*Membranacei* (Huang Qi) and *Radix Angelicae Sinensis* (Dang Gui) as in *Tuo Li Huang Qi Tang* (Out-thrust the Interior Astragalus Decoction) (Flaws, 1999d).

- To treat impotence and retention of cold in the uterus due to the deficiency of spleen-yang, palpitations with asthma of the insufficiency type, etc. Chinese cassia bark is mostly used together with *Radix Aconiti Praeparata* (monkshood root), prepared rehmannia, shelled medicinal cornel fruit (*Fructus Corni*), etc., e.g., Shenqi Wan, You Gui Yin (Anonymous, 2009f).
- Cold pain in the abdomen due to invasion of cold into the interior or deficiency-cold in the spleen and stomach: Chinese cassia bark can be ground alone into powder and decocted with wine for oral administration or used together with dried ginger, lesser galangal (*Rhizoma Alpiniae Officinarum*), long pepper (*Fructus Piperis Longi*), etc. (Anonymous, 2009f).
- Vomiting with abdominal pain, cold limbs and loose stools due to yang deficiency of the spleen and kidneys: Chinese cassia bark is often used together with monkshood root (*Radix Aconiti Praeparata*), ginseng, dried ginger, etc., e.g., Gui Fu Lizhong Wan (Anonymous, 2009f).
- Lumbago with arthralgia due to algor: this herb is mostly used together with angelica root (*Radix Angelicae Pubescentis*), parasitic loranthus, eucommia bark, etc., e.g., Duhuo Jisheng Tang (Anonymous, 2009f).
- Epigastric pain due to obstruction of qi in the chest as a result of suppression of chest yang and invasion of pathogenic cold into the interior: Chinese cassia bark can be used together with monkshood root (*Radix Aconiti Praeparata*), dried ginger, zanthoxylum, etc. (Anonymous, 2009f).
- Deep-rooted carbuncles due to deficiency of yang and stagnation of cold: Chinese cassia bark can be used together with deerhorn glue, blast-fried ginger, ephedra, etc., e.g., Yang He Tang (Anonymous, 2009f).
- To treat amenorrhea and dysmenorrhea: Chinese cassia bark can be used together with Chinese angelica, chuanxiong (*Rhizoma Ligustici Chuanxiong*), fennel, etc., e.g. as Shaofu Zhuyu Tang (Anonymous, 2009f).

## Dosage and method of use

Cinnamon bark is usually taken by powder or pill, since decoction causes a loss of volatile oils. If this herb is decocted, prepare it for 5 minutes (maximum); crushed it into small pieces (Leite, 2005b; Tierra, 1997b). According to Flaws (1999d), when decocted, add later. It may also be ground into powder and washed down with the rest of the decocted prescription, taking 1-2g each time.

The dosage varies between 0.9 to 5g according to different authors:

- Use 1.5-4.5 g (Leite, 2005b; Gongwang, 2001b; Tierra, 1997b);
- 1-5g (Chu, 2009; Flaws, 1999d) used as powder form or added to the decoction when they are ready for use (Chu, 2009);
- 2-5g. It should be decocted later or administered separately. Grind it into powder for oral administration with boiled water (Anonymous, 2009f);
- 2-5g is used in decoction for oral use and decocted later or soaked in water for taking;
- 1-2g of the powder is taken after it is mixed with water (Yanfu, 2002d);
- 1-1.5g each time with water (Gongwang, 2001b);
- 0.9-3g decocted (Greten, 2007).
-1-4.5g (CP, 2005b).

### Precautions and contraindications

Because this medicinal is acrid and hot and stirs the blood, it is contraindicated in those with yin vacuity fire effulgence, those with interior replete heat (Flaws, 1999d; Leite, 2005b), and in pregnant women (CP, 2005b; Flaws, 1999d; Gongwang, 2001b; Leite, 2005b; Tierra, 1997b; Yanfu, 2002d). Do not use this herb in the presence of deficient heat (Tierra, 1997b), excessive heat (Gongwang, 2001b; Tierra, 1997b). Contraindicated for bleeding due to blood heat (Gongwang, 2001b; Tierra, 1997b; Yanfu, 2002d), and used with caution for hypermenorrhea (Yanfu, 2002d). Contraindicated in patients with hyperactivity of fire caused by yin deficiency (Gongwang, 2001b).

## 7.3.2. *Ramuli cinnamomi cassiae* (桂枝) according to Traditional Chinese Medicine

The source is from the tender branch of *C. cassia* Presl, family Lauraceae. Its producing areas are mainly the provinces of Guangdong, Guangxi, and Yunnan. The medicinal material is collected in spring and summer, and dried in shade or in the sun, then is cut into pieces or segments for use (Ganzhong et al., 2003c; Yanfu, 2002c).

### Common Name

Cassia twig (Anonymous, 2009n; Ganzhong et al., 2003d; Gongwang, 2001c), cinnamon twig (Anonymous, 2009n; Chu, 2009; Liu et Tseng, 2005c; Ganzhong et al., 2003d; Tierra, 1997b).

## Pharmaceutical Name

*Ramulus Cinnamomi* (Ganzhong et al., 2003d; Gongwang, 2001c; Yanfu, 2002c), *Ramuli cassiae* (Greten, 2007), *Ramulus Cinnamomi Cassiae* (Anonymous, 2009n; Chu, 2009; Flaws, 1999e).

## Pynin name

Gui Zhi (Anonymous, 2009m; Anonymous, 2009n; Chu, 2009; Liu et Tseng, 2005c; Ni, 1991b; Ody, 2004b; Tierra, 1997b), Guizi (Gongwang, 2001c; Greten, 2007).

## Part used

Twig (Anonymous, 2009n; Greten, 2007; Ganzhong et al., 2003d; Gongwang, 2001c; Ody, 2004b; Tierra, 1997b).

## Classification

Causes sweat and dispels repletion in flesh and extima. Belongs to the group "*Liberantia extimae acria et calida- I a)*" (Greten, 2007), i.e. "Warm, Spicy Herbs that Release the Exterior" (Anonymous, 2009n).

## Sapor &Temperature

Pungent (Anonymous, 2009m; Anonymous, 2009f; Chu, 2009; Ganzhong et al., 2003d; Gongwang, 2001c; Greten, 2007; Liu et Tseng, 2005c; Ni, 1991b; Ody, 2004b; Tierra, 1997b; Yanfu, 2002c), sweet (Anonymous, 2009n; Anonymous, 2009f; Chu, 2009; Ni, 1991b; Gongwang, 2001c; Greten, 2007; Ody, 2004b; Yanfu, 2002c), warm (Anonymous, 2009m; Anonymous, 2009n; Anonymous, 2009f; Chu, 2009; Ni, 1991b; Ganzhong et al., 2003d; Gongwang, 2001c; Greten, 2007; Liu et Tseng, 2005c; Ody, 2004b; Tierra, 1997b; Yanfu, 2002c).

## Orbs

Pulmonal, Cardial, Vesical (Anonymous, 2009m; Anonymous, 2009n; Anonymous, 2009f; Chu, 2009; Ganzhong et al., 2003d; Gongwang, 2001c; Greten, 2007; Leite, 2005c; Liu et Tseng, 2005c; Ni, 1991b; Ody, 2004b; Tierra, 1997b; Yanfu, 2002c).

## Functions

Induces diaphoresis to dispel pathogenic factors from the exterior of the body (Anonymous, 2009f; CP, 2005c; Flaws, 1999e; Ganzhong et al., 2003d), warms the channels to relieve pain, stimulates menstruation, and reinforces Yang to promote the flow of Qi (Flaws, 1999e; Ganzhong et al., 2003d). Balances Ying/Wei Qi, warms channel, disperses wind–cold–damp, circulates Yang Qi, strengthens Heart Yang, warms uterus (Liu et Tseng, 2005c). Warms the channels to ensure the flow of the yang-qi (Anonymous, 2009f). Induces sweating to relieve superficies and activate yang and circulate qi by warming channel (Gongwang, 2001c; Yanfu, 2002c). To get better Yang Qi (Ody, 2004b). To dispel algor **(**Leite, 2005c; Gongwang, 2001c; Ody, 2004b).

## Indications

Cinnamon twigs are used to treat common colds due to pathogenic algor venti (Anonymous, 2009f; Gongwang, 2001c). For algor venti for sligth fever, aversion to cold, headeache, stiff neck (Gongwang, 2001c). Reumathic arthritis for excessive algor-humor, pain and heavy sensation of the joints, especially the shoulders (Gongwang, 2001c). For the treatment of arthralgia due to wind-cold-dampness (Anonymous, 2009f). Warms the channels and collaterals (Anonymous, 2009n; Ody, 2004b), for wind-cold damp bi pain, arthritic complaints, especially in the shoulders (Anonymous, 2009n). Unblocks the Yang Qi of the Chest (Anonymous, 2009n; Ody, 2004b), for chest pain, palpitations, edema, dysuria, and abdominal fullness (Anonymous, 2009n). Algor in the stomach and abdominal pain for cold pain in the epigastric regions relieved by pressure and warmth, pale or sallow complexion (Gongwang, 2001c). Congested fluids syndrome for fullness, stuffiness and discomfort in the chest and hypochondriac regions, vertigo, palpitation, cough due to shortness of breath, etc. due to deficiency of the heart and the spleen yang, poor circulation of yang qi and water retention (Gongwang, 2001c). Water retention syndrome from urine retention, edema, headache, fever, irritability and thirst, vomiting right after drinking, a white and greasy coating of the tongue or a white and thick coating (Gongwang, 2001c). Obstruction in the chest due to hyperactivity of the heart yang accompanied by chest congestion, shortness of breath and radiating precardialgia (Gongwang, 2001c). Cinnamon twigs alleviate colds, flu, fever, joint, shoulder, limb and abdominal pain, edema, weakness of the heart and muscular contractions. It also warms the hands (Tierra, 1997b). Used for exterior cold with underlying deficiency, painful shoulder joints, palpitations, connects heart fire and kidney water, painful menses due to cold (Liu et Tseng, 2005c). Used in external contraction wind cold with symptoms of headache, aversion to cold, etc. (Flaws, 1999e; Gongwang, 2001c). For arthralgia due to wind cold dampness with pain in the shoulder, back, limbs, and joints (Ganzhong et al., 2003d). It is used for pains due to xue stasis due to stagnation of cold (Yanfu, 2002c). For cold obstructing the flow of xue in dysmenorrhea and other gynecological conditions (Anonymous, 2009n; Ganzhong et al., 2003d; Gongwang, 2001c) like menostasis and dysuria, amenorrhea, irregular menstruation, climacteric syndrome (Ganzhong et al., 2003d) and edema due to the loss of control of the bladder-qi (Anonymous, 2009f).

### Chinese therapeutic actions and examples of major combinations

- Combination with White Peony Root (Baishayao) and Cassia Twig (Guizi) can be used for influenza with sweating, while combination with Ephedra (Mahuang) can be used to treat influenza without sweating (Gongwang, 2001c).
- For headache, fever, and aversion to cold due to algor venti, it is used with *Radix Paeoniae Alba* (Bai Shao), uncooked *Rhizoma Zingiberis* (Sheng Jiang), *Fructus Zizyphi Jujubae* (Da Zao), and *Radix Glycyrrhizae* (Gan Cao) in “The Cinnamon Twig Decoction” (Gui Zhi Tang) (Ganzhong et al., 2003d).
- It is often used together with Mahuang for algor venti, headache, pain all over the body, pain in the joints, aversion to cold and absence of sweating (Gongwang, 2001c), to produce a stronger diaphoresis (ex: Mahuang Decoction) (Ganzhong et al., 2003d).
- Add Licorice Root (Gancao) for deficiency of the heart yang, palpitation (Gongwang, 2001c).
- Add Twotooth Achyrantes Root (Niuxi) for pain of the back, lumbar and legs due to algor, amenorrhea and dysmenorrhea due to algor and stasis of qi and xue (Gongwang, 2001c).
- Add Fresh Ginger (Shengjiang) for pain in the epigastrium, vomiting of watery fluid, nausea, vomiting, and hiccups caused by cold in the stomach or water retention in the stomach (Gongwang, 2001c).
- Add White Peony Root (Baishaoyao) for aversion to cold, fever, spontaneous perspiration, aversion to wind, superficial and slow pulse (The Taiyang channel is affected by ventus) when externally contracted with algor venti and disharmony of the qi nutritivum and qi defensivum (Gongwang, 2001c).
- Add Tuckahoe (Fuling) for water retention, palpitation and shortness of breath due to heart yang deficiency (Gongwang, 2001c).
- Add Medicinal Evodia Root (Wuzhuyu) for irregular menstruation and cold pain in the lower abdomen due to deficiency cold of Impedimental and Respondens channels (Gongwang, 2001c).
- Add Peach Seed (Taoren), Tree Peony Bark (Mudanpi) for hysteromyoma (Gongwang, 2001c).
- Add Chinese Angelica Root (Danggui), Manchurian Wildginger Herb (Xixin) for cold stagnation in the channel, extremely cold hands and feet, pain in the lumbar region and knees (Gongwang, 2001c).

- Add Tuckahoe (Fuling), Lagerhead Atractylodes Rhizome (Baizhu) for urine retention (Gongwang, 2001c).
- Add Apricot Seed (Xingren), Oficinal Magnolia Bark (Houpo) for cough and asthma due to a reversal upward flow of qi (Gongwang, 2001c).
- Add Snakegourd Fruit (Gualou), Longstament Oion Bulb (Xiebai) for radiating precardialgia, palpitation, knotty and regularly-intemittent pulse caused by hyperactivity of the heart yang (Gongwang, 2001c).
- Add White Peony Root (Baishayao), Malt Sugar (Yitang) for pain in the epigastrium due to insufficiency and coldness in the spleen and stomach (Gongwang, 2001c).
- In terms of its effects of regulating qi nutritivum and promoting the flow of yang qi, Guizhi is used together with Mahuang for the treatment of excessive exterior syndromes of ventus-algor-humor; in this case, Guizhi assists Mahuang in exerting a diaphoretic effect, for example the Mahuang Decoction (Ganzhong et al., 2003d).
- For exterior repletion lack of sweating, one can combine *Ramulus Cinnamomi Cassiae* with *Herba Ephedrae* (Mahuang), etc. as in Mahuang Tang (Ephedra Decoction) (Flaws, 1999e; Ganzhong et al., 2003d).
- Based on its effects of dispelling wind, cold and damp, and relieving by warming and activating conduits, guizhi is usually used together with Fuzi *(Radix Aconiti Lateralis Praeparata*) to treat wind-cold-damp arthralgic syndrome, for example the Guizhifuzi Decoction (Ganzhong et al., 2003d).
- Because of its effect of warming, and removing water retention, Guizhi is usually employed in association with Fuling (*Poria*), Baizhu, and so on, to produce associate effects of warming and circulating splenic yang, resolving dampness and discharging water, for the treatment of diseases caused by humor and phlegmy fluid. Based on its effects of warming visceral qi, guizhi is often in conjunction with Fuling and Zexie (*Rhizoma Alismatis*) to produce associate effects of discharging water and excreting humor for treatment of oedema and difficult urination, for example the Wuling Decoction (Ganzhong et al., 2003d).
- It is combined with *Poria alba* (Fuling), *Rhizoma Atractylodis Macrocephalae* (Baizhu), etc. such as Ling Gui Zhu Gan Tang for the treatment of palpitation, dizziness and fullness in the chest due to retention of fluids (Yanfu, 2002c).
- Combined with *Polyporus* (Zhuling), *Rhizoma Alismatis* (Zexie), etc., such as Wuling San (Powder) for dysuria and edema (Yanfu, 2002c).
- In terms of its effect of warming and circulating yang qi in the chest, Guizhi is frequently used in company with *Fructus Auratii Immaturus* (Zhishi), *Fructus*

*Trichosanthis* (Gualou), *Bulbus Alli Macrostemonis* (Xiebai), and so on, for the treatment of palpitations due to blockage of qi in the chest, for example, the Zhishi-xiebai-guizhi Decoction (Ganzhong et al., 2003d).

- In the line with its effect of assisting yang and normalizing the pulse, guizhi is often used jointly with *Radix Glycyrrhizae* (Gancao) baked with honey, ginseg, *Colla Corri Asini* (Ejiao), and so on, for the treatment of knotty and intermittent pulse, for example the Zhigancao Decoction (Ganzhong et al., 2003d).
- Combined with *Semen Persicae* (Taoren), *Cortex Moutan* (Mudanpi) etc. such as Guizhi Fuling Wan (Pill) for the treatment of irregular menstruation, dysmenorrhea, amenorrhea or abdominal mass due to blood stagnation caused by invasion of cold (Yanfu, 2002c).
- Combined with *Radix Aconiti Lateralis Praeparata* (Fuzi) as in Guizhi Fuzi Tang for the treatment of arthralgia due to stagnation of wind-cold-damp (Yanfu, 2002c).
- If there is an insufficiency of qi constructivum and defensivum with xue impediment stubborn numbness, one can combine *Ramulus Cinnamomi Cassiae* with *Radix Astragali Membranacei* (Huang Qi) and *Radix Paeoniae Lactiflorae* (Shao Yao) as in Huang Qi Gui Zhi Wu Wu Tang (Astragalus & Cinnamon Twig Five Materials Decoction) (Flaws, 1999e).
- Used for women's blood cold stasis and stagnation with menstrual irregularity, blocked menstruation, abdominal pain, and concretions and conglomerations, *Ramulus Cinnamomi Cassiae* is commonly combined with *Radix Angelicae Sinensis* (Dang Gui), *Radix Paeoniae* (Shao Yao), *Radix Ligustici Wallichii* (Chuan Xiong), *Semen Pruni Persicae* (Tao Ren), *Cortex Radicis Moutan* (Dan Pi), and other such blood-quickening, freeing the flow of the channels medicinals as in Wen Jing Tang (Warm the Channels Decoction) or Gui Zhi Fu Ling Wan (Cinnamon Twigs & Poria Pills) (Flaws, 1999e).
- To warm and circulate the xue for dispelling cold and xue stasis, Guizhi is employed together with *Radix Angelicae Sinensis* (Danggui) and *Rhizoma Chuanxiong* (Chuanxiong), for example the Wenjing Decoction (Ganzhong et al., 2003d).
- Used for middle burner vacuity cold with stomach and venter insidious pain with a liking for obtaining warmth and pressure. In that case, *Ramulus Cinnamomi Cassiae* is commonly combined with *Radix Albus Paeoniae Lactiflorae* (Bai Shao), Maltose (Yi Tang), and *Radix Astragali Membranacei* (Huang Qi) as in Huang Qi Jian Zhong Tang (Astragalus Fortify the Center Decoction) (Flaws, 1999e).
- Used for heart-spleen yang vacuity, yang qi not moving, with water dampness gathering internally. The symptoms of this are upper back pain and rib-side

distention, cough counterflow, and dizziness. In that case, *Ramulus Cinnamomi Cassiae* is commonly combined with *Sclerotium Poriae Cocos* (Fu Ling) and *Rhizoma Atractylodis Macrocephalae* (Bai Zhu) as in Ling Gui Zhu Gan Tang (Poria, Cinnamon Twig, Atractylodes & Licorice Decoction).

- If there is urinary bladder qi transformation not moving inhibited urination and water swelling, *Ramulus Cinnamomi Cassiae* is commonly combined with *Sclerotium Poriae Cocos* (Fu Ling) and *Sclerotium Polypori Umbellati* (Zhu Ling) as in Wu Ling San (Five [Ingredients] Poria Powder) (Flaws, 1999e).
- Used for chest impediment and chest pain or heart stirring palpitations and a bound, regularly intermittent pulse. For the former, *Ramulus Cinnamomi Cassiae* is commonly combined with *Fructus Immaturus Citri Aurantii* (Zhi Shi), *Fructus Trichosanthis Kirlowii* (Gua Lou), and *Bulbus Allii* (Xie Bai) as in Zhi Shi Xie Bai Gui Zhi Tang (Immature Aurantium, Allium & Cinnamon Twig Decoction) (Flaws, 1999e).
- For the latter, *Ramulus Cinnamomi Cassiae* is commonly combined with mix-fried *Radix Glycyrrhizae* (Gan Cao), *Radix Panacis Ginseng* (Ren Shen), and *Gelatinum Corii Asini* (E Jiao) as in Zhi Gan Cao Tang (Mix-fried Licorice Decoction) (Flaws, 1999e).
- For Yang Stagnation and retention of water in the body due to Deficiency of the Heart Yang and Spleen Yang, which presents as a cold feeling in the back, hypochondriac distension, cough, dyspnea, hiccups, vertigo, difficulty in urination, and edema, it is used with *Sclerotium Poriae Cocos* (Fu Ling), *Sclerotium Polypori Umbellati* (Zhu Ling), and *Rhizoma Alismatis* (Ze Xie) in “Wu Ling Powder” (Wu Ling San) (Ganzhong et al., 2003d).
- For chest pain due to Qi obstruction, it is used with Fructus Trichosanthis (Gua Lou), Bulbus Allii Macrostemi (Xie Bai), and Fructus Aurantii Immaturus (Zhi Shi) (Ganzhong et al., 2003d).
- For palpitations or slow pulse with irregular intervals, it is used with honey-processed licorice root (Gan Cao), ginseng (Ren Shen), and Colla Corii Asini (A Jiao) in “The Processed Licorice Decoction” (Zhi Gan Cao Tang) (Ganzhong et al., 2003d).
- For irregular menstruation, amenorrhea, dysmenorrhea, and masses in the abdomen caused by Cold in the Blood, it is used with herbs that promote the circulation of Blood and restore regular menstrual flow, such as *Radix Angelicae Sinensis* (Dang Gui), *Rhizoma Ligustici Chuanxiong* (Chuan Xiong), *Cortex Moutan* (Mu Dan Pi), and *Semen Persicae* (Tao Ren) in “The Warming Channels

Decoction” (Wen Jing Tang) or “The Cinnamon Twig and Sclerotium Poriae Cocos Pill” (Gu Zhi Fu LingWan) (Ganzhong et al., 2003d).

## Precautions and contraindications

As a drug with a pungent taste and a warm nature, the use of Guizhi is prohibited in the treatment of diseases and syndromes involving yin deficiency (Flaws, 1999e; Ganzhong et al., 2003d; Gongwang, 2001c; Wu, 2005b) and excessive yang, and bleeding due to heat in blood (Ganzhong et al., 2003d; Gongwang, 2001c). Contraindicated in warm febrile diseases (Anonymous, 2009n; Flaws, 1999e; Gongwang, 2001c; Ody, 2004b; Wu, 2005b). Caution should be taken when this drug is used for treating pregnant women (Anonymous, 2009n; Flaws, 1999e; Ganzhong et al., 2003d; Gongwang, 2001c; Ody, 2004b; Wu, 2005b; Yanfu, 2002c) or patients with menorrhagia (Anonymous, 2009n; Flaws, 1999e; Ganzhong et al., 2003d; Wu, 2005b). Contraindicated for the syndromes such as exuberant heat impairing yin in seasonal febrile diseases, hyperactivity of yang due to yin deficiency in miscellaneous diseases and bleeding due to blood-heat (Yanfu, 2002c). Use cautiously in women with excessive menses (Gongwang, 2001c).

## Dosage and method of use

According to Liu *et* Tseng (2005) and Tierra (1997) cinnamon twigs should be prepared as an infusion: use 3-9g to treat exterior conditions and 9-15g to treat pain (Anonymous, 2009n; Leite, 2005c; Tierra, 1997b). Use 3–10 g, decocted (Anonymous, 2009f; Chu, 2009; Flaws, 1999e; Ni, 1991b; Wu, 2005b) or 3-9g (CP, 2005c; Gongwang, 2001c; Greten, 2007; Ody, 2004b; Yanfu, 2002c). According to Ganzhong *et al.* (2003c) an oral dose of Guizhi is 5-10g, in the form of decoction, pills or powder.

## Ramuli *versus* Cortex

The both medicines can expel cold and strengthen yang, *Ramuli cinnamomi cassiae* dominates going up to be a bit on the side of expelling cold to relieve exterior syndrome while *Cortex Cinnamomi cassiae*; dominates warming the interior to enter the lower energizer, being a bit on the side of warming kidney-yang (Yanfu, 2002d). Cassia bark and cassia twigs have the functions of warming blood, supporting the transformation of qi and dispelling the accumulation of algor. Cassia twig, being light, tends to go upwards and has the functions of invigorating yang and transforming qi, relieving the exterior syndrome and expelling algor. Cassia twig also acts in the limbs and has the functions of warming and dredging the channels, and invigorating qi and xue. While cassia bark tends to go downwards and has the functions of invigorating kidney yang and letting the fire back to the gate of life. Thus it is applied to cases due to excessive yin and algor in the intima and kidney yang deficiency (Gongwang, 2001b).

*Ramuli* is hot, sweet, warm, belongs to Cardial, Pulmonal and Vesical conduit. It induces sweat, opens muscle, warms and opens the conduits, helps *yang*, transforms *qi*, has the function of against heteropathy and is a common used as a "*Liberantia extima calida"* herb. *Cortex* tastes hot, sweet and belongs to Renal, Lienal, Cardial and Hepatical conduit, has the function of strength *ardor*, helps *yang*, leads ardor to the origin, leads out *algor*, stops pain, moves *xue* and opens the conduits, which is a common used group "*IX Tepefacientia intimae"* herb. Both herbs have the essential oil content, which the main ingredient is cinnamaldehyde (Shen *et al.,* 2002). *Cortex* is considered warmer than *Ramuli*, affecting the interior of the body, whereas *Ramuli* is used for the exterior (Ody, 2004b). According to Chu (2009) usually *Cortex* is used in tonic while *Ramuli* is used for expelling wind and dampness but they can be used interchangeably.

## *7.4. Radix Glycyrrhizae*

### Introduction

*Glycyrrhiza* has been described as “the grandfather of herbs” (Asl *et* Hosseinzadeh, 2008). The genus *Glycyrrhiza,* belongs to the Family Leguminosae (Anonymous, 2009; Anonymous, 2009l; Asl *et* Hosseinzadeh, 2008; Isbrucker *et* Burdock, 2006; Leite, 2005e; Newall et al., 1996b; Shin et *al.,* 2008)/Fabaceae (Anonymous, 2009; Anonymous, 2009l; Dhingra *et* Sharma, 2006; Gupta et *al.,* 2008; WHO, 1999b; Visavadiya *et* Narasimhasharya, 2006) or Papilionaceae (Gupta *et al.,* 2008; Visavadiya *et* Narasimhasharya, 2006). *Glycyrrhiza* genus includes about 30 species including *G. glabra, G.uralensis, G.inflata* (Anonymous, 2009l; Asl *et* Hosseinzadeh, 2008)*, G.aspera, G.korshinsky* and *G.eurycarpa* (Asl *et* Hosseinzadeh, 2008). But according to Isbrucker *et* Burdock (2006) there are only about 14 species known.

*G glabra* (Fig. 50) also includes 3 varieties: Persian and Turkish licorices are assigned to *G. glabra* var. *violacea,* Russian licorice is *G. glabra* var. *gladulifera,* and Spanish and Italian licorices are *G. glabra* var. *typica* (Asl *et* Hosseinzadeh, 2008). *Glycyrrhiza uralensis Fish* is a well-known Chinese herbal medicine used for the treatment of various diseases (Cheng *et al*., 2008; Ma *et al*., 2005) as well as a tonic medicine for thousands of years (Cheng *et al*., 2008).

**Fig. 50.** *Glycyrrhiza glabra* (adapted from Shen *et al.,* 2007).

Chinese licorice roots can be obtained from the three species of *Glycyrrhiza* genus, *G. glabra, G. uralensis* or *G. inflata* (Anonymous, 2009l; Asl *et* Hosseinzadeh, 2008; Blumenthal, 2003; WHO, 1999b). By definition, *Radix Glycyrrhizae* consists of the dried roots and rhizomes of *Glycyrrhiza glabra* L. (Blumenthal, 2003; Sweetman, 2009d; WHO, 1999b) and its varieties or of *Glycyrrhiza uralensis* Fisch (Fig.51-52), (Blumenthal, 2003; WHO, 1999b) or other varieties of *Glycyrrhizae*, and contains no less than 4% glycyrhhizic acid (glycyrrhizin). The roots of *Glycyrrhiza glabra* L. are popularly known as liquorice (Dhingra *et* Sharma, 2006; Newall et al., 1996b), *Liquiritiae radix* (FP, 2005) or *Liquiratae* *officinalis* Moench (WHO, 1999b) and are used as a folk medicine both in Europe and in Eastern countries (Visavadiya *et* Narasimhasharya, 2006).

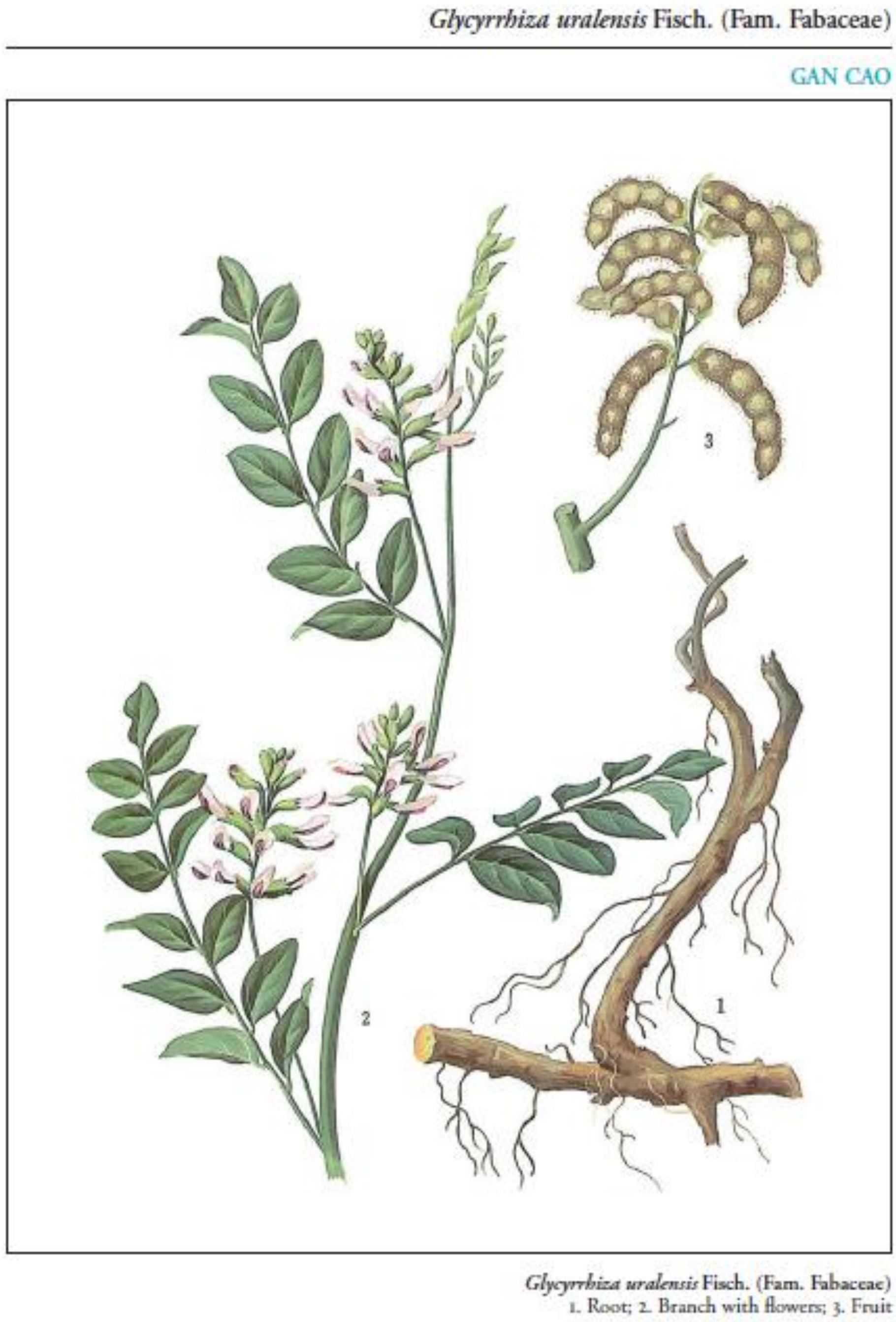



**Fig. 51.** *Glycyrriza uralensis* Fisch (adapted from Wu, 2005c).

## Historical perspective

The licorice (liquorice) plant has a long and storied history of use in both Eastern and Western cultures pre-dating the Babylonian and Egyptian empires (Isbrucker *et* Burdock, 2006). Historically, the dried rhizome and root of this plant were employed medicinally by the Egyptian, Chinese, Greek, Indian, and Roman civilizations (Anonymous, 2005; Fiore *et al.,* 2008) as an expectorant and carminative (Anonymous, 2005). The genus name *Glycyrrhiza* is derived from the ancient Greek word for ‘sweet root’ (Gr. *glykos* (sweet) + *rhiza* (root)) (Anonymous, 2005; Anonymous, 2009l; Isbrucker *et* Burdock, 2006), which was later Latinized to *liquiritia* and eventually to licorice. The two principal forms in commerce are licorice root (*Liquiriti radix*) and the extract (*Glycyrrhizae extractum crudum* or *Succus liquiritiae*). The ancient Greeks and Romans are known to have cultivated the plants in the third century (Isbrucker *et* Burdock, 2006; Verma *et* Thuluvath, 2007). The first report of medicinal use comes from Greeks, who recommended it for the treatment of gastric and peptic ulcers (Gupta *et al.,* 2008). Licorice was a prescriptive agent of Hippocrates in the treatment for asthma, dry cough, and other “pectoral diseases” and was also thought to be effective in preventing thirst (Isbrucker *et* Burdock, 2006; Verma *et* Thuluvath, 2007). Furthermore, Alexander the Great distributed the root to his soldiers to alleviate thirst (Huang, 1999). Licorice was used in Arabic medicine during the middle Ages, as documented by the *Canone* of Ibn Sina (980–1037 AD), a summary of Hippocrates and Galen’s medicine (Fiore *et al.,* 2008). The use of liquorice (*Gan Cao*) is documented in the oldest source on remedies in China, the *Shennong bengao* created 200 B.C. According to legend this work is based on sources dating back to the Emperor Shennong (ca. 2700 B.C.) (Fiore *et al.,* 2005). In Chinese traditional medicine, licorice (*Gan Cao*) remains one of the oldest and most commonly prescribed herbs and has been used in the treatment of numerous ailments ranging from tuberculosis to peptic ulcers (Isbrucker *et* Burdock, 2006; Verma *et* Thuluvath, 2007). Licorice is one of the oldest and widely used herbs from the ancient medical history of Ayurveda, both as a medicine and a flavoring herb to disguise the unpleasant flavor of other medications. Licorice is used to relieve ‘Vata’ and ‘Kapha’ inflammations, eye diseases, throat infections, peptic ulcers, arthritic conditions, and liver diseases in Indian Ayurveda system (Gupta *et al.,* 2008). The uses of *Glycyrrhiza glabra* (in Sanskrit: klitaka, madhuka, yasti or yastimadhuka) reported here apart from its use in antidote mixtures for a variety of acute and chronic poisonings, include improvement of the voice, an indication mentioned in the context of viral respiratory tract infections, wound infections, operation wounds of the ear, excessively bleeding punctures from bloodletting and acute and chronic liver diseases like hepatitis (Fiore *et al.,* 2005). European, Indian and Chinese traditions all contain references to antiviral effects in the context of viral induced voice changes in laryngitis, pharyngitis, most likely viral induced cough, viral hepatitis and viral skin diseases like condyloma and ulcers (Fiore *et al.,* 2005). The reported indications for licorice include some which were common in Europe like: pharyngitis, cough, palpitations, gastric pain, ulcers in the intestinal tract and sores. In addition to this, an area of application not found in Europe is intoxication by drugs and poisoned food (Fiore *et al.,* 2005).

In modern medicine, licorice extracts are often used as a flavoring agent to mask bitter taste in preparations, and as an expectorant in cough and cold preparations. Licorice extracts have been used for more than 60 years in Japan to treat chronic hepatitis, and also have therapeutic benefit against other viruses, including human immunodeficiency virus (HIV), cytomegalovirus (CMV), and *Herpes simplex*. Deglycyrrhizinated licorice (DGL) preparations are useful in treating various types of ulcers, while topical licorice preparations have been used to sooth and heal skin eruptions, such as psoriasis and herpetic lesions (Anonymous, 2005).

## Geographical Distribution

Licorice species are perennial herbs native to the Mediterranean Region (Anonymous, 2005; Asl *et* Hosseinzadeh, 2008; Fiore *et al.,* 2008), central to southern Russia, and Asia Minor to Iran, now widely cultivated throughout Europe, the Middle East and Asia (Asl *et* Hosseinzadeh, 2008, Fiore *et al.,* 2008). Commercially important sources are Spain, Iraq, Iran, Turkey, Russia and China, and although there are no known prohibitions against use of any species, variety or country of origin, some types are not sweet enough to have commercial value (Isbrucker *et* Burdock, 2006). Chinese licorice (*G. uralensis* and *G. pallidiflora*) are somewhat smaller, related plants, regarded as separate species of *Glycyrrhiza* (Isbrucker *et* Burdock, 2006). *Glycyrrhiza uralensis* is native to Northern China, Mongolia, and Siberia (WHO, 1999b). *Glycyrrhiza glabra* is native to central and south-western Asia (Fiore *et al.,* 2008; WHO, 1999b) and the Mediterranean region (Fiore *et al.,* 2008; Isbrucker *et* Burdock, 2006; WHO, 1999b). It is cultived in the Mediterranean basin of Africa, in southern Europe, and in India (WHO, 1999b). *Glycyrrhiza glabra* is a hardy herb or under shrub, erect grows to about 2m height. The roots are long, cylindrical (Gupta *et al.,* 2008; WHO, 1997d), fibrous, flexible 20-22cm long and 15mm in diameter, with or without corks, corks reddish, furrowed, ligth-yellow inside, sweet taste (WHO, 1997d) thick and multibranched (Gupta *et al.,* 2008). It has oval leaflets, white to purplish flower clusters, and flat pods. Below ground, the licorice plant has an extensive root system with a main taproot and numerous runners. The main taproot, which is harvested for medicinal use, is soft, fibrous, and has a bright yellow interior (Anonymous, 2005). Licorice also grows in the United States (var. *lepidota*) and England (var. *typica*) but neither represents a significant contribution to world production (Isbrucker *et* Burdock, 2006). The harvesting of licorice root occurs in the autumn of its third or fourth year of growth. The roots are dug up, washed and transported to warehouses for bailing, sorting and drying. The dried roots are crushed by millstones and the pulp is boiled to make the extract. After removal of the solids, the extract is vacuum dried to a dark paste, which is cast into blocks or short sticks, or may be dried to a powder. Licorice paste is the preferred form for flavoring tobacco whereas licorice powder is preferred for confectionery and pharmaceuticals (Isbrucker *et* Burdock, 2006).

## Selected vernacular names

***Glycyrrhiza glabra* L. and its varieties**

Adimaduram, akarmanis, asloosoos, aslussos, athimaduram, athimaduramu, athimathuram, bekh-e-mahak, bois doux, cha en thet, estameee, gancao, glycyrrhiza, herbe aux tanneurs, hsi-pan-ya-kan-tsao, irk al hiel, irk al hilou, irksos, jakyakgamcho-tang, jashtimadhu, jethimadh, jethimadha, kanpo, kanzo, kan-ts´ao, kum cho, Lakritzenwurzel, licorice, licorice root, liquiritae radix, liquorice, liquorice root, madhuyashti, madhuyasthi rasayama, mulathee, muleti, mulhatti, neekhiiyu, Persian licorice, racine de reglisse, racine douce, reglisse, reglisse, oficinalis, rhizoma glycyrrhizae, Russian licorice, Russisches Sussholz, si-pei, sinkiang licorice, Spanish licorice, Spanish liquorice, Spanisches Sussholz, Susshlzwurzel, sweet root, sweet wood, ud al sus, velmi, walmee, welmi, xi-bei, yashti, yashtimadhu, yashtimadhukam, yashtomadhu (WHO, 1999b).

***Glycyrrhiza uralensis* Fisch.**

Chinese licorice, Chinese liquorice, gancao, kan-ts´ao, kanso, kansoh, licorice root, liquiritae radix, north-eastern Chinese licorice, saihokukanzoh, tohoku kanzo, tongpei licorice, tung-pei-kan-tsao. Ural loquorice, uraru, kanzo (WHO, 1999b).

**Fig. 52.** *Glycyrrhiza uralensis* Fisch (adapted from Shen *et al.,* 2007).

***Other names***

Alcacuz, Alcazuz, Deglycyrrhized Licorice, Gan Cao, Gan Zao, Glabra, Glycyrrhiza, Glycyrrhiza radix, Glycyrrhizae, Glycyrrhizic Acid, Glycyrrhizinic Acid, Isoflavone, Jethi-Madh, Lakritze, Liquiritiae radix, Liquirizia, Liquorice, Mulhathi, Orozuz, Phytoestrogen, Radix Glycyrrhizae, Regliz, Russian Licorice, Spanish Licorice, Subholz, Sussholz, Sweet Root, Yashti-Madhu, Yashti-Madhuka, Zhi Gan Cao (Anonymous, 2009).

## Plant material of interest

Dried root and rhizome (Anonymous, 2005; WHO, 1999b; WHO, 1997d).

## Organoleptic properties

Odour slight characteristic; taste, very sweet (WHO, 1999b).

## General identity tests

Macroscopic, microscopic, and microchemical examinations; thin layer chromatographic analysis for the presence of glycyrrhizin (FP, 2005; WHO, 1999b) and isoliquirritin (FP, 2005).

## Purity tests

***Microbiology***

The test for *Salmonella* spp. in *Radix Glycyrrhizae* products should be negative. The maximum acceptable limits of other microorganisms are as follows. For preparation of decoction: aerobic bacteria—not more than 107/g; fungi—not more than 105/g; *Escherichia coli*—not more than 102/g. Preparations for internal use: aerobic bacteria—not more than 105/g or ml; fungi—not more than 104/g or ml; enterobacteria and certain Gram-negative bacteria—not more than 103/g or ml; *Escherichia coli*—0/g or ml (WHO, 1999B).

***Total ash***

Not more than 7% (WHO, 1999b), not more than, 10,0 % on uncruded drug and not more than, 6,0 % on crude drug (FP, 2005).

***Acid-insoluble ash***

Not more than 2% (WHO, 1999b), not more than, 2.0 % on uncruded drug and not more than, 0.5 % on crude drug (FP, 2005).

***Sulfated ash***

Not more than 10% (WHO, 1999b).

***Water-soluble extractive***

Not less than 20% (WHO, 1999b).

***Dilute alcohol-soluble extractive***

Not less than 25% (WHO, 1999b).

***Pesticide residues***

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for *Radix Glycyrrhizae* is not more than 0.05 mg/kg (WHO, 1999b).

***Heavy metals***

Recommended lead and cadmium levels are no more than 10 and 0.3mg/kg, respectively, in the final dosage form of the plant material (WHO, 1999b).

***Radioactive residues***

Analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239 (WHO, 1999b).

***Other purity tests***

Alcohol-soluble extractive, chemical, and foreign organic matter tests to be established in accordance with national requirements (WHO, 1999b).

***Loss on drying*** not more than 10%, in 10,0 g of pulverised sample determined in greenhouse in 100-105°C, for 2 h (FP, 2005).

***Chemical assays***

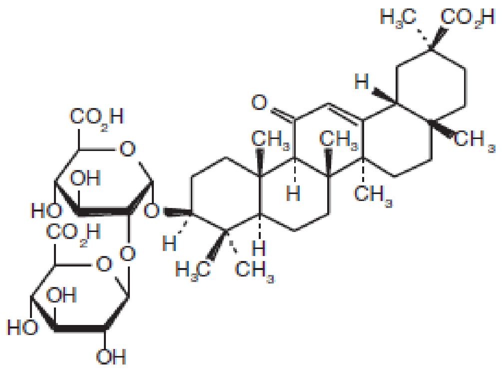
Assay for glycyrrhizin (glycyrrhizic acid, glycyrrhizinic acid) content (at least 4%) by means of spectrophotometric, thin layer chromatographic densitometric or high performance liquid chromatographic methods (WHO, 1999b). Determination by liquid chromatography to determine the content in glycyrrhizic acid: at least 4.0 % of glycyrrhizic acid ($C_{42}H_{62}O_{16}$, *Mr* 823) (dried plant) (FP, 2005).

## Chemicals constituents

As with most plant extracts, the number of chemical constituents is potentially vast and greatly influenced by a constellation of genetic, environmental, and processing factors; licorice root extract is no exception (Isbrucker *et* Burdock, 2006). A number of components have been isolated from licorice, including a water-soluble, biologically active complex that accounts for 40-50 % of total dry material weight. This complex is composed of triterpene saponins, flavonoids, polysaccharides, pectins, simple sugars, amino acids, mineral salts, and various other substances (Anonymous, 2005). The main components are the triterpene saponin glycyrrhizin (also known as glycyrrhizic or glycyrrhizinic acid) and the respective aglycone, the glycyrrhetic acid or glycyrrhetinic acid (Shin *et al.,* 2008; Visavadiya *et* Narasimhasharya, 2006), which are believed to be partly responsible for anti-ulcer, anti-inflammatory, anti-diuretic, anti-epileptic anti-allergic and antioxidant properties of the plant as well as their ability to “fight” low blood pressure (Visavadiya *et* Narasimhasharya, 2006).

***Saponins***

The major constituents are triterpene saponins, 4-20% (Asl *et* Hosseinzadeh, 2008; WHO, 1999b), 3-15% according to Cunha *et al.,* 2007 (mostly glycyrrhizin, (Fig.53), the major component, about 2-9%, 5-9% according to Cunha *et al.,* 2007, is glycyrrhizin, a glycoside of glycyrrhetinic acid (Fig.54) (Asl *et* Hosseinzadeh, 2008; WHO, 1999b). According to Isbrucker *et* Burdock (2006) glycyrrhizin constitutes 10–25% of licorice root extract and is considered the primary active ingredient.




**Glycyrrhizin or glycyrrhizic acid or glycyrrhizinic acid**

**Aglycone = glycyrrhetic acid or glycyrrhetinic acid**

**Fig. 53.** Chemical structure of glycyrrhizin and its aglycone (adapted from WHO, 1999b)

Glycyrrhizin is a monodesmoside, which on hydrolysis releases two molecules of D-glucuronic acid (Cunha et al., 2007; Fiore *et al.,* 2008, WHO, 1999b) and the aglycone glycyrrhetic (glycyrrhetinic) acid (enoxolone) (Fig.) (WHO, 1999b).

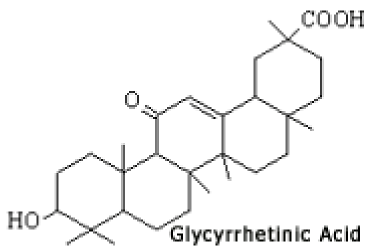



**Fig. 54.** Structure of glycyrrhetinic acid (adapted from http://www.glabridin.com/glab.htm ) (visited 9-6-2009).

By other words, glycyrrhizin is a saponin compound comprised of a triterpenoid aglycone, glycyrrhetic acid (glycyrrhetinic acid; enoxolone) conjugated to a disaccharide of glucuronic acid. Both glycyrrhizin and glycyrrhetic acid can exist in the 18α- and 18β-stereoisomers. As a tribasic acid, glycyrrhizin can form a variety of salts and occurs naturally in licorice root as the calcium and potassium salts. Carbenoxolone (18β-glycyrrhetinic acid hydrogen succinate), an analog of glycyrrhetic acid (Fig.55), is used in the treatment of some alimentary tract ulcerative conditions, such as peptic ulcers (Isbrucker *et* Burdock, 2006).

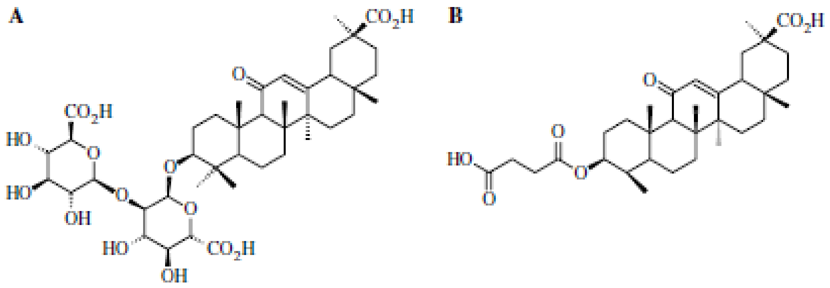


**Fig. 55.** Chemical structure of glycyrrhizin (A) and carbenoxolone (B) (adapted from Isbrucker *et* Burdock, 2006).

Other triterpenes present are liquiritic acid, glycyrretol, glabrolide, isoglaborlide and licorice acid (Asl *et* Hosseinzadeh, 2008).

### *Flavonoids*

Other constituents include flavanones such as liquiritigenin and liquiritin (Asl *et* Hosseinzadeh, 2008; WHO, 1999b) (Fig. 56) rhamnoliquiritin, and chalcones such as isoliquiritigenin and isoliquiritin (Asl *et* Hosseinzadeh, 2008; Newall et al., 1996b; WHO, 1999b) (Fig. 56), chalcones isoliquiritin, neoisoliquiritin, licuraside and licoflavonol (Asl *et* Hosseinzadeh, 2008). Other chalcones includes licuraside, echinatin, licochalcones A and B and neolicuroside (Newall et al., 1996b). The bright yellow color of licorice root is provided by flavonoids, particularly liquiritin, isoliquiritin and their corresponding aglycones, which typically comprise 1-1.5% of the water soluble extract (Isbrucker *et* Burdock, 2006).

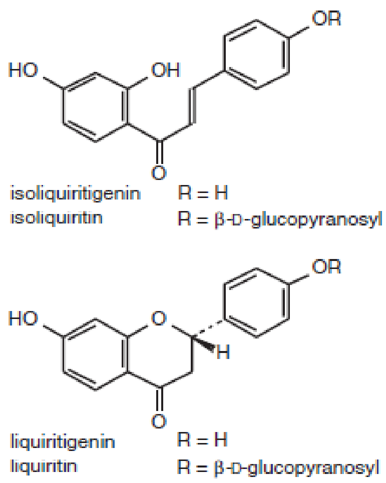



**Fig. 56.** Chemical structure of liquiritin, isoliquiritin, isoliquiritigenin, liquiritigenin (adapted from WHO, 1999b)

Licorice include flavonols and isoflavones including formononetin, glabrin, glabrol, glabrone, glyzarin, glycyrol, glabridin (Fig. 57) and derivatives, kumatakenin, licoflavonol, licoisoflavones A and B, licoisoflavanone, licoricone, liquiritin and derivatives, phaseollinisoflavan (Newall et al., 1996b).

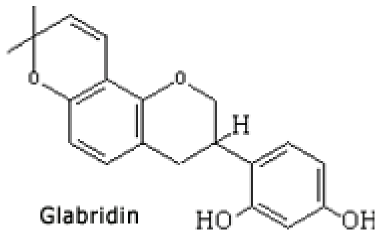



**Fig. 57.** Chemical structure of glabidrin (adapted from http://www.glabridin.com/glab.htm) (visited 9-6-2009)

Other isoflavonoid derivatives present in licorice include glabrene, glabrone, shinpterocarpin, licoisoflavones A and B, formononetin, glyzarin, kumatakenin. More recently, hispagladribin A, hispaglabidrin B, 4´- *O*-methylgladridin and 3´-hydroxy-4´-*O*-methylgladribin and glabroisoflavanone A and B have been found (Asl *et* Hosseinzadeh, 2008).

Recently 5,8-dihydroxy-flavone-7-*O*-β -D-glucuronide, glychionide B were isolated from the roots of *G. inflata* and the minor flavonoids, isotrifoliol and glisoflavanone, from the underground part of *G. uralensis* (Asl *et* Hosseinzadeh, 2008).

Besides, the isolates from *Glycyrrhiza glabra* roots, glabridin (an isoflavan) and isoliquiritigenin (a chalcone), are known to be pharmacologically active compounds. Glabridin is reported to be potent antioxidant towards LDL oxidation whereas isoliquiritigenin is known to exert vasorelaxant effect, anti-platelet, anti-viral, estrogenic activities and has the protective potential against cerebral ischemic injury (Visavadiya *et* Narasimhasharya, 2006). The isoflavones glabridin and hispaglabridins A and B have significant antioxidant activity, and both glabridin and glabrene possess estrogen-like activity (Anonymous, 2005).

***Coumarins***

Coumarins present in *G. glabra* include glabrocoumarone A and B (Asl *et* Hosseinzadeh, 2008), umbelliferone**,** liqcoumarin, herniarin, glycyrin (Asl *et* Hosseinzadeh, 2008, Newall et al., 1996b), glycocoumarin, licofuranocoumarin, licopyranocoumarin, glabrocoumarin (Asl *et* Hosseinzadeh, 2008) and GU-7 (a-arylcoumarine derivative (Newall et al., 1996b) Although glycycoumarin (Fig. 58) is a minor ingredient in the hot water extracts of licorice (approximately 0.10%), it is an important species-specific ingredient of *G. uralensis* (Nagai *et al.,* 2006).

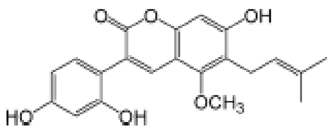



**Fig. 58.** Chemical structure of glycycoumarin (adapted from Nagai *et al.,* 2006)

Glycyrol (Fig.59) is a benzofuran coumarin isolated from *Radix Glycyrrhizae* (Shin *et al.,* 2008a). Whereas the anti-inflammatory activity of glycyrol has not been well known, glycyrol has been reported to have antibacterial activity against upper-airway respiratory tract bacteria such as *Streptococcus pyogenes*, *Haemophilus influenzae* and *Moraxella catarrhalis*. In order to investigate the anti-inflammatory activity of glycyrol in LPS-stimulated RAW264.7 macrophages, several important inflammation mediators were examined. Glycyrol showed dose-dependent inhibitory effects on NO production, iNOS mRNA and protein expression. In addition, glycyrol dose dependently down-regulated LPS-induced COX-2 production, both on mRNA and protein level. Furthermore, glycyrol was tested at different times against LPS stimulations, and showed dose-dependent inhibitory effects on NO, iNOS and COX-2 production, regardless of pre or post-administration. Additionally, glycyrol showed the pronounced inhibitory effect on IL-1β mRNA expression in the LPS-stimulated RAW264.7 macrophages. However, glycyrol was revealed to have no inhibitory effect on the mRNA of TNF-α, due to its competitive dose-dependent TNF-α producing activity (Shin *et al.,* 2008).

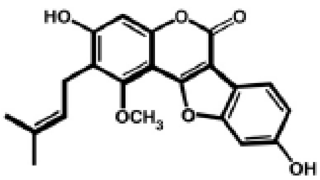



**Fig. 59.** Chemical structure of glycyrol (adapted from Shin *et al.,* 2008)

### *Stilbenoids*

Four new dihydrostilbenes, dihydro-3, 5-dihydroxy-4´-acetoxy-5´-isopentenylstilbene, dihydro-3,3´,4´-trihydroxy-5-*O*-isopentenyl-6-isopentenylstilbene, dihydro-3,5,3´-thrihydroxy-4´-methoxystilbene and dihydro-3,3´-dihydroxy-5-β-d-O-glucopyranosyloxy-4´-methoxystilbene were isolated from the leaves of *G. glabra* grown in Sicily (Asl *et* Hosseinzadeh, 2008).

***Licochalcone***

Licochalcone A (LicA) (Fig. 60), a major phenolic constituent of the licorice species *Glycyrrhiza inflata*, has recently been reported to have anti-inflammatory as well as anti-microbial effects. These anti-inflammatory properties might be exploited for topical applications of LicA. Topical LicA causes a highly significant reduction in erythema relative to the vehicle control in both the shave- and UV-induced erythema tests, demonstrating the anti-irritative properties of LicA. Furthermore, LicA is a potent inhibitor of pro-inflammatory in vitro responses, including N-formyl-MET-LEU-PHE (fMLP)- or zymosan-induced oxidative burst of granulocytes, UVB-induced $PGE_2$ release by keratinocytes, lipopolysaccharide (LPS)-induced $PGE_2$ release by adult dermal fibroblasts, fMLP-induced $LTB_4$ release by granulocytes, and LPS-induced IL-6/TNF-a secretion by monocyte-derived dendritic cells. The reported data suggest therapeutic skin care benefits from LicA when applied to sensitive or irritated skin. Licochalcone A, a reversely constructed chalcone or ‘‘retrochalcone’’ extracted from the licorice species. *Glycyrrhiza inflata*, has drawn pharmacological attention in the recent past due to its anti-bacterial, anti-protozoan, and anti-tumor properties. Besides these properties, suppressive effects of LicA on phorbol-ester-driven processes, like the mouse ear edema formation induced by arachidonic acid and tetradecanoylphorbol acetate (TPA), have been described. Furthermore, direct immunosuppressive effects of LicA on mitogen-induced T cell proliferation and IFN-c production, as well as on LPS-induced cytokine production by monocytes, have been reported (Kolbe *et al.,* 2006).

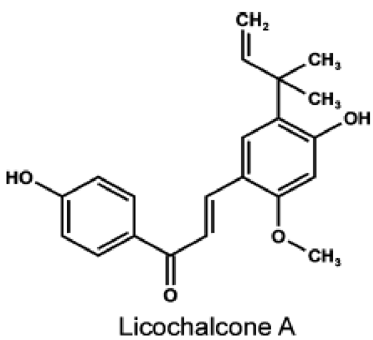



**Fig. 60.** Chemical structure of licochalcone A (adapted from Kolbe *et al.,* 2006).

Even though LicA’s mode of action is still not resolved on a molecular level, the results suggest therapeutic skin care benefits from LicA when applied to sensitive or irritated skin (Kolbe *et al.,* 2006).

***Polysaccharide***

*Glycyrrhiza* polysaccharide (GP), one of the main active ingredients of *Glycyrrhiza* is attributed to many healing properties of the herb. Recently, it has been reported that GP had many functions such as immunity regulation, phagocytosis, anti-virus, anti-tumor, anti-complement, and it has low cellular toxicity. The aqueous extracts from *Glycyrrhiza* and the structure of their oligo and polysaccharides have been described. Studies indicate that GP at least includes three core structures: firstly, a backbone chain composed of β-1,3-linked D-galactosyl residues, three-fifth of the galactose units glycosidic units in the backbone carry side chains composed of β-1,3- and β-1,6-linked D-galactosyl residues at position 6; secondly, glycosidic units in the backbone carry side chains composed mainly α-1,5- linked L-arabino-β-1,6- or 1,3-linked D-galactosyl residues at position 6,; thirdly, glycosidic units were composed of α (1→4) linked D-glucan (Cheng *et al*., 2008).

***Miscellaneous compounds***

Minor components occur in proportion that varies depending on the species and geographical location (WHO, 1999b). Licorice extract also contains reducing and nonreducing sugars, starch (Asl *et* Hosseinzadeh, 2008; Isbrucker *et* Burdock, 2006), plant gums, resins, essential oils, inorganic salts and low levels of nitrogenous constituents such as proteins, individual amino acids, and nucleic acids (Isbrucker *et* Burdock, 2006). *G. glabra* extract also contains fatty acids ($C_2$-$C_{16}$) and phenols (phenol, guaiacol), together with common saturated linear γ-lactones ($C_6$-$C_{14}$). A series of new 4-methyl- γ-lactones and 4-ethyl- γ-lactones in trace amounts also has been found. Asparagines, polysaccharides (arabinogalactants), sterols (β-sitosterol, dihydrostigmasterol) are also present (Asl *et* Hosseinzadeh, 2008). It also contains trace elements, including zinc and manganese (Ganzhong et al., 2003e).

## Mechanism of Action

- Glycyrrhizin is metabolized to its aglycone 18-β-glycyrrhetinic acid in the intestine by human intestinal bacteria (Anonymous, 2009; Blumenthal, 2003; Isbrucker *et* Burdock, 2006; Newall et al., 1996b; Shin *et al.,* 2007), which is then absorbed into the blood (Blumenthal, 2003; Isbrucker *et* Burdock, 2006; Shin *et al.,* 2007);
- Protects liver through 18-β-glycyrrhetinic acid and glycyrrhizin (Anonymous, 2005; Asl *et* Hosseinzadeh, 2008; Blumenthal, 2003; Fiore *et al.,* 2008; Isbrucker *et* Burdock, 2006; Newall et al., 1996b; WHO, 1999b);
- Relieves gastric inflammation, possibly by inhibiting prostaglandin synthesis and lipoxygenase (Blumenthal, 2003);

- Antigastric ulcer activity is due to the FM 100 fraction (licorione), which lowers gastric acidity, reduces pepsin activity and inhibits gastric secretion (Blumenthal, 2003; Borrelli *et* Izzo, 2000; Takagi *et al.,* 1971);
- Glycyrrhetinic acid inhibits 11-β-hydroxysteroid dehydrogenase (11-β-OHSD), the enzyme that deactivates cortisol (Asl *et* Hosseinzadeh, 2008; Anonymous, 2005; Anonymous, 2009; Blumenthal, 2003; Chan *et* Kritchley, 1996; Cunha et al., 2007; Fiore *et al.,* 2008; Newall et al., 1996b; WHO, 1999b) and bacterial 3-α, 20-β-hydroxysteroid dehydrogenase (Blumenthal, 2003);
- Inhibits human 11- β-hydroxysteroid dehydrogenase (Asl *et* Hosseinzadeh, 2008; Anonymous, 2005; Anonymous, 2009; Blumenthal, 2003; Breidthardt *et al.*, 2006; Chan *et* Kritchley, 1996; Cunha et al., 2007; Fiore *et al.,* 2008; Newall et al., 1996b; Newall et al., 1996b; Newall et al., 1996b; WHO, 1999b), which minimizes the binding of cortisol to mineralocorticoid receptors, creating a miniralocorticoid-like effect (Asl *et* Hosseinzadeh, 2008; Blumenthal, 2003; Chan *et* Kritchley, 1996; Fiore *et al.,* 2008);
- Inhibits peripheral metabolism of cortisol, which binds mineralocorticoid receptors in the same way that aldosterone (Blumenthal, 2003; Cunha et al., 2007b);
- May also inhibit 17- β-hydroxysteroid dehydrogenase and 17, 20-lyase, which catalyzes conversion of 17-hydroxyprogesterone to androstenedione (Blumenthal, 2003);
- Modulates the cell- mediated immune system, which may be due to glycyrrhizin stimulating the induction of contrasuppressor cells (Blumenthal, 2003);
- Demulcent and expectorant actions due to stimulating tracheal mucous secretion (Blumenthal, 2003; Ganzhong et al., 2003e; WHO, 1999b);
- Antioxidant action may be related to absorption and binding of licorice´s flavonoids (e.g. glabridin) to the LDL particle from oxidation (Blumenthal, 2003).

## Effects and uses

Licorice is one of the most widely used medicinal plants, found in traditional formulas since antiquity (Fiore *et al.,* 2008). Liquorice approved its use by the German Commission E for the treatment of cough, bronchitis and gastritis (Cunha et al., 2007b). This herb has long been valued to relieve respiratory ailments (Cheng *et al.*, 2008; Gupta *et al.,* 2008; Verma *et* Thuluvath, 2007), as an expectorant (Dhingra *et* Sharma, 2006; Fiore *et al.,* 2005; Isbrucker et Burdock, 2006; WHO, 1999b), as antitussive (Anonymous, 2009; Cheng *et al.*, 2008; Fiore *et al.,* 2005; Gupta *et al.,* 2008; Isbrucker et Burdock, 2006; Verma *et* Thuluvath, 2007; WHO, 1999b), as an anti-inflammatory agent (Cheng *et al.*, 2008; Dhingra *et* Sharma, 2006; Shin *et al.,* 2008; WHO, 1999b), antipyretic (Dhingra *et*

Sharma, 2006; Isbrucker et Burdock, 2006; Ma *et al*., 2005; Shin *et al.,* 2008; Verma et Thuluvath, 2007). It is been used to treat sore throats (Anonymous, 2009; Fiore *et al.,* 2005; Ganzhong et al., 2003e; Isbrucker et Burdock, 2006; WHO, 1999b), asthma (Ganzhong et al., 2003e; Isbrucker et Burdock, 2006), bronchitis (Anonymous, 2009; Ganzhong et al., 2003e; Isbrucker *et* Burdock, 2006; Ma *et al*., 2005) and tuberculosis (Anonymous, 2009; Ganzhong et al., 2003e; Gupta *et al.,* 2008; WHO, 1999b).

The most consistent use is as a demulcent for the digestive system (Cheng *et al*., 2008; Isbrucker *et* Burdock, 2006). Licorice has antacid activities (Dhingra *et* Sharma, 2006), used in dyspepsia (Anonymous, 2009; Fiore *et al.,* 2005; Isbrucker et Burdock, 2006; WHO, 1999b), and among its traditional uses licorice is felt to be effective in the treatment of ulcer disease (Anonymous, 2009; Cheng *et al*., 2008; Cunha et al., 2007; Dhingra *et* Sharma, 2006; Ganzhong et al., 2003e; Gupta *et al.,* 2008; Isbrucker *et* Burdock, 2006; Ma *et al*., 2005; WHO, 1999b), stomachache (Anonymous, 2009; Ganzhong et al., 2003e; Gupta *et al.,* 2008; WHO, 1999b), gastritis (Anonymous, 2005; Cheng *et al*., 2008; Verma *et* Thuluvath, 2007). It also has been used as a laxative (Anonymous, 2009; Asl *et* Hosseinzadeh, 2008; Cheng *et al*., 2008; Fiore *et al.,* 2005; Gupta *et al.,* 2008; Isbrucker et Burdock, 2006; Verma *et* Thuluvath, 2007; WHO, 1999b). Also used as an anti-inflammatory agent (Cheng *et al*., 2008; Dhingra *et* Sharma, 2006; Shin *et al.,* 2008; WHO, 1999b), in the treatment of allergic reactions (Cheng *et al*., 2008; WHO, 1999b; Shin *et al.,* 2008), contact dermatitis (Anonymous, 2009; Ganzhong et al., 2003e), alergic dermatitis and eczema (Ganzhong et al., 2003e), urticaria (Ganzhong et al., 2003e), and other skin diseases (Cheng *et al*., 2008; Ganzhong et al., 2003e). Studies also show licorice constituents to be effective in the treatment of eczema and melasma (Anonymous, 2005).

Other uses of the plant include the treatment of sex-hormone imbalances and menopausal symptoms in women (Gupta *et al.,* 2008). Licorice has held claim for therapeutic use for liver ailments (Cheng *et al*., 2008; Gupta *et al.,* 2008; Isbrucker et Burdock, 2006; Shin *et al.,* 2008; Verma *et* Thuluvath, 2007; WHO, 1999b), hepatitis (Ganzhong et al., 2003e; Ma *et al*., 2005; Shin *et al.,* 2008), *Addison´*s disease (adrenocortical insufficiency) (Anonymous, 2009; Asl *et* Hosseinzadeh, 2008; Ganzhong et al., 2003e; Isbrucker et Burdock, 2006; WHO, 1999b), and rheumatoid arthritis (Isbrucker et Burdock, 2006; WHO, 1999b). Its hypocholesterolaemic and hypoglycemic activities have been reported (Ragesh *et* Latha, 2004). Furthermore, *Glycyrrhiza glabra* extracts have been shown to possess antidepressant-like, and produce antithrombotic effects. On the other hand, the root extracts are reported to exhibit antiangiogenic, antitumor activity and radio-protective effects (Visavadiya *et* Narasimhasharya, 2006), anticonvulsant activities (Dhingra *et* Sharma, 2006) and memory enhancing activities (Dhingra *et* Sharma, 2006; Visavadiya *et* Narasimhasharya, 2006).

Orally, licorice is used for colic, osteoarthritis, systemic lupus erythematosus (SLE), and for bacterial and viral infections. It is also used orally for cholestatic liver disorders, hypokalemia, hypertonia (Anonymous, 2009; Ganzhong et al., 2003e), malaria (Anonymous, 2009; Ganzhong et al., 2003e), Leishmania (Anonymous, 2005), abscesses, food poisoning, diabetes insipidus (Anonymous, 2009; Ganzhong et al., 2003e), chronic fatigue syndrome (CFS) (Anonymous, 2009). Licorice can be used to treat thrombocytopenic purpura, hypercholesterolemia, herpetic keratitis, scleritis and acute iridocyclitis (Ganzhong et al., 2003e), eosinophilic peritonitis, postural hypotension (Anonymous, 2005), used as a diuretic (Asl *et* Hosseinzadeh, 2008; Dhingra *et* Sharma, 2006; Gupta *et al.,* 2008), antimicrobial, anxiolytic (Dhingra *et* Sharma, 2006), and in other diseases as: treatment for wounds, cystitis, diabetes, kidney stones (Gupta *et al.,* 2008), as a anabolic and to improve the voice (Asl *et* Hosseinzadeh, 2008; Gupta *et al.,* 2008), as a contraceptive and to improve male sexual function (Asl *et* Hosseinzadeh, 2008).

***Other uses***

Licorice root is not only used in Chinese traditional medicine and pharmaceutics, but also used in cosmetic, food, ink and cigarette industries (Shen et al., 2007). Licorice is used as a as a flavoring agent (Anonymous, 2009; Isbrucker *et* Burdock, 2006) in foods, beverages, and tobacco (Anonymous, 2009). Glycyrrhizin (one of the major components) is responsible for the sweetness of licorice, which is 50 times that of sucrose (Asl *et* Hosseinzadeh, 2008; Isbrucker *et* Burdock, 2006; WHO, 1999b). Although glycyrrhizin is considered much sweeter than sucrose, the associated licorice flavor makes direct comparison difficult and affords it little commercial value as a sweetener. Because glycyrrhizin also imparts an undesirable brownish color to foods and the sweetness is lost in acidic solutions, as occurs in most beverages, glycyrrhizin remains of little value to the food and beverage industries. The primary use for licorice products and glycyrrhizin is limited to flavoring tobacco and candy. The tobacco industry is the primary user of licorice derivatives in the United States, with the remainder equally divided among the food and pharmaceutical industries. Some minor consumer use for licorice root extract and glycyrrhizin has been in beer and ales, where they provide good surfactant (foaming) properties and take the edge off these potentially bitter-tasting beverages. Similarly, licorice root extract and glycyrrhizin may be used to alleviate the bitter after taste in some saccharinated products and pharmaceutical preparations. Industrial uses for glycyrrhizin include an adhesive agent in insecticides and a wetting agent (surfactant) for various industrial processes (Isbrucker *et* Burdock, 2006). Licorice has Generally Recognized as Safe (GRAS) status in the US (Anonymous, 2009).

## Pharmacological activities

### *Anti-inflammatory activities*

Pharmacological studies showed a marked anti-inflammatory action by licorice (Cunha et al., 2007b). The similarity in structure of glycyrrhetic acid to the structure of hormones secreted by the adrenal cortex accounts for the mineralocorticoid and glucocorticoid activity of glycyrrhizic acid. Licorice constituents also exhibit steroid-like anti-inflammatory activity, similar to the action of hydrocortisone. This is due, in part, to inhibition of phospholipase $A_2$ activity, an enzyme critical to numerous inflammatory processes (Anonymous, 2005). *In vitro* research has also demonstrated that glycyrrhizic acid inhibits cyclooxygenase activity and prostaglandin formation (specifically prostaglandin $E_2$), as well as indirectly inhibiting platelet aggregation, all factors in the inflammatory process (Anonymous, 2005; Cunha et al., 2007b). This action has been put in evidence that there is a strong inhibition of the enzyme 11β-hydroxysteroid dehydrogenase involved in the conversion of cortisol (hydrocortisone) and cortisone in enzymes involved in the metabolism of sterols (5-β-reductase and 3-β- hydroxysteroid dehydrogenase). Thus, at the adrenal level there is an increase in cortisol content with activation of mineralocorticoid receptors, with reabsorption of sodium and depletion of potassium, in addition to the reduction in the metabolism of aldosterone, desoxicorticosterone and glucocorticoids. The subsequent accumulation of these compounds leads to a pseudo-hyperaldosteronism syndrome (Cunha et al., 2007b). Glycyrrhizin and glycyrrhetic acid (enoxolone) act indirectly by potentiating the activity of corticosteroids. *In vitro*, glycyrrhetic acid inhibits $\Delta^4$β-reductase, an enzyme that competitively inactivates steroid hormones besides 11β-hydroxysteroid dehydrogenase, the enzyme that deactivates cortisol (WHO, 1999b). Newall *et al.* (1996) refer that 18-α-glycyrrhetinic acid exhibited stronger anti-inflammatory action compared to its stereoisomer 18-β-glycyrrhetinic acid.

Glycyrrhizin has been found to significantly and dose-dependently decrease neutrophil-generated $-O_2$ •, $-H_2O_2$ • and −OH•. These reactive oxygen species (ROS) are considered to be the most potent inflammatory mediators at the site of inflammation (Shin *et al.,* 2008). It was thought that one of its anti-inflammatory effects was due to this inhibitory effect (Asl *et* Hosseinzadeh, 2008). Also, the generation of reactive species was also suppressed by glabridin treatment in RAW 264.7 cells (Asl *et* Hosseinzadeh, 2008). Glycyrrhetinic acid did not inhibit either cyclo-oxigenase 1 or 2 catalysed prostaglandin biosynthesis with an $IC_{50}$ value of 425μm in an *in vitro* study. However, in another study

*G.radix* was believed to be involved in COX-2 inhibition. Also, glycyrrhizin and glycyrrhetinic acid have shown their inhibitory activity against interleukin-1b (IL-1b)-induced prostaglandin $E_2$ ($PGE_2$) production in normal human dermal fibroblasts (Asl *et* Hosseinzadeh, 2008).

Chalcones isolated from *G.inflata* Bat. have been reported to inhibit leukotriene production and increase cyclic AMP concentrations in human polymorphonucleares neutrophils *in vitro*. Glycyrrhetinic acid derivatives, but not glycyrrhetinic acid, have exhibited inhibitory effects on writhing and vascular permeability tests and on type IV allergy in mice (Newall et al., 1996b). Also significant anti-inflammatory action is exhibited by glycyrrhetinic acid against UV eritema (Newall et al., 1996b).

The extract of radix Glycyrrhizae equivalent to 100, 200 or 500 mg/kg of glycyrrhizin, or the same doses of glycyrrhizin and glycyrrhetinic acid were used to treat induced inflammation by subcutaneous injection of carrageenan into the palm of the hind paw of rats. It was found that carraheen induced edema was not affeted by 100 mg/kg, attenuated by 200 mg/kg, and potentated by 500 mg/kg of these the tested drug. Glycyrrhhizin inhibited to some extent prostaglandin E2 biosynthesis by the activated rat peritoneal macrophage, whereas in the cell-free experiment glycyrrhizin and glycyrrhetinic acid showed little effect on the inhibition of cyclooxygenase. The anti-inflammatory principles were found to be glycyrrhizic acid and glycyrrhitic acid. Glycyrrhizic acid 25 or 50 mg/kg given by IV injection to mice inhibited passive cultaneous anaphytazoxis response. Glycyrrhizic acid antagonized the contraction of isolated rabbit illum and guinea pig trachea induced by histamine acetylcholine or slow reacting substance of anaphytaxis in a concentration dependent fashion. The anti-inflammatory effects of glycyrrhetinic acid and its derivatives on TPA-induced mouse ear edema were studied. Glycyrrhetinic acid derivatives examined strongly inhibited ear edema. The mechanism of the anti-inflammatory effect was to a certain degree related to the adrenal cortex, suppression of vascular permeability and antagonism to inflammation as well. Sodium glycyrrhinic acid (SGA) inhibited significantly paw edema of rats with ajuvant arthritis (AA), reduced proliferation of synovial cells and pannus formation, and eleminated the destruction of articular cartilage in inflammed joints of AA rat. T-lymphocyte ratio was increased in normal mice and decreased in rats with ajuvant arthris by SGA. The result showed that SGA possesses two-way regulating activity for immune functions (Shen *et al.,* 2007).

***Antiallergic effects***

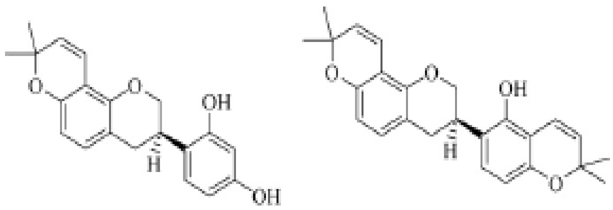
Glycyrrhizin showed an anti-allergic activity. It inhibited the passive cultaneous anaphylaxis (PCA) response in rats. It inhibited the contraction of rabbit ileum and guinea

pig trached induced by histamine, acetylcholine or slow-reacting substances of anaphylaxis. Glycyrrhizin has clinically been employed as an anti-allergic agent. Thus it can be as a lead compound, and modified its molecule to study the anti-allergic actions of the modified compunds on Type I, II and IV allergy in experimental animals. The effect of deoxoglycyrrhetol and its derivatives against the type IV allergy in mice was studied in the PCA test. The preventing effective dose is 25-200 mg/kg (Shen *et al.,* 2007). Glycyrrhizin and 18-β-glycyrrhetinic acid administered orally exhibited the most potent inhibition against the PCA reaction. However, this effect was not observed with the intraperitoneally administered glycyrrhizin. This suggests that the inhibitory effect of glycyrrhizin against the PCA reaction might be due to the metabolism of 18-β-glycyrrhetinic acid by the intestinal microflora. This suggestion is supported by previous reports showing that the intestinal microflora hydrolyze glycyrrhizin to 18-β-glycyrrhetinic acid (Shin *et al.,* 2007). In other hand, liquiritigen most potently inhibited the degranulation of peritoneal mast cells and RBL-2H3 cells, followed by 18-β-glycyrrhetinic acid (Shin *et al.,* 2007). Liquiritigenin and 18-β-glycyrrhetinic acid exhibited antiscratching behavioral effects. These effects were in proportion to their inhibitory effects against the vascular permeability. This suggests that antischatching behavioral effect of licorice might be due to the inhibition of vascular permeability. Glycyrrhizin and 18-β-glycyrrhetinic acid reduced the IgE level in the blood of the mice induced by ovalbumin (OVA). In addition, many studies have reported that glycyrrhizin inhibits the production of nitric oxide and cytokines in RAW264.7 cells as well as in an *in vivo* test. Glycyrrhizin, that seems to be transformed to 18-β-glycyrrhetinic acid in the digestive tract, may be absorbed with liquiritigenin into the blood, and regulate the degranulation and cytokine biosynthesis in mast cells and basophils, which cause allergic diseases. Overall, it is believed that orally administered licorice can treat IgE-induced allergic diseases such anaphylaxix, rhinitis and asthma. Its effect might be due to its main constituents, glycyrrhizin, 18-β-glycyrrhetinic acid and liquiritigenin (Shin *et al.,* 2007).
Liquiritigenin and isoliquiritigenin have been shown to have an inhibition of xanthine oxidase activity *in vitro* and dose-related anti-allergic activities (Ma *et al*., 2005).

***Antibacterial activities***

The methanol extract of aerial parts of *G. glabra* showed antibacterial activity against several kinds of bacteria. Several flavonoids with C5 aliphatic residues were isolated as the effective constituents of licorice against methicillin-resistant *Staphylococus aureus* (MRSA) and restore the effects of oxacillin and β-lactam antibiotic against MRSA. Glabridin, glabren and lincochalcone A exhibited antimicrobial activity against *Helicobacter pylori in vitro*. The ether-water extracts of *G. glabra* were found to have effective antibacterial activity against all the five bacteria, *E.coli, B. subtilis, E. aerogenes,* *K. pneumonia* and *S. aureus* (Asl *et* Hosseinzadeh, 2008). *In vitro*, the drug inhibits the growth of *Bacillus subtilis, Mycobacterium tuberculosis, Aspergilus spp.* (WHO, 1999b), *Staphylococcus aureus, Mycobacterium smegmatis*, and *Candida albicans* (Newall et al., 1996b; WHO, 1999b) and this antimicrobial activity is attributed to the isoflavonoid constituents (grabidrin, glabrol and their derivatives) (Newall et al., 1996b).

The antitubercular phenolic compounds from *Glycyrrhiza glabra* and *Glycyrrhiza inflata* were previously identified as licoisoflavone and licochalcone A. Additionally, glabridin was more active against Gram-positive strains than Gram-negative. Glabridin has been reported to exhibit multiple pharmacological activities such as antimicrobial activity against *Helicobacter pylori*, MRSA, effect on adenosine 3´,5´-cyclic monophosphate phosphodiesterase, melanogenesis, inflammation, low-density lipoprotein oxidation, inhibition of human cytochrome P450s 3A4, 2B6 and 2C9 activities and protection of mitochondrial functions from oxidative stresses. Having the structural similarity in glabridin and hispaglabridin B, the study provides some insight to structure and activity relationship to some extent. Glabridin was active against *Mycobacterium* while hispaglabridin was inactive (Fig. 61). There are two free phenolic hydroxyls in glabridin at 1,3-positions which might be crucial in inducing the activity. The inactivity of hispaglabridin might be due to one of the hydroxyl in protected form by an isoprenyl group as benzopyrene ring (Gupta *et al.,* 2008).




1 2

**Fig. 61.** Chemical structures of glabridin (1) and hispaglabridin B (2) (adapted from Gupta *et al.,* 2008).

This findings support ethnomedical uses of *Glycyrrhiza glabra* to cure coughs and chest related ailments with the establishment of glabridin as a potent lead molecule for antimycobacterial activity (Gupta *et al.,* 2008).

***Anti-cariogenic studies***

Ammonium glycyrrhizate (from licorice root) is used in toothpastes, mouth rinses and other products for the control of periodontal disease (Asl *et* Hosseinzadeh, 2008). Several studies have been conducted on the effects of licorice and glycyrrhizin on the growth and acid production of oral bacteria associated with the development of dental caries. It was reported that glycyrrhizin could significantly reduce the growth and acid production of *Streptococcus*, *Actinomyces*, and *Bacterionema* species. Licorice powder, ammoniated glycyrrhizin, and monoammonium glycyrrhetic acid competitively reduced the metabolism of sucrose, glucose, and fructose, but were themselves minimally fermentable. In contrast to these results, it was reported that neither licorice “juice,” nor glycyrrhizin inhibited the growth of seven *Streptococcus mutans* strains. In the presence of sucrose, 0.5–1% glycyrrhizin had no effect on growth, but significantly inhibited bacterial adherence to glass by nearly 100% at the highest concentration tested. Licorice juice had similar anti-adherent properties with concentrations of 5 and 10% providing almost 100% activities. The buffering capacity of glycyrrhizin was not sufficient to affect the fall in pH caused by bacterial sucrose degradation. In an additional study evaluating the mechanism of the anti-adherent property of glycyrrhizin, its effect was examined on bacterial glucosyltransferase activity—an enzyme required in the formation of insoluble glucans required in plaque development. A crude preparation of *S. mutans* glucosyltransferase was significantly inhibited by glycyrrhizin in a concentration-dependent manner. The authors concluded that inhibition of bacterial glucosyltransferase activity may be a mechanism by which glycyrrhizin inhibits oral bacterial adherence, but that additional enzyme systems may also be affected (Isbrucker *et* Burdock, 2006). According to Asl et Hosseinzadeh (2008), glycyrrhizol A and 6,8-diisoprenyl-5,7-4´-trihydroxyisoflavone from the root of *G. uralensis* exhibited potent antibacterial activity against *Streptococcus mutans* with minimum inhibitory concentrations of 1 and 2 µg/mL, respectively.

***Antiviral activities***

The threat to global public health by pandemics of viral diseases like those induced by influenza and HIV viruses requires the urgent evaluation of herbal drugs which showed promise in traditional herbal medicine. The lack of effective drugs against influenza virus and the increasing problem with multiresistance in HIV infection makes *Glycyrrhiza* sp.-derived compounds important candidates for drug development. The data reviewed showed that several constituents of licorice roots have a potential as effective alternatives in combating a wide variety of respiratory, hepatic and systemic viral diseases by general immune modulatory and membrane effects, as well as specific effects on enzyme activity and expression related to selected viruses (Fiore *et al.,* 2008). Glycyrrhizin and polysaccharides of licorice can inhibit proliferation of viruses, especially multiplication of hepatitis virus, because they can directly inhibit nucleocapsid, induce formation of interferon and enhance the activity of natural killer lymphocytes (Ganzhong et al., 2003e). *In vitro* antiviral effects of licorice were observed for viruses causing respiratory tract infections like influenza virus and the severe acute respiratory syndrome (SARS) corona virus, the hepatitis B virus and *Epstein Barr* virus (Fiore *et al.,* 2005), human immunodeficiency virus (HIV) (Anonymous, 2005; Fiore *et al.,* 2005; Isbrucker *et* Burdock, 2006), encephalitis causing viruses like *Herpes simplex* virus and Japanese encephalitis virus (Fiore *et al.,* 2005). Glycyrrhizin has also been shown to inhibit viral replication and infectivity of *Herpes zoster*, *Varicella zoster*, and CMV (Anonymous, 2005). In another study glycyrrhizic acid induced apoptosis of primary effusion lymphoma (PEL) cells that were transformed by *Kaposi* sarcoma-associated herpesvirus and terminated latent infection in B lymphocytes (Asl *et* Hosseinzadeh, 2008).

The first report of an antiviral property of licorice constituents dates to the year 1979. Following screening investigations of plant extracts, it was found that glycyrrhizic acid, had antiviral activity inhibiting the growth and cytopathic effect of several DNA and RNA viruses, such as vaccinia (Fiore *et al.,* 2008; Isbrucker *et* Burdock, 2006; Newall et al., 1996b), herpes simplex (Fiore *et al.,* 2008; Newall et al., 1996b), *Newcastle* disease *(*Fiore *et al.,* 2008; Isbrucker *et* Burdock, 2006; Newall et al., 1996b) and vesicular stomatitis viruses *in vitro (*Fiore *et al.,* 2008; Isbrucker *et* Burdock, 2006; Newall et al., 1996b). *In vitro* studies have demonstrated that glycyrrhizin is effective at inhibiting the growth of a host of viruses under culture conditions including pathogenic flaviviruses, alphaviruses. *In vivo* and human studies tend to agree with the anti-viral efficacy of glycyrrhizin, but the mechanism of action may be more complex and promote an immune response (Isbrucker *et* Burdock, 2006).

***Effects of glycyrrhizin on hepatitis viruses***

***Hepatitis A***

It has been reported that licorice inhibits growth and cytopathology of many unrelated DNA and RNA viruses, while not affecting cell activity or cellular replication. Hepatitis A virus (HAV) causes acute hepatitis, a major public health concern in numerous countries. *In vitro* research with glycyrrhizin and a human hepatoma cell line has demonstrated glycyrrhizin completely suppresses the expression of the HAV antigen. In comparison to ribavirin, glycyrrhizin proved to be 10 times more potent at reducing infectivity of HAV, as measured by reduction in viral titres. Glycyrrhizin also exhibited five-fold greater cell selectivity than ribavirin in that it was less cytotoxic to the hepatoma cells (Anonymous, 2005). Another study referred a complete concentration-dependent inhibition of the expression of the hepatitis A virus (HAV) antigen and HAV infectivity by glycyrrhizin in the human hepatoma cell line PLC/PRF/5. The mechanism of this antiviral effect was the inhibition of the penetration and endocytosis in liver cells. Proposed mechanisms were the induction of a decrease in the negative charge on the cell surface and/or a decrease of membrane fluidity (Fiore *et al.,* 2008). These results indicate glycyrrhizin may be a potential therapeutic adjunct in fighting HAV infections (Anonymous, 2005).

***Hepatitis B and C***

Clinical studies on the efficacy of glycyrrhizin in the treatment of hepatitis B have generally shown favorable outcomes with the treatment normalizing elevated serum transaminases and improving liver function (Fiore *et al.,* 2008; Isbrucker *et* Burdock, 2006), with occasional complete recovery from hepatitis (Fiore *et al.,* 2008). In randomized controlled trials, glycyrrhizin, usually administered intravenously, induced a significant reduction of serum liver enzymes and caused an improvement in liver histology in comparison with placebo (Asl *et* Hosseinzadeh, 2008; Fiore *et al.,* 2008). In hepatitis B the virustatic effect could depend on inhibition of the intrahepatic transport and sialylation of the hepatitis B-virus (HBV) surface antigen (HBsAg) observed *in vitro*. In isolated rat hepatocytes glycyrrhizin suppressed the release of transaminase in the presence of either anti-liver cell membrane antibody or phospholipase $A_2$. The results indicated that the treatment of liver cells with antibody activates phospholipase $A_2$ in cell membranes leading to disintegration of the cell membrane and cell death, which resulted in the release of transaminases. Glycyrrhizin, suppressing the increase in phospholipase $A_2$ activity, inhibited the release of transaminases, which demonstrated its anticytolytic effect. *In vitro* experiments demonstrated that glycyrrhizin suppresses the secretion of hepatitis B surface antigen (HBsAg) by inhibiting the intracellular transport of HBsAg at the trans-Golgi area after *O*-linked glycosylation and before sialylation. Glycyrrhizin, as an immunomodulatory agent, given intravenously in combination with lamivudine was also useful in the treatment of subacute hepatitis due to hepatitis B (Fiore *et al.,* 2008). The antiviral proposed mechanisms include glycyrrhizin´s action on nuclear factor κ B, inhibition of tumor necrosis factor (TNF), induction of endogenous interferon production, and suppression of hepatitis B surface antigen (HBsAg) secretion (Verma *et* Thuluvath, 2007).

Glycyrrhizin (GL) is metabolized into 18-β-glycyrrhetinic acid (GA) and 18-β-glycyrrhetinic acid-3-*O*-β-D-glucuronide (GAMA) by β-D-glucuronidase in the liver and intestines (Fig. 64) (Asl *et* Hosseinzadeh, 2008; Wang *et al.,* 2007).

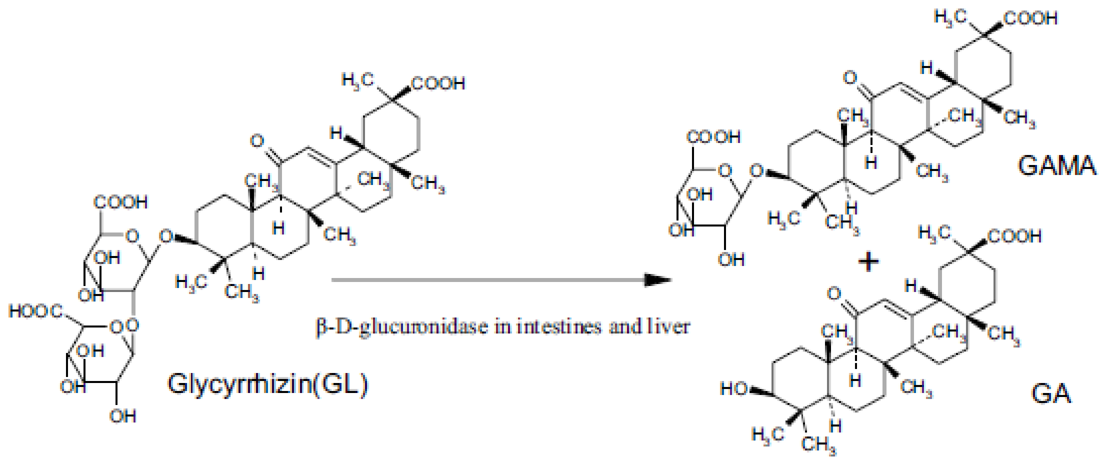



**Fig. 62.** Metabolism of glycyrrhizin catalyzed by β-D-glucuronidase in human liver and intestines (adapted from Wang *et al.,* 2007).

Structure-bioactivity relationship studies indicate that GA is the most active ingredient against platelet aggregation, tumor cell lines, rotavirus infection and growth of *Helicobacter pylori*, followed by GAMA and GL. Thus, GA is a better hepatoprotective drug than GAMA or GL (Wang *et al.,* 2007). It has been suggested that GL binds to hepatocytes (Fiore *et al.,* 2008; Wang *et al.,* 2007) to modify the expression of HBV (hepatitis B virus)-related antigens (Anonymous, 2009; Fiore *et al.,* 2008; Wang *et al.,* 2007) and suppress sialylation of HBV-surface antigen (HbsAg) (Fiore *et al.,* 2008; Wang *et al.,* 2007). This also applies to its hydrolytic metabolites (GAMA, GA) (Wang *et al.,* 2007).

Among the most recent studies, the effect of a formulation (Stronger Neo-Minophagen C, SNMC) containing 40 mg glycyrrhizin (2mg/ml), administered by injection to patients with chronic viral hepatitis should be mentioned (Fiore *et al.,* 2008; Asl *et* Hosseinzadeh, 2008). In Japan, SNMC is a commonly prescribed glycyrrhizin solution administered intravenously for the treatment of chronic hepatitis B and C (Anonymous, 2005; Asl *et* Hosseinzadeh, 2008; Isbrucker *et* Burdock, 2006). The formulation was evaluated at different doses and frequency of administration, and the overall short-term therapeutic response consisted of a dose-dependent effect suppressing alanine aminotransferase (ALT) levels in patients with chronic viral hepatitis. SNMC, although without specific activity against hepatitis virus, showed an antiinflammatory effect and was able to improve the clinical condition of patients with liver disease at various stages. Daily intravenous administration of 100 and 40 mL of the glycyrrhizincontaining preparation SNMC for 4 weeks was a safe and efficacious treatment in lowering or normalizing ALT levels in patients with chronic hepatitis B. Intravenous administration for 1 year of glycyrrhizinic acid in patients with chronic viral hepatitis B was able to produce a positive effect on the evolution of the disease, with a 30%–40% success rate, comparable to the results obtained with interferon (IFN) (Fiore *et al.,* 2008). On the basis of clinical and histological markers, it was concluded that SNMC can suppress liver necrosis and inflammation in patients with chronic hepatitis C, suggesting that a long-term treatment with the product might be useful in preventing liver cirrhosis and hepatocellular carcinoma (Asl *et* Hosseinzadeh, 2008; Fiore *et al.,* 2008). In several clinical trials, SNMC has been shown to significantly lower aspartate transaminase (AST), alanine transaminase (ALT), and gamma-glutamyltransferase (GGT) concentrations, while simultaneously ameliorating histologic evidence of necrosis and inflammatory lesions in the liver (Isbrucker *et* Burdock, 2006; Anonymous, 2005). In a double-blind, randomized, placebo-controlled trial investigating IV infusions of SNMC, short-term efficacy of licorice was confirmed with regard to ALT levels. The study showed the need for daily IV administration of SNMC, which may be impractical for patients. The study also demonstrated that after cessation of therapy the ALT-decreasing effect of licorice disappeared, suggesting the need for long-term administration (Anonymous, 2005). The European experience with SNMC in the treatment of hepatitis has also shown good results, equivalent to those produced with interferon treatment. However, in a doubleblind, randomized, placebo-controlled trial involving 57 patients with hepatitis C, the *i.v.* administration of 80–240mg glycyrrhizin/day, 3 days per week for 4 weeks improved serum alanine aminotransferase, but had no effect on hepatitis C RNA levels (Isbrucker *et* Burdock, 2006).

In a recent study in chronic HBV patients, SNMC at 2 doses (40 and 100 mL for 4 weeks followed by oral glycyrrhizin for 4 more weeks) resulted in normalization of ALT levels in more than 50% in both groups, although details on HBV DNA levels were lacking. SNMC also is being used increasingly in patients with chronic hepatitis C (CHC). Two studies with glycyrrhizin in 226 patients with CHC, although well designed, were disappointing because viral clearance was not achieved in any of the patients. In other study (n =170), the patients received either ursodesoxycholic acid plus intravenous glycyrrhizin (200 mg 3 times/wk) or glycyrrhizin alone, and those on combination therapy showed a better improvement (AST, 23% *vs* 9%; ALT, 33% *vs* 10%) and normalization (AST, 54% *vs* 22%; ALT, 32% *vs* 18%) of liver enzyme levels. In another large, retrospective, nonrandomized Japanese study with a 15-year follow-up period, it was observed significantly lower (*P* =.03) prevalence of cirrhosis (21% *vs* 35%) and HCC (hepatocellular carcinoma) (12% *vs* 25%) in those treated with SNMC. However, 10% developed hypokalemia and 3% developed hypertension. Furthermore, limited information was provided on viral loads and follow-up biopsy results, and variable doses of glycyrrhizin were used (200 mg 2–7 days/wk). These clinical trials showed that the beneficial effects of glycyrrhizin were largely biochemical (improvement in liver enzyme levels), but side effects (fluid retention, hypokalemia) were seen in up to 20%. Based on current evidence, the use of this drug cannot be recommended to patients with liver disease (Verma *et* Thuluvath, 2007).

Natural killer (NK) cell activity is known to play an important role in the elimination of virus-infected cells during chronic hepatitis. NK cell activity is also elevated in response to γ-interferon and interleukin-2. Due to the prior reports on elevation of γ-interferon by glycyrrhizin investigated NK cell activity among control subjects and patients with chronic liver diseases following the intravenous administration of 80–200mg glycyrrhizin/day (duration unknown). Glycyrrhizin administration was found to have no effect on NK cell activity and no further data was reported (Isbrucker *et* Burdock, 2006).

Preliminary evidence suggests that isolated constituents of licorice may be effective for treating hepatitis B and C. Glycyrrhizin- and glycyrrhizic acid-containing intravenous preparations show activity against hepatitis B and hepatitis C in humans, but the trials are too small to draw any definitive conclusions (Anonymous, 2009).

***Oral Lichen Planus***

Patients with chronic hepatitis C often experience oral lichen planus, an inflammatory disease characterized by lymphocytic hyperkeratosis of the oral mucosa. It is rarely cured and effective treatments are limited. In an open clinical trial, 17 hepatitis C-positive patients with oral lichen planus were given either routine dental care or 40 mL IV glycyrrhizin daily for one month. Among nine patients taking glycyrrhizin, six (66.7%) noted improved clinical symptoms, such as decreased redness, fewer white papules, and less erosion of the mucosa. In the non-glycyrrhizin group of eight patients, only one (14.3%) reported any improvement (Anonymous, 2005).

***Antiretrovirus effects***

Glycyrrhizin achieved a dose-dependent inhibition of the replication of human immunomoduficiency virus type 1 (HIV-1) in Mot-4 cells within the concentration range of 0.075 to 0.6 mmol. Within this concentration range, glycyrrhizin also effected a dose-dependent reduction in the protein kinase D activity of Mot-4 cells. Glycyrrhizin sulfate completely inhibited HIV-induced plaque formation in Mot-4 cells at a concentration of 1 mg.ml-1, the 50% inhibitory dose was 0.055 mg.ml-1. Glycyrrhizin was foud to be an effectient inhibitor for reverse transcriptase. The effect of glycyrrhizin sulfate was 4 times stronger than that of glycyrrhizin in molar terms (Shen *et al.,* 2007). Glycyrrhizin inhibited the cytopathic effect and the virus-specific antigen expression in HIV-infected MT-4 cells. Furthermore glycyrrhizin inhibited giant cell formation caused by HIV-infection in Molt-4 cells, which are sensitive to HIV and fuse to giant cells after infection, providing a parameter for determining the cytopathic effect of HIV. Glycyrrhizin sulphate was found to both inhibit cell-free viral infection and cell to cell infection. Some of these effects may be due to its ability to reduce membrane fluidity. Reduced membrane fluidity by glycyrrhizin could explain how it can inhibit cell-to-cell fusion by suppression of the formation of virological synapses. It was found that HIV-1 reverse transcriptase (rRT) functioned as an effective phosphate acceptor for recombinant human casein kinase II (rhCK-II) *in vitro*; this phosphorylation was inhibited by the glycyrrhetinic acid derivative, quercetin and a high dose (100 µg) of glycyrrhizin. RNA-Dependent DNA-polymerase (RDDP) activity was stimulated by about 2.5-fold after full phosphorylation of rRT by rhCK-II. Recent investigations have evaluated the effect of glycyrrhizin on HIV replication in cultures of peripheral blood mononuclear cells (PBMC) from HIV-infected patients. In 31% of the samples, glycyrrhizin inhibited more than 90% of HIV replication, including a non-syncytium-inducing variant of HIV (NSI-HIV). Glycyrrhizin induced the production of CC chemokine ligand (CCL) 4 and CCL5 in a dose-dependent manner, suggesting that the drug possesses the potential to inhibit NSI-HIV by stimulating the production of beta-chemokines which compete with the chemokine receptor mediated infection of cells by HIV. Among a variety of natural products described as anti-HIV agents, glycyrrhizin was found to have a mechanism of action which may at least in part be attributed to interference with virus–cell binding. More recently, an increasing quantity of data suggested that the antiviral effects of glycyrrhizin are linked to the induction of endogenous interferon gamma. Further, glycyrrhizin affects other cellular signalling pathways such as protein kinase II, casein kinase II and transcription factors such as activator protein1 and nuclear factor κB (Fiore *et al.,* 2008).

Two coumarins of *G. glabra*, glycocoumarin and licopyranocoumarin, were able to inhibit giant cell formation in HIV-infected cell cultures whithout any cytotoxicity. Also, it was also shown that lichochalcone A had anti-HIV activity (Asl *et* Hosseinzadeh, 2008).

**Effects on *herpesviridae***

Studies show licorice and its constituents, specifically glycyrrhizin, have antiviral activity against *Herpes simplex* and are capable of irreversibly inactivating the virus (Anonymous, 2005). Following this landmark study glycyrrhizin was evaluated for any *in vitro* antiviral action against varicella-zoster virus. In human embryonic fibroblast cells inoculated with five strains of the virus, glycyrrhizin produced an inhibitory effect on viral proliferation with an $IC_{50}$ (inhibitory concentration reducing activity to 50% of controls) of 0.71 mM. The selectivity index, defined as the ratio of $IC_{50}$ for host-cell DNA synthesis to $IC_{50}$ for virus replication, was estimated to be 30 (this value is not as high as for the most commonly used antiviral drugs, the selectivity index for acyclovir is close to 600). Pretreatment of cells with the drug 24h before inoculation was able to inhibit replication of the virus. Incubation of the virus for 30 min with a concentration of 2.4 mM glycyrrhizin was effective in inactivating more than 99% of the virus particles, and glycyrrhizin demonstrated an additive effect with other conventional antiviral drugs such as acyclovir, and also with human β-interferon. In studies demonstrating the inhibition of HSV-1 by glycyrrhizic acid *in vitro* a synergism of the inhibitory effect with the endogenous antiviral substance lactoferrin was found (Fiore *et al.,* 2008).

In a clinical trial of 31 patients with severely painful herpes zoster lesions, 12 patients were given 20 mg IV glycyrrhizin on six separate occasions. The remaining 19 patients received zoster immune gamma-globulin, recombinant β-interferon, or acyclovir. Glycyrrhizin ranked next to acyclovir for pain resolution at the end of one month (Anonymous, 2005).

A case report demonstrated a two-% topical glycyrrhizic acid cream (carbenoxolone sodium) applied six times daily in 12 patients with acute oral herpetic (*Herpes simplex*) infections resolved pain and dysphagia within 24-48 hours of beginning use. Moreover, the accompanying ulceration and lymphadenopathy gradually healed within 24-72 hours (Anonymous, 2005).

Recently, it has been demonstrated that a treatment with glycyrrhizic acid of cells latently infected with *Kaposi* sarcoma-associated herpesvirus (KSHV) is able to reduce the synthesis of a viral latency protein and to induce apoptosis of infected cells. This finding suggests that glycyrrhizic acid may be the key to find a novel way to interrupt latency in infected cells (Fiore *et al.,* 2008).

***Effects in murine herpes encephalitis***

Glycyrrhizin has also been demonstrated as effective in the treatment of herpes simplex-induced encephalitis in mice. Animals were administered 50 µg glycyrrhizin/g *i.p.*, on the third, fourth and fifth days following viral inoculation. The survival rate of among treated mice was 82% and only 38% in untreated animals. The mean virus yield per brain hemisphere in glycyrrhizin treated animals was approximately half that of control (Isbrucker *et* Burdock, 2006). In another study, intraperitoneal administration of glycyrrhizin increased the survival rate of the animals by about 2.5 times, and the viral replication in the brain was reduced to 45.6% of the control (Fiore *et al.,* 2008).

***Licorice and influenza virus***

New strategies for the cure of influenza are needed, since conventional antiviral agents, such as amantadine and ribavirin, are not very effective and have toxic side effects (Fiore *et al.,* 2008). Recently, olseltamivir and zanamivir were added to the available panel of antivirals, especially with regard to the $H_1N_1$ virus.

Glycyrrhizic acid has been shown to inhibit the recovery of hemagglutinins from influenza virus-infected embryonated hen eggs. The substance did not affect viral viability nor impair hemagglutinating activity of the virions, but was able to affect the growth of viruses in embryonic tissues, particularly at the late viral replication steps. A recent study was conducted using *Glycyrrhiza uralensis* ethanol extract in a culture of A549 human bronchial epithelial cells infected with influenza virus $H_1N_1$. The extract produced an inhibitory effect on the production of RANTES, the potent chemotactic cytokine for monocytes, basophils and T cells, typically detected in nasal secretions of patients with upper respiratory tract infection, and involved in the epithelial cell-mediated inflammatory process. The licorice extract was evaluated at concentrations in the range 20–200 µg/mL; at a maximal concentration, a 97.0 ± 1.8% inhibition in RANTES production was, suggesting that compounds derived from *Glycyrrhiza* spp. may be beneficial for the treatment of inflammatory processes related to viral infection (Fiore *et al.,* 2008).

BALB/c mice infected with influenza virus $A_2$ ($H_2N_2$) were unable to survive 10 times the mean lethal dose ($LD_{50}$) of virus. However, a complete survival was observed when these animals were treated with 10 mg glycyrrhizin/kg, *i.p.*, on the day prior to, the day after, and on the fourth day after infection. This same dosing regimen conferred 70% survival in mice infected with 50 times the viral $LD_{50}$. This response was demonstrated to be dose-dependent with improved survival in animals administered greater than 2.5mg glycyrrhizin/kg. Although the lung viral titers were decreased in glycyrrhizin-treated animals, *in vitro* assays demonstrated that this compound did not inhibit viral replication in cell cultures. This suggested that the anti-viral mechanism of glycyrrhizin was indirect, and possibly stimulated endogenous viral defense mechanisms. In examining this theory, the authors reported that the transplanting of splenic T-cells from glycyrrhizin-treated mice conferred resistance to infected mice that had not been treated with glycyrrhizin. The transplanting of other splenic cell subsets did not improve the survival of infected mice, indicating that glycyrrhizin was a specific inhibitor of the cell-mediated immunological response. The administration of gamma-interferon monoclonal antibody to infected mice blocked the anti-viral activity of glycyrrhizin treatment (Isbrucker *et* Burdock, 2006). These results confirm that the anti-viral activity of glycyrrhizin is due to its stimulating of gamma -interferon production by T-cells (Fiore *et al.,* 2008; Isbrucker *et* Burdock, 2006).

When mice were treated intraperitoneally with 10 mg of glycyrrhizin/kg body weight 1 day before exposure to 10 $LD_{50}$ (lethal dose killing 50% of animals) of the influenza virus $A_2$ and 1 and 4 days after the infection, all of the animals survived over the experimental period of 21 days. Conversely, the mean survival time in control mice was 10.5 days, and there were no survivors. The grade of pulmonary consolidation and the virus titers in the lung tissues of infected mice treated with glycyrrhizin were significantly lower than those in the lung tissues of infected mice treated with saline. An interesting finding was that when splenic T cells from glycyrrhizin-treated mice were transferred to mice exposed to influenza virus, all the recipients survived, while no survivor was seen in recipient mice inoculated with native T cells, or with splenic B cells and macrophages from glycyrrhizintreated mice. The administration of glycyrrhizin to infected mice in combination with anti-gamma interferon monoclonal antibody did not produce any antiviral effect. Other previously reported studies indicated that in mice glycyrrhizin and glycyrrhetinic acid were able to induce the production of interferon, suggesting this as a possible mechanism of action against viral infection (Fiore *et al.,* 2008).

***Licorice and Severe Acute Respiratory Syndrome (SARS) related coronavirus***

A new coronavirus has been identified in patients with SARS, and the disease has drawn enormous attention and caused fear worldwide since early 2003 (Fiore *et al.,* 2008). Although the disease is now under control, the possibility of a return of the pathology has stimulated the search for a remedy (Cinatl *et al.,* 2003; Fiore *et al.,* 2008). Several studies have been reported, but a specific treatment for SARS has not yet been established. Various pharmacological treatments have been suggested, such as steroids, ribavirin, interferon and also glycyrrhizin (Fiore *et al.,* 2008). Preliminary evidence suggests that glycyrrhizin may inhibit the growth of the coronavirus, which is associated with SARS. The exact mechanism of the antiviral effect of glycyrrhizin is not known (Anonymous, 2009; Cinatl *et al.,* 2003; Fiore *et al.,* 2008).

Glycyrrhizin inhibits SARS-associated coronavirus (SARS-CoV) replication in *Vero* cells with a selectivity index of 67. In addition to inhibition of virus replication, glycyrrhizin is able to inhibit adsorption and penetration of the virus during the early steps of the replicative cycle. The activity of glycyrrhizin is lower when added during the adsorption period than after virus adsorption ($EC_{50}$ is 600 mg/L *vs* 2400 mg/L, respectively). Glycyrrhizin has been found to be most effective when given both during and after the adsorption period (Fiore *et al.,* 2008). Glycyrrhizin affects cellular signalling pathways such as protein kinase C; casein kinase II; and transcription factors such as activator protein 1 and nuclear factor KB. Furthermore, glycyrrhizin and its aglycone metabolite 18-β-glycyrrhetinic acid upregulate expression of inducible nitrous oxide synthase and production of nitrous oxide in macrophages (Cinatl *et al.,* 2003). Studies show that glycyrrhizin induces nitrous oxide synthase in *Vero* cells and that virus replication is inhibited when a nitrous oxide donor (DETA Nonoate) is added to the culture medium (Cinatl *et al.,* 2003; Fiore *et al.,* 2008). Since glycyrrhizin was shown to be able to inhibit SARS-CoV replication *in vitro*, the activity of several glycyrrhizic acid derivatives was evaluated. The introduction of 2-acetamido-beta-D-glucopyranosylamine into the glycoside chain of glycyrrhizin produced a 10-fold increase of the anti-SARS-CoV activity. Other compounds, such as amides and conjugates of glycyrrhizin with two amino acid residues presented up to 70-fold increased activity against the virus; however, the cytotoxicity increased as well in those derivatives, resulting in a decreased selectivity index (Fiore *et al.,* 2008).

***Effects on Cytomegalovirus***

Cytomegalovirus (CMV) is the most common cause of congenital and perinatal viral infections throughout the world. It manifests with profound liver dysfunction and poor weight gain (Anonymous, 2005). Investigation of the effects of glycyrrhizin on CMV infection of human monocytic and human embryonic lung cell lines showed that it inhibited viral antigen expression (Fiore *et al.,* 2008). In a series of studies, both oral and IV preparations of licorice (SNMC) were administered to infants with CMV. Liver dysfunction and weight gain improved in nearly all cases compared to groups without treatment (Anonymous, 2005).

***Effects on other viruses***

Glycyrrhizin was tested *in vitro* for antiviral activities against several pathogenic flaviviruses involved in diseases such as dengue, Japanese encephalitis, mammalian tick-borne encephalitis and yellow fever. Glycyrrhizin was found to be able to inhibit the replication of flaviviruses at high non-cytotoxic concentrations (Fiore *et al.,* 2008). The target for glycyrrhizin action against the vesicular stomatitis virus (VSV) has been identified as enzyme kinase P, which is essential for the early stages of viral replication. Glycyrrhizin at low doses was found to selectively inhibit protein phosphorylation by kinase P, without any significant effect on other kinases. It has been reported that this direct binding of glycyrrhizin to the virus-associated kinase results in its inactivation and a reduction of viral infectivity (Fiore *et al.,* 2008). In *Hela* cell culture, *Radix Glycyrrhizae* was found to be a inhibitor of respiratory syncytial virus (RSV) (Dong *et al.*, 2004; Shen *et al.,* 2007). An effect of glycyrrhizic acid was also reported against *Epstein-Barr* virus (EBV), which produces infectious mononucleosis. The inhibition of EBV replication *in vitro* is dose-dependent. It has been suggested that the drug interferes with an early step of EBV replication, possibly penetration, without any effect on viral adsorption, or inactivation (Fiore *et al.,* 2008). Glycyrrhizin was also effective against varicella-zoster virus (VZV) replication when human embryonic fibroblast (HEF) cells were treated 24 h before the inoculation (Shen *et al.,* 2007).

***Antiprotozoal activities***

Chinese licorice roots were found to potentially inhibit the growth of *Plasmodium falciparum* and *Leishmania donovani* in *in vitro* studies. Chalcones such as licochalcone A from Chinese licorice roots are known to possess antiplasmodial activity. Also, chalcones have a potent antileishmanial activity and might be developed into a new class of antileishmanial drugs. It was found that chalcones, such as lichochalcone A, alter the ultrastructure of the parasite mitochondria and inhibit their function by selectively inhibiting fumarate reductase in the respiratory chain of the parasite (Asl *et* Hosseinzadeh, 2008).

***Antioxidative activites***

The constituents of *G. inflata*, licochalcone A, B, C, D and echinatin, were effective in preventing microsomal lipid peroxidation induced by Fe (III)-ADP/NADPH and lincochalcone B, D showed potent antioxidative and superoxide scavenging activities. Furthermore, the isoflavone derivatives of *G. glabra* such as glabridin inhibited lipid peroxidation in rat liver microsomes and protected mitochondrial functions from oxidative stresses (Asl *et* Hosseinzadeh, 2008). Glabridin has also been reported to possess antioxidant properties (Cui *et al.,* 2008). Moreover, glabridin was a potent antioxidant toward LDL oxidation in *in vitro* and *in vivo* studies (Asl *et* Hosseinzadeh, 2008; Fiore *et al.,* 2005). The consumption of licorice or glabridin by atherosclerotic apolipoprotein E-deficient ($E^{o}$) mice caused a significant reduction not only in their LDL oxidation (Asl *et* Hosseinzadeh, 2008; Fiore *et al.,* 2005), but also in the development of atherosclerotic lesions. It seems that glabridin may possess this property by two mechanisms: first it binds to the LDL and substantially protects its oxidation. The hydroxyl groups on the B ring of glabridin were found to be most important for its antioxidative properties. Second, it accumulates in cells such as macrophages, causing a reduction of cellular oxidative stress by reducing cellular glutathione. In addition, other constituents of *G. glabra* such as isoflavones hispaglabridin A, hispaglabridin B and 4´-*O*-methylglabridin, the two chalcones, isoprenylchalcone derivative and isoliquiritigenin were antioxidants against LDL oxidation (Asl *et* Hosseinzadeh, 2008).

*G. glabra* extracts showed great antioxidant and free radical scavenging activities in topical formulations and may be used in topical formulations in order to protect the skin against damage caused by free radical and reactive oxygen species (Asl *et* Hosseinzadeh, 2008).

Certain licorice constituents possess significant antioxidant and hepatoprotective properties. Glycyrrhizin and glabridin inhibit the generation of reactive oxygen species (ROS) by neutrophils at the site of inflammation. *In vitro* studies have demonstrated licorice isoflavones, hispaglabridin A and B, inhibit $Fe^{3+}$-induced mitochondrial lipid peroxidation in rat liver cells (Anonymous, 2005). Hispaglabridin A, especially, showed a potent antioxidative activity against peroxidation induced by Fe-ascorbate (Asl *et* Hosseinzadeh, 2008). Other research indicates glycyrrhizin lowers lipid peroxide values in animal models of liver injury caused by ischemia reperfusion (Anonymous, 2005).

### *Anticarcinogen and antitumor actions*

Licorice root has been identified by the National Cancer Institute (US) as possessing cancer-preventive properties (Asl *et* Hosseinzadeh, 2008). The effects first reported referring to beneficial effects on excessive tissue growth around nails, in the eye and in form of tumours have been confirmed *in vitro* by demonstrating that liquorice causes apoptosis. This is evident from its antineoplastic effect against melanoma and gastric cancer cells (Fiore *et al.,* 2005). It was reported that the water extract of *G. glabra* effectively inhibits growth of *Ehrlich* ascites tumor (EAT) cells *in vivo* and *in vitro* (Sheela *et al.,* 2006; Asl *et* Hosseinzadeh, 2008) and also acts as an inhibitor of vascular endothelial growth Factor (VEGF) (Sheela *et al.,* 2006) inhibiting angiogenesis in *in vivo* assay (Asl *et* Hosseinzadeh, 2008; Sheela *et al.,* 2006). Inhibition of EAT cell growth *in vivo* with corresponding reduction in cell number, body weight and ascites volume confirms the early findings of *G. glabra* as anti-neoplastic agent. Treatment with the *soxhlet* extracted solvent fractions of *G. glabra* on EAT-bearing mice showed that methanol extract and water extract induced inhibition of proliferation of tumor cells *in vivo* and *in vitro*. A compound licocoumarone isolated from methanolic extract of *G. glabra* has been shown to be an apoptosis-inducing component. Some results indicate that the methanolic extract inhibits EAT cell proliferation *in vivo*. This effect may probably be due to the presence of licocoumarone (Fig. 63) (Sheela *et al*., 2006).

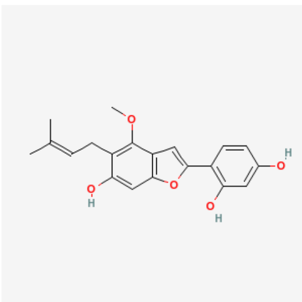



**Fig. 63.** Chemical structure of licocoumarone (adapted from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=503731&loc=ec_rcs) visited 1/1/2010).

A decrease in the cell number of EAT cells treated with *G. glabra* aqueous extract *in vitro* explains the strong antiproliferative effect of proteins present in the water extract of *G.*

*glabra.* Results show that there is inhibition of neovascularization by *G. glabra* extract in chorioallatoic membrane (CAM). Since there is inhibition of neovascularization by *G. glabra* extract, it supports our view that *G. glabra* extract may repress the expression of VEGF like factors thereby inhibiting the formation of new blood vessels and this was confirmed by ELISA. Results suggest that the extract from *G. glabra* may be a potential supplemental source for cancer treatment, and deserves further studies. Further work is ongoing to delineate the underlying mechanism and signalling cascades involved in targeting angiogenesis (Sheela *et al*., 2006). Also, the ethanol extract of *G. uralensis* root induced apoptosis and G1 cell cycle arrest in MCF-7 human breast cancer cells. On the other hand, there are many studies about the anticancer effects of several derivatives of its components both in *in vivo* and *in vitro* studies (Asl *et* Hosseinzadeh, 2008). Glycyrrhetinic acid could also trigger the proapoptotic pathway by inducing mitochondrial permeability transition and this property may be useful for inducing apoptosis of tumor cells. Recently, licochalcone E, a new retrochalcone from the roots of *G. inflata*, exhibited the most potent cytotoxic effect compared with the known antitumor agents, licochalcone A and isoliquiritigenin (Asl *et* Hosseinzadeh, 2008). Isoliquiritigenin caused great interest after it was found to have effects in: inhibiting proliferation of the human non-small cell lung cancer A549 cell line, inducing apoptosis and locking cell cycle progression in the G1 phase, suppressing azoxymethane-induced colon carcinogenesis in *ddY* mice, and inhibiting the growth of prostate cancer. It had been suggested that isoliquiritigenin merits investigation as a potential cancer-chemopreventive agent in humans (Ma *et al*., 2005).

Licorice appears to have anti-estrogenic and estrogenic action. Preliminary research indicates that licorice does not stimulate the growth of estrogen dependent breast cancer cells. However, the estrogenic effects of licorice might be concentration dependent. Glabridin, an isoflavone constituent of licorice, seems to have an estrogen receptor-dependent growth-promoting effect at low concentrations. At higher concentrations, it seems to have an estrogen receptor-independent antiproliferative effect (Anonymous, 2009).

It was previously reported on the inhibitory effect of *Glycyrrhizae radix* on mouse endometrial carcinogenesis. Both *Glycyrrhizae radix* and glycyrrhizin exerted a significant decrease in the COX-2, IL-1 α and TNF-α mRNA expressions. Glycyrrhizin (GL) generated a significant decrease in the incidence of endometrial adenocarcinoma. Accordingly, the preventive effects of *Glycyrrhizae radix* may be attributable to glycyrrhizin, thus being related with the suppression of COX-2, IL-1α and TNF-α. Gl radix and GL could therefore be a promising formula for the chemoprevention of human endometrial cancer (Shen *et al.,* 2007).

Several animal and *in vitro* studies indicate glycyrrhizin and its constituents possess anticarcinogenic activity against a variety of cancers, warranting further investigation in clinical trials (Anonymous, 2005).

***Hepatoprotective effects***

It is known in the traditional system of medicine for the licorice use in liver diseases. It is a major component of many antihepatotoxic polyherbal formulations. Isoflavan derivatives glabridin, hisplaglabridin A, hisplaglabridin B and 4'-*O*-methyl glabridin have been isolated from *G. glabra*. These chemicals were reported to provide protection against oxidative stress. The biochemical damage produced by active oxygen species and free radicals has emerged as a fundamental pathway of liver injury. Despite the use of *G. glabra* in liver disorders, no systematic studies on its active oxygen scavenging properties have been reported. In short, $CCl_4$-induced damage produces alteration in the antioxidant status of the tissues, which is manifested as an abnormal histopathology. In a recent study, *G. glabra* restored all these changes. So, it can be concluded that the herb is a potential antioxidant and attenuates the hepatotoxic effect of $CCl_4$ by acting as an *in vivo* antioxidant and thereby inhibiting the initiation and promotion of lipid peroxidation or by an accelerated scavenging of free radicals and their products by conjugation with glutathione aided by glutathione-S-transferase (Ragesh *et* Latha, 2004). Also glycyrrhizin and glycyrrhetinic acid show hepatoprotective effects (Blumenthal, 2003). Glycyrrhetinic acid is thought to act by inhibition of the cytochrome P-450 system required for the metabolism of $CCl_4$ to the highly reactive radical $CCl_3$ (Newall et al., 1996b). In an *in vitro* study, glycyrrhizin was hepatoprotective, probably by preventing changes in cell membrane permeability (Asl *et* Hosseinzadeh, 2008). Nevertheless it was suggested that glycyrrhetinic acid is a better hepatoprotective drug than glycyrrhizin *in vitro* study (Asl *et* Hosseinzadeh, 2008), namely against $CCl_4$- induced toxicity (Asl *et* Hosseinzadeh, 2008; Newall et al., 1996b) and retrorsine-induced liver damage, respectively, in mice and rats. Furthermore, in a hepatocyte model of cholestatic liver injury, glycyrrhizin exhibited pro-apoptotic properties, whereas glycyrrhitinic acid is a potent inhibitor of bile acid-induced apoptosis and necrosis (Asl *et* Hosseinzadeh, 2008). Results of *in vitro* and animal (rat) studies supported further that glycyrrhizin inhibits lipid peroxidation, thereby protecting the rat hepatocytes. It was shown that glycyrrhizin inhibits immunomediated cytotoxicity against hepatocytes and the murine NFκB activity in the murine liver injury induced by $CCl_4$-ethanol. Moreover, glycyrrhizin inhibited anti-FAS antibody-induced elevation of ALT in mice. Another group demonstrated that glycyrrhizin reduced ALT levels, steatosis and fibrosis in the mouse model of liver injury induced by $CCl_4$ and ethanol. This experiment showed a concomitant reduced nuclear factor-kappa B binding (Fiore *et al.,* 2008).

It was showed that liquiritigenin (LQ), an aglycone of liquiritin in *G. radix*, exerts cytoprotective effects against heavy metal-induced toxicity in vitro. This study investigated in vivo protective effects of LQ against acute liver injuries induced by acetaminophen (APAP) or APAP plus buthionine sulfoximine (BSO) (Shen et al., 2007). Licorice constituents also exhibit hepatoprotective activity by lowering serum liver enzyme levels and improving tissue pathology in hepatitis patients (Anonymous, 2005). Glycyrrhizin reduces the toxic action of carbon tetrachloride- and galactosamine- induced cytotoxicity in cultures rat hepatocytes, through its antioxidant activity. Glycyrrhizin inhibited histamine release from rat mast cells and prevent carbon tetrachloride-induced liver lesions and macrophage-mediated cytotoxicity. Glycyrrhizin protected the liver apparently through its membrane stabilization effects (WHO, 1999b).

In a recent study, SNMC reduced serum level of alanine aminotransferase (ALT), albumin (ALB) and total bilirubin (TBIL), and attenuated hepatocyte apoptosis, leading to the secondary liver injury induced by lipopolysaccharide (LPS). Its related mechanisms such as reducing the release of NO and endothelin-1 (ET-1), restraining the formation of hepatic sinusoid microthrombi and microcirculation dysfunction, inhibiting immunologic injury caused by cytokines especially TNF-α, and suppressing the formation of endotoxin, may contribute to the protective effect against fulminant hepatic failure (FHF). However, in this study, SNMC failed to raise the albumin levels during FHF, probably due to the longer half life of albumin. The results suggest that SNMC can effectively attenuate hepatocyte apoptosis. The release of cytochrome C (Cyt-C) is a key event in the apoptosis process. Cyt-C has a duplex function as an initiator to activate cell apoptosis and participate in electron transfer. Cyt-C shifting to the cytoplasm could bring about a cascade of reactions of caspases, finally activate caspase-3 and result in hepatocyte apoptosis. Meanwhile, we speculated that SNMC inhibited the progression of hepatocyte apoptosis mainly by stabilizing the mitochondrial membrane and inhibiting the release of Cyt-C and subsequent caspase-3 activations. A study demonstrated that SNMC not only reduced serum aminotransferase and bilirubin, but also attenuated the hepatocyte apoptosis. SNMC reduced the necrotic area and increased the survival rate of mice by promoting hepatocyte regeneration and recovery of denatured cells, and protecting the undamaged cells. However, the dosages of SNMC in the treatment of FHF and the therapeutic time have not yet been firmly established. In summary, the results of the present study support SNMC treatment for FHF, but the precise mechanism should be further studied (Yang *et al.,* 2007).

***Antidepressant effects***

A recent study show that aqueous extract of *G. glabra* produced antidepressant-like effect in mice, and this effect seems most likely to be mediated through an interaction with adrenergic and dopaminergic systems. Glycyrrhizin inhibited monoamine oxidase, thereby increased the levels of monoamines like epinephrine and dopamine in brains of mice (Dhingra *et* Sharma, 2006). Glabridin inhibited serotonin reuptake. In addition, recently, the aqueous extract of *G. glabra* L. showed antidepressant activity in both the forced swimming test (FST) and tail suspension test (TST) in mice (Asl *et* Hosseinzadeh, 2008). It was demonstrated that two flavonoids, liquiritin and isoliquiritin, isolated from *G. uralensis* appeared to produce antidepressant-like effect in the FST and TST in mice. In addition, there were no differences in antidepressant-like effect between liquiritin and isoliquiritin. And the study suggested that the increase in 5-hydroxytryptamine and norepinephrine in the CNS might be one of the possible mechanisms (Zhao *et al.,* 2008).

***Enhancing-memory effects***

*Glycyrrhiza glabra* has also been reported to enhance memory, but licorice from other genera has not been reported to have such an activity. The active component for this effect is still unknown (Cui *et al.,* 2008). More recently, animal studies indicate aqueous extracts of *G. glabra* may have memory-enhancing activity via reversal of chemically-induced amnesia, as measured by maze and passive avoidance testing in mice (Anonymous, 2005). Immunohistochemical studies suggested the existence of chronic inflammation in certain regions of the brain in *Alzheimer´*s disease patients. It has also been observed that elderly patients suffering from *Alzheimer´*s disease show reduced symptoms upon chronic use of anti-inflammatory drugs. Grabridin showed anti-inflammatory activity, which would certainly help *Alzheimer* patients by reducing the inflammatory components of *Alzheimer´*s disease (Cui *et al.,* 2008). Oxygen free radicals are implicated in the process if ageing and may be responsible for the development of *Alzheimer´*s disease in elderly persons. Oxigen-containing free radicals and other products of oxidative metabolism have been shown to be neurotoxic, and antioxidant-rich diets improved cerebellar physiology and motor learning in aged rats. Glabridin has also been reported to possess antioxidant properties. The neuroprotective effect of glabridin may be attributed to its antioxidant properties, which results in susceptible brain cells being exposed to less oxidative stress, in reduced brain damage and improved neuronal function. Thus, the combination of anticholinesterase, anti-inflammatory and antioxidant effects exhibited by glabridin may all be eventually responsible for its memory-enhancing effect (Cui *et al.,* 2008). In addition, isoliquiritigenin showed protective effects in cerebral ischemia-reperfusion injury in rats. Carbenoxolone has shown anticonvulsant, sedative and muscle relaxant activities in mice and in genetically epilepsy prone rats (GEPRs) (Asl *et* Hosseinzadeh, 2008). Also, it was able to suppress the generation of superoxide anions and hydrogen peroxide in macrophages and it also showed protective effects in the skeletal muscle and hippocampus against acute ischemic-reperfusion effects in rats. In addition it could decrease the learning performances of rats in a spatial memory task (Asl *et* Hosseinzadeh, 2008).

***Cardiovascular effects***

Licorice showed an antiplatelet aggregation effect. In other experiments, glycyrrhizin has been identified as a thrombin inhibitor in *in vitro* and *in vivo* studies and it was believed that glycyrrhizin might be used as a model for searching new antithrombotic drugs (Asl *et* Hosseinzadeh, 2008). Antiplatelet activity in vitro has been documented for a 3-arylcoumarin derivative, GU-7, isolated from liquorice. Gu-7 was thougth to inhibit platelet aggregation by increasing intraplatelet cyclic AMP concentration (Newall et al., 1996b). A recent study reported that glycyrrhizin reduced thrombosis formation in rats in a dose-dependent manner. The $IC_{50}$ for intravenous glycyrrhizin was 75mg/kg in a stasis-induced model, but only 230mg/kg in an arteriovenous shunt model. Interestingly, the antithrombic activity was very time-dependent with an effective half life of less than 60min in both models. The mechanism of action did not appear to be similar to that of heparin (Isbruker *et* Burdock, 2006). Also, *G. glabra* accelerated the metabolism of cells in the bone marrow erythroid stem and increased the animal's resistance to stress. Isoliquiritigenin is reported to have a vasorelaxant effect. It could also able to decrease tube formation in vascular endothelial cells. Thus, the anti-angiogenic effect of licorice extract depended on the anti-tube formation effect of isoliquiritin. On the other hand, as for the estrogen-like activities of glabridin in *in vivo* and *in vitro* studies, it was demonstrated that it could modulate vascular injury and atherogenesis. Therefore, it is suggested for the prevention of cardiovascular diseases in post-menopausal women (Asl *et* Hosseinzadeh, 2008).

***Immunomodulatory activities***

Several immunomodulatory activities have been attributed to glycyrrhizin and glycyrrhetinic acid. The same results were seen with lichochalchone A and some analogues which showed immunomodulatory effects. On the other hand, glycyrrhizin selectively activated extrathymic T cells in the liver and in human T cell lines and glycyrrhizic acid enhanced Fas-mediated apoptosis without alteration of caspase-3-like activity. Glycyrrhizin also improved the impaired resistance of thermally injured mice to herpes virus infection. Moreover, glycyrrhetinic acid was an inducer of type 2 antagonistic $CD_{41}$ T cells in *in vivo* and *in vitro* studies. It improved the resistance of mice infected with LP-BM5 murine leukemia virus (MAIDS) mice to *Candida albicans* infection. Also, it stimulated macrophagederived NO production, and was able to up-regulate iNOS expression through nuclear factor *k*B (NF- *k*B) transactivation in murine macrophages. Both of them could induce interferon activity and augment natural killer cell activity and in this study glycyrrhizin was superior to glycyrrhetinic acid in inducing interferon. It also has inhibitory effects on TNF-alpha-induced IL-8 production in intestinal epithelial cells. In addition, there are some studies on the immunomodulatory effects of polysaccharide fractions obtained from shoots of *G. glabra* and hairy roots of *G. uralensis in vitro*. GR-2IIa and GR-2IIb, two isolated acidic polysaccharides of *G. uralensis*, have shown anticomplementary activity. Also, GR-2IIc had both anticomplementary activity and mitogenic activity. Recently, the haemolytic activities of *G. uralensis* saponins (GLS) and its adjuvant potentials against ovalbumin (OVA) were established in mice (Asl *et* Hosseinzadeh, 2008).

Glycyrrhizin inhibited to some extent prostaglandin E2 bio-synthesis by the activated rat peritoneal macrophage, whereas in the cell-free experiment glycyrrhizin and glycyrrhetinic acid showed little effect on the inhibition of cyclo-oxygenase. The *in vitro* immunomodulatory activities of a number of saponins and glycyrrhizic acids are described. Addition of these saponin preparations to mouse spleen cell cultures resulted in significant cell proliferation. B-cells were induced to proliferate in the presence of the saponin. On the other hand, glycyrrhizic acid stimulated both T- and B-lymphocytes equally. The selective proliferation of subtypes of lymphocytes correlated with restimulation responses by polyclonal mitogens. Incubation of lymphocytes in the presence of saponins caused effector cell generation as determined in a one-way mixed lymphocyte reaction. In the case of lymphocytes cultured in the presence of saponins or glycyrrhizic acid, the supernatants contained active soluble factors. It was demonstrated by the observation that glycyrrhizic acid has the most profound immunomodulatory activity *in vitro* (Shen *et al.,* 2007).

***Renal effects***

Glabridin showed an antinephritis effect in the mouse glomerular disease model. Also, glycyrrhizin could ameliorate renal defects in gentamicininduced acute renal failure in rats. Also, the extract of *Radix Glycyrrhyzae* could protect the kidneys against peroxynitrite (ONOO−)-induced oxidative stress *in vivo* through scavenging ONOO− and/or its precursor NO (Asl *et* Hosseinzadeh, 2008).

***Respiratory effects***

Licorice has been used as a cough-relieving medicinal herb from ancient times. It seems that mucilage present in it or secretion produced under the influence of the active substances covers the oral and throat mucosa soothing its irritability and relieving dry cough (Asl *et* Hosseinzadeh, 2008). Choline ester of glycyrrhetinic acid can produce a central antitussive effect. After oral administration of licorice, the drug may cover the mucosa of the throat and relieve local local inflammatory irritation to control cough and promote secretion of mucus from the throat and bronchi to produce an expectorant effect (Ganzhong et al., 2003e). The demulcent action of the drug is due primarily to glycyrrhizin. The antitussive and expectorant properties of the drug have also been attributed to glycyrrhizin, which accelerates tracheal mucus secretion (WHO, 1999b). Recently in one study, *Radix Glycyrrhyzae* produced a persistent antitussive effect in the guinea-pig, suggesting that liquiritin apioside, a main antitussive component, plays an important role in the earlier phase, while liquiritigenin and liquiritin play an important role in the late phase. This result is keeping with the previous antitussive effects of licorice (Asl *et* Hosseinzadeh, 2008).

***Gastrointestinal effects***

***Antiulcer activity***

Licorice has been used as a demulcent and emollient for 2,000 years to promote the healing of ulcers by acting on the mucosal layer (Anonymous, 2005). The antiulcer activity of *Radix Glycyrrhyzae* has been demonstrated both experimentally and clinically. Intraperitoneal, intraduodenal, or oral administration of aqueous or alcoholic extracts of *Radix Glycyrrhyzae* reduced gastric secretions in rats, and it inhibited the formation of gastric ulcers induced by pyloric ligation, aspirin, and ibuprofen (Anonymous, 2009). Glycyrrhizin and its aglycone (glycyrrhetic acid, enoloxone) both have antiphlogistic activity and increase the rate of mucus secretion by the gastric mucosa (WHO, 1999b). Glycyrrhizinic acid seems to act by raising the local concentration of prostaglandins that promote mucous secretion and cell proliferation in the stomach, leading to healing of ulcers in experimental studies (Asl *et* Hosseinzadeh, 2008). In cases of acetic acid-induced chronic gastric ulcer in rats, oral administration of glycyrrhizic acid afforded a cure rate of 97.7%. Glycyrrhizic acid not only decreased gastric acidity but also promoted healing of ulcers (Shen *et al.,* 2007). The anti-stress ulcerogenic activity of deoxoglycyrrhhetol, a reducted compound of glycyrrhetinic acid, was studied by the experiment of restraint water immersion using mice and rats. This compound was administered orally to the animals. It was effective to inhibit stress-induced ulcer in mice at 200 mg/kg. It was noted that the molecular modified compounds brought a remarkable enhancement of therapeutic effect (Shen *et al.,* 2007). Glycyrrhetic acid (enoxolone) produced its antiulcer activity by inhibiting 15-hydroxyprostaglandin dehydrogenase and $\Delta^{13}$-prostagladin reductase. Inhibition of these two enzymes stimuled an increase in the concentration of prostaglandins E and $F_{2\alpha}$ in the stomach, which promoted the healing of peptic ulcers owing to a cytoprotective effect on the gastric mucosa (WHO, 1999b). Glycyrrhizin (as carbenoxolone sodium) speeds healing of gastric ulcers and protects against aspirin-induced damage to the gastric mucosa (Anonymous, 2005). Carbenoxolone stimulates gastric mucus production, enhances the rate of incorporation of various sugars into gastric mucosal glycoproteins, promotes mucosal cell proliferation, inhibits mucosal cell exfoliation, inhibits prostaglandin degradation, increases the release of PGE2 and reduces the formation of thromboxane B2 and regulates DNA and protein synthesis rates in gastric mucosa. More recently nitric oxide has been claimed to contribute to the anti-ulcer effect of carbenoxolone (Borrelli *et* Izzo, 2000). In view of the wide range of alternative therapies now available and of the numerous side effects, carbenoxolone use has been limited; indeed carbenoxolone produces effects similar to those of aldosterone excess (sodium retention and hypokalaemia leading to hypertension, oedema and cardiac failure) (Borrelli *et* Izzo, 2000; Newall et al., 1996b). Unfortunately, the side effects of licorice limit its potential to be used on a long-term basis for treatment of peptic ulcer disease (Anonymous, 2005).

To avoid the side effects of glycyrrhizin in liquorice preparations, a glycyrrhizin-free fraction of liquorice extracts was studied (Borrelli *et* Izzo, 2000). The glycyrrhizin-free fraction, called FM 100 fraction, was found to be effective for gastric ulcers in rats by inhibiting gastric juice secretion (Borrelli *et* Izzo, 2000; Takagi *et al.,* 1971). New isoflavonoids and chalcones from the fraction FM 100 were isolated, which could contribute to the anti-ulcer activity of liquorice (Borrelli *et* Izzo, 2000). A processed form of licorice, DGL (removal of the glycyrrhizin), was produced to eliminate potential adverse effects, including licorice-induced hypertension (Anonymous, 2005). DGL is an effective anti-ulcer agent (Anonymous, 2009; Borrelli *et* Izzo, 2000) without the fluid retention or electrolyte imbalance of carbenoxolone (Anonymous, 2009). DGL protected against gastric ulceration in rats induced by pyloric ligation and increased healing of peptic ulcer in patients. Moreover, DGL reduced bile acid-induced hydrogen ion back-diffusion across the canine gastric mucosa and diminished acute gastric mucosal damage due to aspirin or aspirin plus taurodeoxycholic acid (Borrelli *et* Izzo, 2000). Deglycyrrhizinated licorice formulations used in the treatment of ulcers do not suppress gastric acid release like other anti-ulcer medications. Rather, they promote healing by increasing mucous production and blood supply to the damaged stomach mucosa, thereby enhancing mucosal healing (Anonymous, 2005). Deglycyrrhizinated liquorice (97% of glycyrrhizin is removed) effectively treated stress-induced ulcers in animal models. The mechanism of antiulcer activity involves acceleration of mucin excretion through increasing the synthesis of glycoprotein at the gastric mucosa, prolonging the life of the epithelial cells, and antipepsin activity (WHO, 1999b). Oral administration of deglycyrrhizinated liquorice (380mg, 3 times daily) to 169 patients with chronic duodenal ulcers was as effective as antiacid or cimetidine treatments. The results indicate that, in addition to glycyrrhitic acid, other unidentified constituents of *Radix Glycyrrhyzae* contribute to its antiulcer activity (WHO, 1999b).

*Helicobacter pylori* infection is prevalent in individuals with peptic ulcer and is also a known risk factor for gastric cancer. Consequently, an *in vitro* study was performed to investigate the effects of licorice flavonoids on the growth of *H. pylori*. These flavonoid components showed promising anti-*H. pylori* activity against clarithromycin- and amoxicillin-resistant strains. As the antimicrobial property seems to be attributed to the flavonoid constituents of licorice, DGL preparations may provide therapeutic benefit for *H. pylori* infection (Anonymous, 2005).

***Spasmolytic activities***

The spasmolytic activity of *Radix Glycyrrhyzae* has been demonstrated *in vivo* (guinea-pig, rabbit, and dog), and appears to be to the flavonoids liquiritigenin and isoliquiritigenin (WHO, 1999b). Liquiritigenin can produce a strong spasmolytic effect to relieve spasms of the intestines induced by histamine, acetylcholine and barium chloride (Ganzhong et al., 2003e), and according to Shen *et al.* (2007) FM-100 and isoliquiritigenin also have this activities. FM-100 at the concentration of 200µg/ml exerted spasmolytic action on the isolated intestinal tract of the guinea pig (Shen *et al.,* 2007). No inhibitory action on the smooth muscles was detected for glycyrrhizic acid and glycyrrhetic acid (Shen *et al.,* 2007). Recently, glycycoumarin has been isolated as an antispasmodic ingredient of licorice, as demonstrated by its ability to relax carbamylcholine (carbachol)-induced contraction of isolated mice jejunum (Nagai *et al.,* 2006).

***Laxative activities***

Liquorice also may have mild laxative activity (Fiore *et al.,* 2005). It is known that roots contain relative high fiber content (Visavadya *et* Narasimhasharya, 2006).

***Dermatological studies***

*G. glabra* L. has been used in herbal medicine for skin eruptions, including dermatitis, eczema, pruritus and cysts. Recently glycyrrhizin treatment has showed protective effects against UVB-irradiated human melanoma cells. Moreover, licorice extract and its active component, glycyrrhizic acid, has been described as effective skin whitening effects. It was suggested that liquiritin causes depigmentation by two mechanisms: first, via melanin dispersion by means of the pyran ring of its flavonoidal nucleus; second the acceleration of epidermal renewal. Concerning the mechanisms of glabridin on melanogenesis and inflammation, it has been shown that it inhibits the tyrosinase activity of melanocytes and as a result, it seems that hydroquinone will be replaced by licorice extract in a new preparation fordermal melasma. However, in a few cases, allergic dermatitis can develop to oil soluble licorice extracts (Asl *et* Hosseinzadeh, 2008). Besides the antiproliferative effects shown with liquorice, new useful applications have recently been described in the treatment of atopic dermatitis, suggesting a potential role for the drug in allergic/inflammatory diseases of the skin. In addition, liquorice has been reported to be useful for inflammatory lesions induced by ultraviolet radiation (Fiore *et al.,* 2005).

***Endocrinological effects***

***Sexual hormones related activities***

*Glycyrrhiza* root has been shown to decrease circulating levels of testosterone in men and women. But it was not able to reduce salivary testosterone in men significantly. Moreover, it induced regular ovulation and pregnancy in infertile hyperandrogenic patients. On the other hand, isoliquiritigenin (ILC), glabrene and glabridin are phytoestrogens. ILC and glabrene can bind to the human estrogen receptor (ER) with higher affinity than glabridin. It was suggested that isoflavenes may serve as natural estrogen agonists in preventing the symptoms and diseases associated with estrogen deficiency. In some traditional Chinese medicine preparations, the root of *G. glabra* is used for treatment menopause-related symptoms. But there are no clinical data regarding its safety or efficacy for treating hot flashes. Moreover, the activity of 11β-HSD-2 potently is blocked *in vivo* and *in vitro* by glycyrrhetinic acid by two mechanisms, direct competitive inhibition and pretranslational inhibition. It seems that this herb acts on the metabolism of steroids with different mechanisms (Asl *et* Hosseinzadeh, 2008). In a recent study it was investigated the effect of licorice on serum testosterone in nine healthy women, ages 22-26, using a licorice preparation, and found total serum testosterone decreased from 27.8 (± 8.2) to 19.0 (± 9.4) ng/dL after one month, and further decreased to 17.5 (± 6.4) ng/dL after the second month of therapy. This is likely due to inhibition of 17-hydroxysteroid dehydrogenase, indicating licorice may be of benefit in treating women with hirsutism and polycystic ovary syndrome (Anonymous, 2005). Licorice also decreases testosterone production in men who eat licorice. This is likely due to the licorice constituent, glycyrrhetinic acid, inhibiting the enzyme 17-hydroxysteroid dehydrogenase, which converts androstenedione to testosterone. Glycyrrhetinic acid also seems to inhibit 17-20 lyase which converts 17-hydroxyprogesterone to androstenedione (Anonymous, 2009). In animal studies, the anti-oestrogenic action documented for glycyrrhizin at relatively high concentrations has been associated with a blocking effect that would be caused by glycyrrhizin binding at oestrogen receptors. However, oestrogenic activity has also been documented for liquorice and attributed to the isoflavone constituens. Liquorice exhibits an alternative action on oestrogen metabolism, causing inhibition if oestrogen concentrations are high and potentiation when concentrations are low (Newall et al., 1996b).

***Antidiabetic effect***

*Radix Glycyrrhiza* was found to exhibit markedly inhibitory effect on aldose reductase. The IC50 was 16.3 µg/mL. It suggests that this herb used in the control of diabetic complication may act through the pharmacological action of inhibiting aldose reductase. This herb can inhibit aldose reductase in steptozotocin-induced diabetic rats. Licorice markedly reduced sorbitol levels in red blood cells and without affecting blood glucose. When the extract of licorice was given orally at dose of 7.5g/kg/day for one week in diabetic rats, licorice extracts reduced sorbitol levels in white blood cell count (WBC) without affecting blood glucose level (Shen *et al.,* 2007). Carbenoxolone significantly decreased the glucose uptake and the incorporation of glucose into triglycerides and $CO_2$ in rats. The effect produced by insulin on these metabolic pathways was reduced when adipose tissue was incubated with insulin in the presence of carbenoxolone. Nasal absorption of insulin in rats was enhanced by addition of sodium glycyrrhetinate, dipotassium glycyrrhizinate and carbenoxolone (glycyrrhetinic acid hydrogen succinate) disodium salt. The latter agent was effective. It suggested that the latter agent is a useful promoter which does not irritate the nasal mucosal membrane or degrade insulin (Shen *et al.,* 2007).

***Hypocholesterolaemic and antioxidant effects***

Although antihyperlipilaemic and antihypertriglyceridaemic properties of *Glycyrrhiza glabra* root have been reported, no detailed reports are available on the synergistic effects of *Glycyrrhiza glabra* root on hyperlipidemia/hypercholesterolemia and oxidative stress in hypercholesterolaemic animal models and its role on body cholesterol metabolism (Visavadiya *et* Narasimhasharya, 2006). The cholesterol-lowering effects of *Glycyrrhiza glabra* (GG) root in hypercholesterolaemic rats is related to an increased excretion of cholesterol, neutral sterols, bile acid and an increase in hepatic bile acid content. In this context, the presence of phytosterols (2.997 gm%), saponins (3.775 gm%) and fiber (12.8 gm%) in GG root could be important in cholesterol elimination and an increase in hepatic bile acid content in GG root fed hypercholesterolaemic rats. Phytosterols are reported to displace intestinal cholesterol and reduce cholesterol absorption from intestine. Saponins on the other hand, are capable of precipitating cholesterol from micelles and interfere with enterohepatic circulation of bile acids making it unavailable for intestinal absorption. Thus, the presently noted reduced cholesterol levels in hypercholesterolaemic animals administered with GG root powder could be due to both phytosterol and saponin content of GG root. The accelerated fecal excretion of cholesterol, neutral sterol and bile acid in these animals could also be a response to the relatively higher fiber content of the root. This view is in accordance with an earlier report suggesting that the cholesterol lowering effect of fibers is primarily due to an increased excretion of cholesterol and bile acids. The significant decreases in hepatic cholesterol in HGG-I and HGG-II groups also indicate the possible influence of GG root fiber as dietary fibers interfere with cholesterol absorption and enterohepatic bile circulation and result in depletion of hepatic cholesterol pools. A significant decline in plasma LDL-cholesterol in these groups could be correlated with the fiber and saponin content of GG root as both fibers and saponins enhance the hepatic LDL-receptor levels, increase hepatic uptake of LDL-cholesterol and aid its catabolism to bile acids. Elevated levels of plasma TG have been correlated with the development atherosclerosis and coronary heart disease. While the hypercholesterolaemic animals (HC) group exhibited significantly higher TG levels, both hypercholesterolaemic animals administered with 5 gm% *Glycyrrhiza glabra* root powder (HGG-I) and hypercholesterolaemic animals administered with 10 gm% *Glycyrrhiza glabra* root powder (HGG-II) groups registered a significant decline of TG in plasma and hepatic tissue indicating the hypotriglyceridaemic effect of GG root. Both dietary fibers and saponins are known to lower TG by decreasing hepatic lipogenesis and inhibiting pancreatic lipase activity, respectively. Furthermore, the decline in VLDLcholesterol levels in HGG groups could be directly correlated to a decline in TG levels of these groups, as it is well established that VLDL particles are the main transporters of TG in plasma. Thus, a simultaneous decline in both TG and VLDL-cholesterol in HGG groups indicates the possible effect of both fiber and saponin on one hand, and on the other hand, the effect of phytosterol content of the root on TG metabolism through a decreased absorption of dietary cholesterol. An increased HMG-CoA reductase activity in both HGG-I and HGG-II groups compared to that of HC group appears to constitute a metabolic alteration occurring in hepatic tissue as a response to dietary fiber and saponin; such a compensatory increase in hepatic cholesterol synthesis is reported to occur when intestinal cholesterol absorption is impaired or when bile acid synthesis is stimulated. Thus, the increased HMG-CoA reductase activity in HGG-I and HGG-II groups alone, and not in HC, normal controls (NC), normal animals administered with 5 gm% *Glycyrrhiza glabra* root powder (NGG-I) and normal animals administered with 10 gm% *Glycyrrhiza glabra* root powder (NGG-II) groups clearly indicates the compensatory inductive effect of GG root on cholesterol synthesis. Presently observed high level of plasma HDL-cholesterol in both hyper- and normo-cholesterolaemic animals administered with GG root powder as compared to HC and NC groups indicates its efficacy in elevating HDL-cholesterol levels. While dietary saponins and fibers are not known to elevate HDL-cholesterol levels, ascorbic acid and flavonoids are reported to increase the HDL-cholesterol concentrations. The GG root contained both ascorbic acid (0.58 gm%) and flavonoids (0.926 gm%) that could have contributed to an increase in HDL-cholesterol concentrations in both GG root powder administered to hyper- and normo-cholesterolaemic animals. High cholesterol diet increases both LDL cholesterol levels and oxidative stress that results in increased oxidized-LDL levels leading to atherosclerotic plaque formation. Several studies suggest that naturally occurring antioxidants such as polyphenols, flavonoids and vitamin-C in diet may play a role as anti-atherogenic agents. In addition to ascorbic acid and flavonoids, the GG root also contained polyphenols (3.22 gm%). While polyphenols and flavonoids scavenge hydroxyl and superoxide anions, ascorbic acid and flavonoids were shown to synergistically decrease lipid peroxidation and improve lipid profile. In this context, it is pertinent to note that the Glycyrrhiza root extract has been shown to possess antioxidant activity *in vitro* and glabridin, one of the major components of the root is reported to be a potent antioxidant that prevents LDL oxidation. Epidemiological studies have revealed that diets containing polyphenols and flavonoids also stimulated catalase and superoxide dismutase (SOD) activities and decreased malondialdehyde concentration. Administration of GG root powder to hypercholesterolaemic animals significantly decreased lipid peroxidation with a concomitant increase in catalase, SOD activities and ascorbic acid levels. Thus, the elevated levels of hepatic antioxidants in GG root powder administered animals might be due to the presence of polyphenols and flavonoids in the diet. Additionally, the root could be a potent source for ascorbic acid as it suppressed lipid peroxidation and reduced the levels of malondialdehyde. It was suggested that the hypolipidaemic/hypocholesterolaemic effect of GG root is mediated through an increased cholesterol turnover via higher fecal sterol excretion. The increased hepatic antioxidant activities in GG root powder administered animals indicate a decreased oxidative susceptibility in these animals. These hypolipidaemic/hypocholesterolaemic and antioxidant effects of GG root powder could be attributed to aforementioned phytoconstituents (Visavadiya *et* Narasimhasharya, 2006).

***Detoxification***

Licorice and its preparations can relieve drug intoxication and neutralize bacterial toxins and toxic metabolites, because glycyrrhizin can reduce the responsiveness of the organism to toxic substances, in the same way that corticoid hormone does, and promotes dissociation of toxic substances through inducing the production of drug metabolizing enzyme in the liver. In addition, licorice can also absorb and conjugate toxic substances to relieve intoxication. Licorice preparations and glycyrhhizin can also protect the livers of animals from injury caused by drug poisoning (Ganzhong et al., 2003e). It has been discovered from experiments on mice that glycyrrhiza extract and glycyrrhizin have obvious antidotal effects on chloral hydrate, strychnine, urethane, cocaine, phenyl arsenic and mercuric bichloride. Glycyrrhizin has an antidotal effect on tetrodentoxin and ophoitoxin, and can relieve the lethal effects of diphitheria toxin and tetanus toxin (Anonymous, 2009l).

***Weight loss activities***

There is conflicting information about the use of licorice for weight loss. Licorice has been shown to reduce body fat; however accompanying fluid retention offsets any change in body weight (Anonymous, 2009). The consumption of licorice extract and glycyrrhetinic acid could decrease body fat mass in humans and a possible mechanism seems to be by inhibiting 11-ß-hydroxysteroid dehydrogenase at the level of fat cells (Anonymous, 2005; Asl *et* Hosseinzadeh, 2008).

A novel flavonoid, licochalcone A possesses multiple bioactive properties including antibacterial, anti-parasitic, estrogenic and antitumor activities. Furthermore, it has been shown that licochalcone A isolated from the roots of *G. uralensis* reduce the lipase activity as a new inhibitor of pancreatic lipase as well. It can be useful in developing a functional food for obesity and a lead compound for the design of new antiobesity drugs. Licochalcone A is a non-competitive and reversible inhibitor on pancreatic lipase (Won *et al.,* 2007).

In a trial of 15 normal-weight subjects (seven males, eight females, ages 22-26), 3.5 mg of a commercial licorice preparation daily for two months resulted in a decrease in body fat mass. Plasma rennin activity and aldosterone were also suppressed. No changes in body mass index were noted (Anonymous, 2005). More evidence is needed to rate licorice for these uses (Anonymous, 2009).

***Other therapeutic considerations***

Reports on the usefulness of liquorice extracts on body fluid homeostasis in patients with *Addison* disease are contradictory. One study found no positive effects, while three other studies noted an increase in weight gain and sodium retention (WHO, 1999b). Glycyrrhizin is classified as a saponin compound, and this property has been tested to determine its interaction with cellular membranes of erythrocytes and hepatic lysosomal preparations. Glycyrrhizin was found to protect erythrocytes against the hemolysis induced by other saponin compounds including digitonin, excin, tomatin, and saponin A. The effect of glycyrrhizin was concentration-dependent but it was only effective at preventing hemolysis at concentrations approximately 400 times greater than the hemolysin. Glycyrrhizin was found to be as eficacious against the sapogenins digitogenin, tomatidine, and sapogenin A, indicating that its mechanism of action is not the result of the inhibition of membrane glycosidases of erythrocytes. The possibility remains that glycyrrhizin prevents access of hemolysin to its receptor, or alters membrane fluidic dynamics at these high concentrations. To test this possibility, the effects of glycyrrhizin on the release and activity of acid phosphatases from hepatic lysosomal preparations were investigated. Both glycyrrhizin and 18β-glycyrrhetic acid attenuated acid phosphatase activity, but did not affect β-*N*-acetylglucosaminidase activity. The reduction of lysosomal acid phosphatase activity was due to its release from the lysosomes rather than a direct inhibition of the enzyme suggesting an alteration in membrane fluidity (Isbruker *et* Burdock, 2006).

***Industrial uses***

Commercially, licorice is added to chewing gum, chocolate candy, cigarettes, smoking mixtures, chewing tobacco and snuff as sweetening agents and as a depigmentation agent in cosmetics. Also, licorice is frequently employed to mask the taste of bitter drugs such as aloe, quinine and others. The surfactant property of the saponins may also facilitate the absorption of poorly absorbed drugs, such as the anthraquinone glycosides. Examples of products containing considerable amounts of glycyrrhizinic acid are: confectionery licorice sticks, bricks, cakes, toffee, pipes, bars, balls, tubes, pastilles and allsorts, chewing gum, throat pearls, licorice flavored cough mixtures, herbal cough mixtures, licorice tea, all types of licorice root Russian, Iranian, Chinese, Turkish, Afghan and unknown origin chewing tobacco, alcoholic drinks (Asl *et* Hosseinzadeh, 2008).

## Pharmacokinetics

Glycyrrhizin has a poor oral bioavailability in both rats and humans. In rats, glycyrrhizin was detectable in plasma samples only after the administration of oral doses exceeding 50mg/kg. Similarly, in humans, glycyrrhizin was detected at very low levels after a single oral dose in the range of 100–1600mg/kg. However, these studies showed that glycyrrhetic acid, the aglycone of glycyrrhizin, is readily detected in plasma following the ingestion of glycyrrhizin or licorice extract by rats and humans. In most species, the peak plasma glycyrrhetic acid levels are lower and occur later when glycyrrhizin is administered in licorice extract than when provided at an equivalent dose as a pure compound; however, the contrary seems to occur in rabbits. In rats fed glycyrrhizin (160 or 200mg/kg) or licorice extract with the same glycyrrhizin load, the area under the plasma curve (AUC) for glycyrrhetic acid was approximately 2.5 times greater for the pure compound. Licorice extract was also found to increase bile flow in, which could partially explain the altered pharmacokinetics. The time to maximum glycyrrhetic acid plasma concentration was 10h for glycyrrhizin and 2h longer with licorice extract. Similar results were found in a study involving eight healthy adult volunteers fed 800 or 1600mg glycyrrhizin as its ammoniated salt or in licorice extract. The lipophilic components of licorice extract were found to reduce the gastric emptying rate and absorption of glycyrrhizin, but the compounds involved in this activity have not been identified. Interestingly, neither glycyrrhizin nor glycyrrhetic acid are detected in the plasma of germ-free rats fed glycyrrhizin. These data, along with the relatively long lag time to maximum plasma glycyrrhetic acid concentrations, suggest a presystemic metabolic process involving the de-glucuronidation of glycyrrhizin by intestinal flora prior to the absorption of glycyrrhetic acid. Indeed, researchers have identified various intestinal bacterial strains, including *Streptococcus* and *Eubacterium* sp., with specialized β-glucuronidase activity capable of glycyrrhizin hydrolysis. Oral bioavailability of glycyrrhetic acid following the administration of glycyrrhizin to rats appears to be dose limiting and may be due to limitations in either the uptake of glycyrrhetic acid or the hydrolysis process. Because orally administered glycyrrhizin is poorly absorbed, and is hydrolyzed to glycyrrhetic acid by intestinal bacteria, it was suggested a two-step microbial hydrolysis of glycyrrhizin first to 3-β-monoglucuronyl-18-β-glycyrrhetic acid (3MGA) and then to glycyrrhetic acid prior to absorption. Interindividual differences in glycyrrhizin response, metabolism and kinetics are influenced, at least in part, by the intestinal microflora profile. Neither glycyrrhizin nor glycyrrhetic acid accumulate in tissues. However, both compounds adhere extensively to human and rat serum albumin, and although binding sites may be specific and non-specific, it is a saturable process. A recent study showed that glycyrrhetic acid is somewhat able to cross the placental barrier and can be detected in the rat fetuses. The enterohepatic circulation of glycyrrhetic acid was demonstrated. In a recent study it was shown less than 2% of the initial dose was excreted in the urine illustrating that this is not considered to be a major elimination pathway. Fecal extracts of rats dosed orally with [3H]glycyrrhetic acid revealed the presence of only the parent compound as an unmodified substance indicating the complete hydrolysis of glucuronyl and sulfate conjugates by intestinal microflora prior to excretion in the feces. The enterohepatic circulation of glycyrrhetic acid has not been studied in humans, but can be expected because glycyrrhetic acid metabolites can be hydrolyzed by human gastrointestinal bacteria. Time curve data for glycyrrhetic acid also provide evidence of enterohepatic circulation in humans. The plasma clearance of glycyrrhizin and glycyrrhetic acid is dose dependent when administered to rats or humans at levels which exceed the saturation of serum protein binding. A recent study reported that the plasma clearance of *i.v.* glycyrrhizin was not dose dependent at doses below 120mg in healthy volunteers. The plasma clearance was in the range of 38–64ml/h/kg and the volume of distribution at steady state (38–64ml/kg) was close to the mean serum volume for humans, 43ml/kg. Plasma clearance was significantly decreased in patients with chronic hepatitis C and liver cirrhosis. Together, these data suggest a hepatic related capacity-limited process in metabolism or excretion in the bile. Because of the enterohepatic recycling of glycyrrhetic acid and the biliary storage process of glycyrrhetic acid metabolites in the gallbladder, plasma glycyrrhetic acid concentrations show several peaks following the oral administration of either glycyrrhizin glycyrrhetic acid or licorice. In summary, the metabolic fate of glycyrrhizin is complex and involves several inter-dependent steps (Fig. 64). Following an oral administration, there is a primary metabolic step involving the enteric microbial metabolism of glycyrrhizin to a monoglycone and/or aglycone compound. The resulting 3MGA and glycyrrhetic acid are absorbed through the intestines with only a minimal absorption of glycyrrhizin. In humans, the hepatic metabolism and processing of 3MGA and glycyrrhetic acid are not yet clearly defined, but it is apparent that each can undergo further conjugation or reduction followed by biliary excretion. Glucuronide compounds and metabolites excreted in the bile are likely remetabolized by the intestinal flora and thereby subject to enterohepatic recycling. In general, the clearance capacity for glycyrrhetic acid would be reduced in patients with compromised hepatic function (Isbrucker *et* Burdock, 2006).

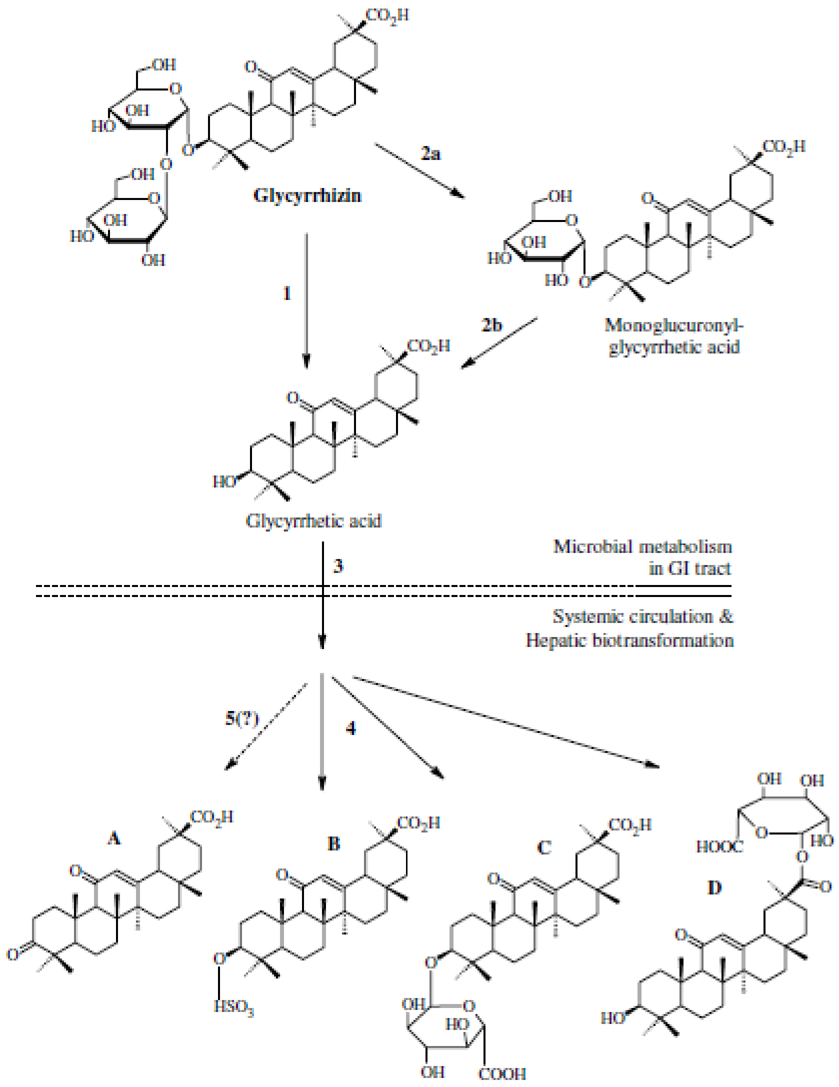



**Fig. 64.** Glycyrrhizin metabolism. Following ingestion glycyrrhizin is deglucuronidated by intestinal microbes either completely (1) or through a two-step intermediary process (2a, 2b). Glycyrrhetic acid is absorbed (3) and undergoes hepatic biotransformation (4) to produce 18-β-glycyrrhetyl-3-*O*-hydrogen sulfate (B), 18-β-glycyrrhetyl-3-*O*-monoglucuronide (C), or 18-β-glycyrrhetyl-3-*0*-monoglucuronide (D). Glycyrrhetic acid may also undergo hepatic dehydrogenation (5) to form 3-ketoglycyrrhetic acid (A), although this step is undocumented in humans (adapted from Isbrucker *et* Burdock, 2006).

## Adverse Reactions

One of the most commonly reported side effects with licorice supplementation is hypertension (Anonymous, 2005; Anonymous, 2009; Asl et Hosseinzadeh, 2008; Blumenthal, 2003; Chan *et* Kritchley, 1996; Coon *et* Ernst, 2004; Cunha et al., 2007; Fiore *et al.*, 2008; WHO, 1999b). This hypertension is caused by decreased 11β-hydroxysteroid hydroxygenase activity. This enzyme is responsible for the renal conversion of cortisol to cortisone. Thus, licorice leads to activation of renal mineralocorticoid receptors by cortisol, resulting in a state of apparent mineralocorticoid excess (Anonymous, 2009; Asl et Hosseinzadeh, 2008; Fiore *et al.*, 2008) and suppression of the rennin angiotensin system

(Asl et Hosseinzadeh, 2008; Fiore *et al.*, 2008). Patients may experience hypokalemia (potassium loss) (Anonymous, 2005; Anonymous, 2009; Asl et Hosseinzadeh, 2008; Blumenthal, 2003; Chan *et* Kritchley, 1996; Coon *et* Ernst, 2004; Cunha et al., 2007; Fiore *et al.*, 2008; WHO, 1999b) and sodium retention (Anonymous, 2005; Anonymous, 2009; Blumenthal, 2003; Chan *et* Kritchley, 1996; Coon *et* Ernst, 2004; Cunha et al., 2007; WHO, 1999b), water accumulation (Blumenthal, 2003; Chan *et* Kritchley, 1996; Cunha et al., 2007; WHO, 1999b) resulting in edema (Anonymous, 2005; Anonymous, 2009; Blumenthal, 2003; Chan *et* Kritchley, 1996; WHO, 1999b). The phenomenon is known as "pseudoaldosteronism" (Anonymous, 2005; Anonymous, 2009; Blumenthal, 2003; Breidthardt *et al.*, 2006; WHO, 1999b). The metabolic abnormalities caused by licorice can lead to electrocardiography (EKG) changes, arrhythmias, rhabdomyolysis, paralysis, and encephalopathy (Anonymous, 2009), headache, muscle weakness, (Anonymous, 2009; Cunha et al., 2007b), lethargy, muscle weakness, dropped head syndrome (DHS), rhabdomyolysis, myoglobinuria, paralysis, encephalopathy, respiratory impairment, hyperparathyroidism, and acute renal failure. These effects are most likely to occur when 30 grams or more of licorice is consumed daily for several weeks (Anonymous, 2009). In rare cases, myoglobinuria (Anonymous, 2005; Blumenthal, 2003; WHO, 1999b) and myopathy can occur (WHO, 1999b). However, some people may be more sensitive, especially those with hypertension, heart problems, or kidney problems (Anonymous, 2009). The water accumulation causes swelling of the hands and feet (Blumenthal, 2003; WHO, 1999b) and can lead to weight gain (Blumenthal, 2003; Coon *et* Ernst, 2004; WHO, 1999b). These effects are associated with prolonged use of large doses (›50g/day) of the drug for extended periods (›6 weeks) (Blumenthal, 2003; WHO, 1999b). Because licorice can decrease serum testosterone and increase 17-hydroxyprogesterone, it might cause decreased libido and sexual dysfunction in men (Asl et Hosseinzadeh, 2008).

The increases in blood pressure, and cortisol to cortisone ratio are proportional to the amount of glycyrrhizic acid ingested (Anonymous, 2009). Generally, the onset and severity of symptoms depend on the dose and duration of licorice intake, as well as individual susceptibility. Patients with delayed gastrointestinal transit time may be more susceptible to these side effects, due to enterohepatic cycling and reabsorption of licorice metabolites. The amount of licorice ingested daily by patients with mineralocorticoid excess syndromes appears to vary over a wide range, from as little as 1.5 g daily to as much as 250g daily (Anonymous, 2005). According to Cunha *et al.,* (2007) high doses (ca. 50g/dia), which corresponds to about 130mg of glycyrrhizinic acid, can produce adverse effects. All symptoms usually disappear with discontinuation of therapy (Anonymous, 2005; Blumenthal, 2003; Newall et al., 1996b). Glycyrrhetinic acid has a long half life, a large volume of distribution, and extensive enterohepatic recirculation. Therefore, it may take 1-2 weeks before hypokalemia resolves. Normalization of the renin-aldosterone axis and blood pressure can take up to several months (Anonymous, 2009). An acceptable daily intake avoiding these effects has been determined as 0.2 mg/kg of glycyrrhizin (Fiore *et al.*, 2008) and no adverse reactions have been associated with the drug when within the recommended dosage and treatment period (Blumenthal, 2003; WHO, 1999b).

Future trials need to address the potential side effects, which have been reported with licorice use, particularly in elderly people with heart disease and on diuretic medication. Further *in vitro* studies working on chemically modified derivatives with greater activity and increased selectivity indices are required (Fiore *et al.*, 2008).

## Drug interactions

***Antihypertensive drugs***

The aldosterone effects of licorice root may counteract the effect of antihypertensive drug therapy (Anonymous, 2009; Asl *et* Hosseinzadeh, 2008). Licorice increases blood pressure in a dose dependent manner (Anonymous, 2009). Because it reduces sodium and water excretion, the effectiveness of drugs used in the treatment of hypertension may be reduced (Beers, 2008a; WHO, 1999b).

***Corticosteroids***

*Radix Glycyrrhizae* should not be taken concurrently with corticosteroid treatment (WHO, 1999b). Theoretically, concomitant use might potentiate the duration of activity of corticosteroids, e.g., hydrocortisone. Concomitant use of licorice and corticosteroids might also increase potassium loss and increase the risk of potassium depletion. Overuse or misuse of licorice can cause potassium depletion (Anonymous, 2009). Causes addictive and enhanced effects of these drugs (Beers, 2008a).

***Cytochrome p450 2b6 (cyp2b6) substrates***

There is preliminary evidence that licorice can inhibit the cytochrome P450 2B6 (CYP2B6) isoenzymes *in vitro*. Theoretically, licorice might increase levels of drugs metabolized by CYP2B6; however, as of yet, these interactions have not been reported in humans. Some drugs that are metabolized by CYP2B6 include ketamine, phenobarbital, orphenadrine, secobarbital, and dexamethasone. Use licorice cautiously or avoid in patients taking these drugs (Anonymous, 2009).

***Estrogens***

Theoretically, licorice might interfere with estrogen therapy due to estrogenic and anti-estrogenic effects (Anonymous, 2009; Newall et al., 1996b). Estrogen-based oral contraceptives may enhance the mineralocorticoid side effects of licorice in susceptible individuals. This may be due in part to estrogens reacting with mineralocorticoid receptors or inhibition of 11-β-hydroxysteroid dehydrogenase (Anonymous, 2005).

***Ethacrynic acid***

Theoretically, ethacrynic acid might enhance the mineralocorticoid effects of licorice by inhibiting the enzyme that converts cortisol to cortisone; however, bumetanide (Bumex) does not appear to have this effect. Theoretically, furosemide might enhance the mineralocorticoid effects of licorice by inhibiting the enzyme that converts cortisol to cortisone; however, bumetanide does not appear to have this effect (Anonymous, 2009).

***Warfarin***

Licorice seems to increase metabolism and decrease levels of warfarin in animal models. This is likely due to induction of cytochrome P450 2C9 (CYP2C9) metabolism by licorice (Anonymous, 2009).

***Aspirin***

May provide protection against aspirin-induced damage to GI mucosa (Beers, 2008a).

***Digoxin***

Herb causes hypokalemia, which predisposes to drug toxicity (Anonymous, 2009l; Beers, 2008a).

***Insulin***

Causes hypokalemia and sodium retention (Beers, 2008a).

***Spironolactone***

Decreases effect of drug (Beers, 2008a).

## Interactions with Herbs & Supplements

***Cardiac glycoside-containing herbs***

Theoretically, the overuse or misuse of licorice can increase the risk of cardiotoxicity due to potassium depletion. Cardioactive herbs include digitalis, lily-of-the-valley, pheasant's eye, and squill (Anonymous, 2009).

***Stimulant laxative herbs***

Theoretically, concomitant overuse or misuse of licorice with stimulant laxatives can increase the risk of potassium depletion. Stimulant laxative herbs include aloe, alder buckthorn, black root, blue flag, butternut bark, colocynth, European buckthorn, fo ti, gamboge, gossypol, greater bindweed, jalap, manna, Mexican scammony root, rhubarb, senna, and yellow dock (Anonymous, 2009).

***Panax ginseng***

Some research shows that *Panax ginseng* appears to compliment licorice by increasing serum cortisol concentrations (Anonymous, 2009).

## Interactions with Foods

***Grapefruit juice***

Theoretically, grapefruit juice and its component naringenin might enhance the mineralocorticoid activities of licorice, by blocking the conversion of cortisol to cortisone (Anonymous, 2009).

***Salt***

A high salt diet can exacerbate adverse effects of licorice such as sodium and water retention and hypertension (Anonymous, 2009).

## Interactions with Laboratory Tests

***17-hydroxyprogesterone***

Licorice can increase serum 17-hydroxyprogesterone concentrations and test results in healthy volunteers who consume 7 grams of licorice per day (Anonymous, 2009).

***Blood pressure***

Excessive use of licorice can cause hypertension and increase blood pressure readings (Anonymous, 2009).

***Potassium***

Excessive use of licorice can cause hypokalemia, reducing serum potassium levels and test results (Anonymous, 2009).

***Testosterone***

Licorice can decrease serum testosterone concentrations and test results in healthy volunteers who consume 7 grams of licorice per day (Anonymous, 2009).

## Contraindications and precautions

***Hypertension***

*Radix Glycyrrhizae* is contraindicated in patients with hypertension (Anonymous, 2009; Anonymous, 2009l; Blumenthal, 2003; Cunha et al., 2007; Cunha et al., 2007c; WHO, 1999b) because patients with underlying essential hypertension are more sensitive to the inhibition of 11-beta-hydroxysteroiddehydrogenase by liquorice (Breidthardt *et al.*, 2006) and the mineralocorticoid effects of licorice can increase blood pressure (Anonymous, 2009).

***Heart disease***

The mineralocorticoid effects of licorice can induce fluid retention and worsen congestive heart failure .Licorice can also cause hypokalemia and increase the risk of arrhythmias (Anonymous, 2009). Advise patients with heart disease to avoid excessive amounts of licorice (Anonymous, 2009; Cunha et al., 2007b).

***Hormone sensitive cancers/conditions***

Licorice might have estrogenic effects. Women with hormone sensitive conditions should avoid using licorice. Some of these conditions include breast cancer, uterine cancer, ovarian cancer, endometriosis, and uterine fibroids (Anonymous, 2009).

***Hypertonia***

The mineralocorticoid effects of licorice can cause hypokalemia. Licorice-induced hypokalemia can worsen hypertonia (Anonymous, 2009).

***Hypokalemia***

The mineralocorticoid effects of licorice can decrease potassium serum levels and exacerbate hypokalemia (Anonymous, 2009; Asl *et* Hosseinzadeh, 2008; Blumenthal, 2003; Cunha et al., 2007c; WHO, 1999b).

***Kidney insufficiency***

The mineralocorticoid effects of licorice may worsen renal function (Anonymous, 2009; Anonymous, 2009l; Blumenthal, 2003; Cunha et al., 2007c; WHO, 1999b).

***Sexual dysfunction***

Theoretically, licorice might decrease libido and worsen erectile dysfunction by decreasing testosterone and increasing 17-hydroxyprogesterone serum concentrations (Anonymous, 2009).

***Surgery***

Licorice might affect blood pressure. Theoretically, licorice might interfere with blood pressure control during and after surgical procedures. Is recommended discontinue licorice at least 2 weeks before elective surgical procedures (Anonymous, 2009).

***Cholestatic disorders or cirrhosis of the liver***

(Asl *et* Hosseinzadeh, 2008; Blumenthal, 2003; Cunha et al., 2007c; WHO, 1999b).

***Diabetes***

Licorice is contraindicated in diabetes by the Belgian Pharmaceutical Association, although this was not confirmed in a subsequent monograph by the WHO (Blumenthal, 2003; WHO, 1999b).

***Pregnancy and lactation***

*Radix Glycyrrhizae* is not mutagenic *in vitro* and is not teratogenic in animal models (WHO, 1999b). According to Anonymous (2009) licorice has abortifacient, estrogenic, and steroid effects; and can cause uterine stimulation. The safety of *Radix Glycyrrhizae* preparations during pregnancy has not been established (Asl *et* Hosseinzadeh, 2008; Cunha et al., 2007c; WHO, 1999b). Stranberg *et al.* (2002) reported that heavy licorice (glycyrrhizin) consumption (≥500 mg/week) has been associated with shorter gestation (Anonymous, 2009l; Asl *et* Hosseinzadeh, 2008; Cunha et al., 2007c; WHO, 1999b). Heavy consumption of licorice has also been associated with an increased risk of preterm birth in cross-sectional and retrospective studies (Fiore *et al.*, 2008). ). In view of the oestrogenic and steroid effects associated with licorice, which may exacerbate pregnancy-realated hypertension, excessive ingestion during pregnancy and lactation shoud be avoided. In addition, liquorice has exhibited a uterine stimulant activity in animal studies, and is traditionally reputed to be abortifacient and to affect the menstrual cycle (emmenagogue) (Newall et al., 1996b). According to the American Herbal Products Association, licorice is classified as Class 2D (not to be used during pregnancy) (Blumenthal, 2003). As a precautionary measure the drug should not be used during pregnancy (Anonymous, 2009l; Asl *et* Hosseinzadeh, 2008; Cunha et al., 2007c; WHO, 1999b).

The safety of *Radix Glycyrrhizae* preparations during lactation has not been established. As a precautionary measure the drug should not be used during lactation except on medical advice (Anonymous, 2009; WHO, 1999b).

## Posology

Average daily dose of crude plant material, 5-15g, corresponding to 200-800mg of glycyrrhizin. Doses of other preparations should be calculated accordingly. *Radix Glycyrrhizae* should not be used for longer than 4-6weeks without medical advice (WHO, 1999b). Because individual susceptibility to various licorice preparations is vast, it is difficult to predict a dose appropriate for all individuals. Nevertheless, a daily oral intake of 1-10 mg of glycyrrhizin, which corresponds to 1-5 g licorice (2% glycyrrhizin), has been estimated to be a safe dose for most healthy adults (Anonymous, 2005).

## Storage

Protect from light (FP, 2005).According to Chinese Pharmacopoeia (2005d) preserve in a ventilated and dry place, protect from moth.

## Regulatory Status

***Austria:*** Unpeeled dried root is official in the *Austrian Pharmacopoeia* (Blumenthal, 2003).

***Belgium:*** Traditional Herbal Medicine (THM) permitted for specific indications (Blumenthal, 2003).

***Canada:*** Approved active ingredient in THM products and in Homeopathic products, both requiring pre-marketing authorization with Drug Identification Number (DIN). Food if no claim statement is made (Blumenthal, 2003).

***China:*** Dried root and rhizome, prepared (stir-fried with honey) root and rhizome, alcoholic fluid extract and dry aqueous native extract, containing not less than (NLT)

20.0% glycyrrhetic acid, are official drugs of the *Pharmacopoeia of the People´s Republic of China* (Blumenthal, 2003).

***Europen Union:*** Dried unpeeled or peeled, root and stolons containing NLT 4.0% glycyrrhetic acid and NMT 5.0% glycyrrhetic acid are official in *European Pharmacopoeia* (Blumenthal, 2003).

***France:*** THM permitted for specific indications, internal or locally (mouth and throat). Official in *French Pharmacopoeia* (Blumenthal, 2003).

***Germany:*** Dried root or dry extract for infusion, decoction, liquid or solid dosage forms, are approved non-prescription drugs in the Comission E monographs. Licorice root tea is approved as an over-the-counter (OTC) drug in the *German Standard License* monographs. Peeled dried root containing NLT 4.0% glycyrrhetic acid and standardized ethanolic fluid extraing containing NLT 5.0% glycyrrhetic acid and NMT 7.0% glycyrrhetic acid are official in *German Drug Codex* supplement to *German Pharmacopoeia*. Standard ethanolic fluid containing NLT 2.0% glycyrrhetic acid and NMT 4.0% glycyrrhetic acid are official in *German Pharmacopoeia.*

***India:*** Dried unpeeled roots and stolons containing NLT 4.0% glycyrrhetic acid are official in *Indian Pharmacopoeia.* Dried unpeeled stolon and root are official in the Government of India *Ayurvedic Pharmacopoeia of India.* Prepared mature root /min. 4 years) is an official single-drug and/or component of multiple-ingredient drugs dispensed in Unani system of medicine. A monograph for dried roots occurs in the *Indian Herbal Pharmacopoeia.*

***Italy:*** Listed in the *Italian Pharmacopoeia.*

***Japan:*** Traditional Kampo medicine. Dried peeled or unpeeled root and stolon are official in the *Japanese Pharmacopoeia.*

***Portugal:*** Listed in the *Portuguese Pharmacopoeia.*

***Russian Federation:*** Official in the *State Pharmacopoeia of the Union of Soviet Socialist Republics.*

***Sweden:*** Classified as foodstuff. As of January 2001, no licorice products are listed in the Medical Products Agency (MPA) “Authorized Natural Remedies”.

***Switzerland:*** Official in the *Swiss Pharmacopoeia.* Licorice is an approved component of multi-ingredient phytomediciness listed in the *Swiss Codex* 2001/2 available in juice, syrup, tea infusion, and tincture dosage forms with positive classification (List D) by *Interkantonale Kontrollstelle fur Heilmittel (IKS)* and corresponding sales Category D with sale limited to pharmacies and drugstores, without prescription.

***U.K.:*** Herbal medicine on the General Sale List, Schedule 1 (requires full Product License), Table A (internal or external use). Dried unpeeled roots containing NLT 4.0% glycyrrhetic acid, ethanolic fluid extract, and DGL dry aqueous extract containing 0.5-2.0% total flavonoids, calculated as liquiritigennin, are official in the *British Pharmacopoeia.*

***U.S.:*** Dietary supplement or food depending on label claim statement. Licorice root and derivatives are affirmed as Generally Recognized as Safe (GRAS) for use as flavoring agent or flavor enhancer in vitamin or mineral dietary supplements, herb and seasoning products and nonalcoholic beverages, including tea. Dried roots, rhizome and stoloms, powdered root, and powdered dry extract are subjects of botanical monographs in development for the *US National Formulary.* Previews of the standards developmemt were published in *Pharmacopeial Forum* (Blumenthal, 2003).

### 7.4.1. Radix Glycyrrhizae (甘草) according to Traditional Chinese Medicine

Liquorice is commonly used in Chinese herbalism, where it is considered to be one of the 50 fundamental herbs. It is considered to be second in importance only to Ginseng (Anonymous, 2009l) and is almost always used in combination with other herbs (Blumenthal, 2003). It is included in almost all Chinese herbal formulae, where it is said to harmonize and direct the effects of the various ingredients (Anonymous, 2009l).

*Radix Glycyrrhizae Uralensis* (Gancao or Gan Cao) is produced mainly in the Chinese provinces of Inner Mongolia, Shanxi, Gansu, and Xinjiang (Anonymous, 2009l; Ganzhong et al., 2003e; Wu, 2005c). It is collected in spring and autumn (Ganzhong et al., 2003e; Wu, 2005c), preferably from plants 3-4 years old (Anonymous, 2009l). After the stem, fibrous roots and bark of the roots are removed (Ganzhong et al., 2003e; Yanfu, 2002e), is sliced and dried in sunlight (Ganzhong et al., 2003e; Wu, 2005c) (Fig.65) and it is used unprepared or rosted with honey (Anonymous, 2009l; CP, 2005d; Wu, 2005c; Yanfu, 2002e).

**Fig. 65.** Processed *Radix Glycyrrhizae* (adapted from http://www.e2121.com/fherb.html) (visited 24/11/09)

Zhi gan cao is Gan Cao that has been coated with honey and baked to dark brown color and often it is being used in tonic (Honey Fried Licorice Root). Sheng gan cao is untreated Gan Cao (Fig. 66) (Chu, 2008).

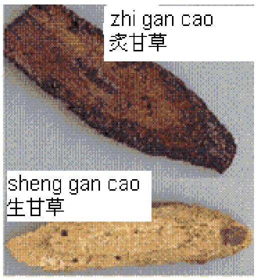



**Fig. 66.** Zhi gan cao and Sheng gan cao (adapted from Chinese Herb Dictionary, Complementary and Alternative Healing University´ available at http://alternativehealing.org/chinese_herbs_dictionary.htm) (visited on 29/11/08)

*Radix Glycyrrhizae* was earliestly recorded in Shengnong Materia Medica (*Shennong Bencao Jing*) (Shen *et al.,* 2007).

### Common name

Licorice root (Ganzhong et al., 2003e; Leite, 2005e; Liu et Tseng, 2005d; Wu, 2005c). Also called Asian Liquorice or Chinese Licorice (Anonymous, 2009l).

### Pharmaceutical name

*Radix Glycyrrhizae Uralensis* (Gongwang, 2000; Wu, 2005c), *Radix Glycyrrhizae* (Anonymous, 2009o; Flaws, 1999g; Ganzhong et al., 2003e)

### Botanical name

*Glycyrrhiza uralensis* Fisch. (Gongwang, 2000; Leite, 2005e).

### Pynin name

Gan Cao (Flaws, 1999g; Gongwang, 2000; Leite, 2005e; Liu et Tseng, 2005d), Gancao (Greten, 2007; Yanfu, 2002e).

### Part used

Dried root (Ganzhong et al., 2003e; Leite, 2005e; Wu, 2005c) or root with rhizome (Leite, 2005e; Wu, 2005c)

## Classification

Supports and strengthens the fluids and buffers. Belongs to the group *"Supplentia qi – XV a)"* (Greten, 2007) i.e. "Herbs that Tonify Qi" (Anonymous, 2009o; Shen *et al.,* 2007; Yanfu, 2002e).

## Sapor &Temperature

Sweet (Anonymous, 2009o; Anonymous, 2009l; Chu, 2008; Flaws, 1999g; Greten, 2007; Leite, 2005e; Liu et Tseng, 2005d; Shen *et al.,* 2007; Wu, 2005c; Yanfu, 2002e) in smell and peculiarly sweet in taste. It is about five hundred times the sweetness of cane sugar (Chu, 2008). Mild in nature (Anonymous, 2009l; Shen *et al.,* 2007; Yanfu, 2002e). Neutral (Chu, 2008; Flaws, 1999g; Greten, 2007; Leite, 2005e; Liu et Tseng, 2005d; Wu, 2005c),

## Orbs

All the 12 orbs (Anonymous, 2009o; Chu, 2008; Greten, 2007; Leite, 2005e; Liu et Tseng, 2005d), mainly the heart, lung, spleen and stomach (Anonymous, 2009l; Chu, 2008; Flaws, 1999g; Ganzhong et al, 2003; Gongwang, 2000; Leite, 2005e; Liu et Tseng, 2005d; Shen *et al.,* 2007; Wu, 2005c; Yanfu, 2002e).

## Functions

In traditional Chinese medicine, the herb is one of herbs that tonify spleen and replenish qi (Flaws, 1999g; Ganzhong et al., 2003e; Gongwang, 2000; Liu et Tseng, 2005d; Shen *et al.,* 2007; Wu, 2005c),). Tonifys the heart and spleen (Anonymous, 2009l; Shen *et al.,* 2007), purges fire, remove toxins (Anonymous, 2009l; Flaws, 1999g; Ganzhong et al., 2003e; Liu et Tseng, 2005d Shen *et al.,* 2007) and relieves spasm to alleviate pain. Being sweet, mild, moist, not dry for invigoration qi, it is a typical herb with many effects of sweet flavor, such as tonifying the heart and spleen, moistening the lung, relieving spasm, clearing toxic substances (Anonymous, 2009l) and harmonizing other herbs (Anonymous, 2009l; Shen *et al.,* 2007).

## Indications

*Radix Glycyrrhizae* is officially listed in the Chinese Pharmacopeia. It is used as a tonic, antiphlogistic, mucolytic, expectorant, and analgesic for the treatment of gastroinstinal and respiratory diseases (Shen *et al.,* 2007).

It is used to invigorate the functions of the heart and spleen (Shen *et al.,* 2007) so it´s indicated for deficiency of the heart-qi and spleen-qi (Anonymous, 2009l; Yanfu, 2002e).

Release spasms (Anonymous, 2009l; Flaws, 1999g; Ganzhong et al., 2003e; Gongwang, 2000; Liu et Tseng, 2005d; Shen *et al.,* 2007; Wu, 2005c) and alleviates pain (Anonymous, 2009l; Flaws, 1999g; Ganzhong et al., 2003e; Gongwang, 2000; Liu et Tseng, 2005d; Wu, 2005c).

Used to treat carbuncles (Ganzhong et al., 2003e; Liu et Tseng, 2005d; Shen *et al.,* 2007), sore throat (Ganzhong et al., 2003e; Liu et Tseng, 2005d; Shen *et al.,* 2007; Wu, 2005c; Yanfu, 2002e) and cellulitis (Ganzhong et al., 2003e). For sores, ulcers, and other skin infections (Wu, 2005c).

As it has the action of moistening the lung (Anonymous, 2009l; Flaws, 1999g; Ganzhong et al., 2003e; Gongwang, 2000; Liu et Tseng, 2005d; Wu, 2005c; Yanfu, 2002e) and resolving phlem (Yanfu, 2002e) it is indicated for many kinds or syndromes of cough (Anonymous, 2009l; Flaws, 1999g; Ganzhong et al., 2003e; Gongwang, 2000; Liu et Tseng, 2005d; Shen *et al.,* 2007; Wu, 2005c; Yanfu, 2002e), wheezing and dyspnea (Liu et Tseng, 2005d; Yanfu, 2002e).

Relieve the side effects of drugs (Anonymous, 2009l; Ganzhong et al., 2003e; Liu et Tseng, 2005d; Shen *et al.,* 2007), regulates and harmonizes the actions of various ingredients in a prescription (Anonymous, 2009l; Flaws, 1999g; Gongwang, 2000; Wu, 2005c). Used for drug poisoning (Anonymous, 2009l; Ganzhong et al., 2003e; Shen *et al.,* 2007; Yanfu, 2002e) and food poisoning (Anonymous, 2009l; Yanfu, 2002e). Because licorice can moderate the side effects of many drugs, it has earned the nickname of Guolao (expert negotiator) (Ganzhong et al., 2003e).

## Chinese therapeutic actions and examples of major combinations

- Used for deficiency of the spleen and stomach (Anonymous, 2009l; Flaws, 1999g; Shen *et al.,* 2007) qi shortness (Flaws, 1999g), weakness (Flaws, 1999g; Ganzhong et al., 2003e; Wu, 2005c), poor appetite (Flaws, 1999g; Ganzhong et al., 2003e; Shen *et al.,* 2007; Wu, 2005c), and loose stools (Flaws, 1999g; Ganzhong et al., 2003e; Shen *et al.,* 2007; Wu, 2005c), and loose stools due to Spleen Deficiency (Shen *et al.,* 2007; Wu, 2005c), for shortness of breath (Ganzhong et al., 2003e; Wu, 2005c), palpitations of the heart due to weakness of the spleen and stomach, and deficiency of qi in the middle energizer (Ganzhong et al., 2003e). In this cases, it is used with *Radix Ginseng* (Ren Shen), *Sclerotium Poriae Cocos* (Fu Ling), and *Rhizoma Atractylodis Macrocephalae* (Bai Zhu) in "The Decoction of Four Noble Herbs" (Ganzhong et al., 2003e; Shen *et al.,* 2007; Wu, 2005c), (Si Jun Zi Tang) (Anonymous, 2009l; Flaws, 1999g; Ganzhong et al., 2003e; Shen *et al.,* 2007; Wu, 2005c), i.e. Four Gentlemen Decoction (Flaws, 1999g)/ "*Quattuor Nobilium*" (Greten, 2007).

- In the case with deficiency of heart-qi manifested as palpitation, spontaneous sweating and knotted or slow-regular-intermittent pulse, *Radix Glycyrrhizae*, honey-fried (Zhigancao), is mainly used together with *Radix Ginseng* (Renshen), *Radix Trichosantis* (Maimendong), *Ramulus Cinnamomi* (Guizhi) and *Cola Corri Asini* (Ejiao), etc. such Zhigancao Tang (Yanfu, 2002e).
- For qi vacuity and scanty blood, heart palpitations, spontaneous perspiration, and a bound or regulary intermittent pulse, *Radix Glycyrrhizae* is often combined with uncooked *Radix Rehmanniae* (Sheng Di), *Radix Codonopsitis Pilosulae* (Dang Shen), *Tuber Ophiopogonis Japonici* (Mai Dong), and *Ramulus Cinnamomi Cassiae* (Gui Zhi) as in Zhi Gan Cao Tang (Mix-fried Licorice Decoction) (Flaws, 1999g; Ganzhong et al., 2003e).
- In the case due to deficiency of the spleen with fatigue, poor appetite or loose stool, it is used with *Radix Codonopsis* (Dangshen), *Rhizoma Atractylodis Macrocephalae* (Baizhu), etc. such as Sijunzi Tang (Yanfu, 2002e).
- For throat swelling and pain, it is commonly combined with *Radix Platycodi Grandiflori* (Jie Geng) as in Jie Geng Tang (Platycodon Decoction) (Anonymous, 2009l; Flaws, 1999g; Ganzhong et al., 2003e; Yanfu, 2002e).
- Licorice root can also be used with Honeysuckle flower and Forsythia fruit for carbuncles, furuncles and swellings (Shen *et al.,* 2007).
- For abdominal pain due to spasms of the stomach or intestines, licorice root is used with White peony root (Shen *et al.,* 2007).
- For epigastric and abdominal pains, it is used with *Ramulus Cinnamoni* (Guizhi), *Radix Paeoniae Alba* (Baishaoyao), and *Sacharum cum Malto* (Yitang), etc. such as Xiao Jianzhong Tang, "The Minor Decoction for Strengthening the Middle Heater" (Ganzhong et al., 2003e; Wu, 2005c; Yanfu, 2002e).
- For spasm and pain of limbs, used with *Radix Paeoniae Alba* (Baishaoyao) as Shaoyao Gancao Tang (Yanfu, 2002e).
- Licorice root with Prepared aconite root and dried ginger can weaken the heating properties and lessen the side effects of some herbs (Shen *et al.,* 2007).
- For wind heat cough, *Radix Glycyrrhizae* can be combined with *Radix Platycodi Grandiflori* (Jie Geng), *Fructus Arctii Lappae* (Niu Xi), *Radix Peucedani* (Qian Hu), and *Folium Mori Albi* (Sang Ye) (Flaws, 1999g; Yanfu, 2002e).
- For cough and asthma due to algor venti, it is used with *Herba Ephedrae* (Mahuang) and *Semen Armeniacae Amarum* (Xing Ren) in "The Decoction of Three Crude Herbs" (San Ao Tang) (Anonymous, 2009l; Ganzhong et al., 2003e;

Shen *et al.,* 2007; Wu, 2005c; Yanfu, 2002e), (Three Rough & Ready [Ingredients] Decoction) (Flaws, 1999g).

- For cough and asthma due to Lung Heat, it is used with *Gypsum Fibrosum* (Shi Gao), *Herba Ephedrae* (Mahuang), and *Semen Armeniacae Amarum* (Xing Ren) (Flaws, 1999g; Ganzhong et al., 2003e; Wu, 2005c) as in Ma Xing Shi Gan Tang (Ephedra, Armeniaca, Gypsum & Licorice Decoction) (Flaws, 1999g; Ganzhong et al., 2003e; Yanfu, 2002e).
- For cough due to stagnation of damp-phlegm, use with *Rhizoma Pinellia* (Banxia), *Poria alba* (Fuling), etc. (Yanfu, 2002e).
- Decoction of Mulberry Leaf and Chrysanthemum (Sangju Yin), composed of mulberry leaf (*Folium Mori*, Sangye), chrysanthemum flower, ballonflower root (*Radix Platycodi*, Jiegeng) and licorice is used to treat cough of wind heat type (Ganzhong et al., 2003e).
- Decoction of Poria, licorice, Schisandra (Magnoliavine fruit, Wuweizi) Dried Ginger and Asarum (wild ginger, Xixin) (Linggan Wuwei Jiangxin Tang) is used to treat cough with cold phlegm (Ganzhong et al., 2003e).
- For poisoning due to foods and medicinal (Flaws, 1999g; Ganzhong et al., 2003e; Wu, 2005c; Yanfu, 2002e), used alone (Ganzhong et al., 2003e; Wu, 2005c; Yanfu, 2002e) or combined with *Semen Phaseoli Munginis* (Lu Dou) or *Radix Ledebouriellae Divaricatae* (Fang Feng) (Flaws, 1999g; Yanfu, 2002e) or combined with mung beans or soybeans (Ganzhong et al., 2003e).
- Licorice can be used with apricot kernel to treat lead poisoning; with black beans to treat arsenic trioxide poisoning; and with talcum power to treat phosporus poisoning (Ganzhong et al., 2003e).
- For sores and open sores swelling and toxins, *Radix Glycyrrhizae* can be combined with *Flos Lonicerae Japonicae* (Jin Yin Hua) and *Fructus Forsythiae Suspensae* (Lian Qiao) (Flaws, 1999g).
- In Decoction of Two Old Drugs (Erchen Tang), it is used with pinellia tuber (*Rhizoma Pinelliae*, Banxia), tangerine peel (*Pericarpium Citri Reticulate*, Chenpi) and poria to treat cough with damp phlegm (Ganzhong et al., 2003e).
- In Decotion for Relieving Dryness in the Lungs (Qingzao Jiufei Tang), it is used with mulberry leaf, gypsum, lilyturf root and ginseng to treat cough due to dryness in the lungs (Ganzhong et al., 2003e).
- In Fairy Decoction for Cutaneous Infections (Xianfang Huoming Yin) licorice is combined with honey suckle flower (*Flos Lonicerae*, Jinynhua), snakegourd root (*Radix Trichosanthis*, Tianhuafeng) and dahurian angelica root (*Radix Angelicae*

*Dahuricae*) to treat sores and ulcers of the skin caused by toxic heat pathogens (Ganzhong et al., 2003e).

## Dosage and method of use

Decoct in water and administer internally. This medicinal should be used uncooked when entered with clearing and draining medicinals. It should be used honey mix-fried when entered with supplementing and boosting medicinal (Flaws, 1999g). For clearing away heat and poisons it is used unprepared (Anonymous, 2009l Gongwang, 2000; Wu, 2005c); for tonifying the Spleen and Stomach, it is honey-baked (Gongwang, 2000; Wu, 2005c). Used stir-baked with auxiliary fluid mainly for others (Anonymous, 2009l). According different authors there are different recommended doses:

- 3–12 g. Up to 30 g for *Addison*'s disease (Liu et Tseng, 2005d).
- 3-6 g (Flaws, 1999g).
- 3-9 g (Gongwang, 2000).
- As the main medicinal in a formula, it can be used from 10-30g (Flaws, 1999g).
- 3-10g for licorice and 2-5ml of licorice extract. They are orally administraded t.i.d. (Ganzhong et al., 2003e).
- 2-10 g (Anonymous, 2009l; Wu, 2005c) or up to 10-30g is used in decoction when used as a dominat herb. It fits to be used crudely in the prescription for clearing or purging while the honey-roasted Gancao is used in the one for tonifying and nourishing (Yanfu, 2002e).
- 1.5-18g (Greten, 2007).
- 1.5-9g (CP, 2005d).

## Herb Interactions

Gan Cao is incompatible with:

1. Gan Sui (*Radix Euphorbiae kansui*), kansui root (Anonymous, 2009l; CP, 2005d; Flaws, 1999g; Ganzhong et al., 2003e; Liu et Tseng, 2005d; Shen *et al.,* 2007; Wu, 2005c; Yanfu, 2002e)

2. Da Ji (*Rx.Euphorbiae seuKnoxiae, Radix Knoxiae*), knoxia root, Peking Euphorbia Root (Anonymous, 2009l; CP, 2005d; Flaws, 1999g; Ganzhong et al., 2003e; Gongwang, 2000; Liu et Tseng, 2005d; Wu, 2005c; Yanfu, 2002e).

3. Yuan Hua (*Flos Daphnis*), Daphne Flower-bud (Gongwang, 2000; Liu et Tseng, 2005d; Wu, 2005c)

4. Sargassum, Hai Zao (*Hb. Sargassii*), seaweed (Anonymous, 2009l; Ganzhong et al., 2003e; Liu et Tseng, 2005d; Shen *et al.,* 2007; Wu, 2005c)

5. Flos Genkwa (Yuan Hua), genka flower (Anonymous, 2009l; CP, 2005d; Flaws, 1999g; Ganzhong et al., 2003e; Shen *et al.,* 2007; Wu, 2005c; Yanfu, 2002e)

## Precautions and contraindications

*Radix Glycyrrhizae* is contraindicated in case of damp exuberance center fullness and vomiting and spitting (Flaws, 1999g; Gongwang, 2000). It is contraindicated in patients with dampness, stuffiness in the chest, abdominal distension, and vomiting (Gongwang, 2000; Wu, 2005c). Enduring administration of relatively large doses easily leads to the arising of water swelling (Flaws, 1999g). With a sweet taste, can cause fullness and distention in the chest and abdomen due to excessive dampness (Gongwang, 2000), so it's contraindicated for the case with fullness of epigastric abdomen, vomiting or edema due to excessive dampness. And it should be avoided using for a long course and in large amount to prevent a case from having edema (Yanfu, 2002e).

# 8. Conclusions

I conclude that Ephedrae Decoction has clinical efectivity by the meanings of Western approach coincident with the traditional Chinese applications.
The effects of the contituients are compatible with its traditional description applications:

- *Herba Ephedrae* contains ephedrine, like epinephrine, that relaxes bronchial muscles and is a potent bronchodilatador owing to its activation of the β-adrenoreceptors in the lungs. The sympathomimetic action of ephedrine leads to an increase in respiratory rate and pulmonary ventilation and it is used to eliminate the cough. Ephedrine promote the release of noradrenaline and adrenaline and inhibit the release of sensitizing substances as histamine, resulting in the dilation of bronchial smooth muscle, the contraction of intra-mucosal blood vessels of the respiratory tract, and eventually, free movement in the air passage. These feactures are coincident with the fact the ephedra acts on the pulmorary orb. Additionally, ephedra has varying degrees of inhibitory effect against several bacteria and virus, including various types of influenza virus. *H. ephedra* was reported to show the *in vitro* anti-influenza viral effects and augments the production of inflammatory cytokines including interleukin-6 and interleukin-1. These features are coincident with the Chinese therapeutic utilization of Ephedrae Decoction on respiratory system symptoms. On the other hand, the most popular application of pseudoephedrine of *Herba ephedrae* is in flu medications to relieve nasal decongestion and perhaps to an anti-inflammatory effect. Pseudoephedrine has also a diuretic function, greater than ephedrine, which is also consistent with the fact that ephedra belongs to the vesical orb. All these features of *Herba ephedrae* are consistent with the Heidelberg model.
The diaphoretic components of *Herba ephedrae* are the volatile compounds and alkaloids. The diaphoretic effect reflects the extima liberating capacity of *Herba ephedrae.* Adicionally, *Herba ephedrae* has saponins in is constitution. Saponins are substances that in aqueous solution are surfactant agents, so they are capable of foaming. The presences of these constituents maybe are the responsible for the foam formed in the decoction process. This foam is considered toxic and irritant. This is consistent with the presence of saponins since we must take into account that orally and in high doses, the saponins irritated pharyngeal mucosa and digestive tract, cause abdominal pain, vomiting and diarrhea and upon contact with blood are haemolytic. That´s why is indicated to remove the foam. According to the literature there are a lot of volatile compounds in the foam responsible fot the diaphoretic action. Removing the foam, the diaphoresis is reduced. Once again these features are coincident with the Chinese literature.

- As saw previously, the amygdalin compound present in *Semen armeniacae* produces a kind of antitussive and antiasthmatic effects, by stimulating the respiratory center reflexively. This is perfectly coincident with the Chinese therapeutic activities against cough and asthma, acting on the pulmonary orb. Also the moisturizing action in the bowels is perfectly justified according the kernel fatty oil content, so the Chinese therapeutic action on the crass intestinal orb is expected.

- Cinnnamon contains essential oil that can expand blood vessels, regulate blood circulation, and make the blood flow toward the superficial part of the body. This action causes diaphoresis and removal of heat, and coincides with the effects of warming and unbloking channels and collaterals, and dispersing heat, of *Ramuli* according to TCM. Being cinnamaldehyde the major component, this suggests that it contributes tremendously for the therapeutic effects of cinnamon. According to the component determination of the essential oils of the different parts of the plant by Shen *et al.* (2002) *Ramuli* has less cinnamaldehyde than the *Cortex* (64.57% *versus* 83.1%). This can explain why the *Cortex* has a stronger effect than the *Ramuli*, and the different uses in TCM. In adition to the study of Shen *et al*., more studies are needed to access the therapeutic effects of cassia and its effective ingredients.

As for the effect of cinnamaldehyde on the CNS, it is known that its action is concentration dependent: the administration of low doses stimulates this system, while high doses cause sedation. The cinnamaldehyde accelerates the release of catecholamines, primarily adrenaline, from adrenergic glands into the bloodstream. So naturally, it opens the lung. Increases peripheral blood flow, slows heart rate, reduces blood pressure, and has antipyretic and hypothermic effects. Cinnamaldehyde is a circulostimulant and it accelerates release of catecholamines (mainly adrenaline) from the adrenal glands into the blood.

Cinnamaldehyde was previously found inhibited the *Mycobacterium tuberculosis* and influenza virus effectively, and could regulate the immunological function. Also eugenol was identified as a major antimicrobial component of cinnamon. In addition, analgesic effects are attributed to: coumarin, eugenol, methyl-salicylate, *p*-cymene and salicylic acid present in cinnamon. Also expectorant, antitussive, antibronchitic and bronchorelaxant effects properties has been attributed to several constituents of cinnamon.

Also 2-methoxycinnamaldehyde and cinnamaldehyde were previously found that relieved fever and pain and could regulate the immunological function. Recent research also showed that it could reduce the amount of cyclooxygenase (COX)-1, COX-2 and PGE2 and perhaps this is the mechanism of its relieving-fever effect. In addition, analgesic effects are attributed to: coumarin, eugenol, methyl-salicylate, *p*-cymene and salicylic acid present in cinnamon. All this constituents contributes to the action of *Ephedrae Decoctum*. In addition, expectorant, antitussive, antibronchitic and bronchorelaxant effects properties has been attributed to several constituents of cinnamon. This is persistent with the action on the Pulmorary orb. These features corroborate with the Chinese therapeutic usage of Ephedrae Decoction, according to the Heiderberg model.

- Licorice and its preparations can relieve drug intoxication and neutralize bacterial toxins and toxic metabolites, because glycyrrhizin can reduce the responsiveness of the organism to toxic substances, in the same way that corticoid hormone does, and promotes dissociation of toxic substances through inducing the production of drug metabolizing enzyme in the liver. In addition, licorice can also absorb and conjugate toxic substances to relieve intoxication. Licorice preparations and glycyrhhizin can also protect the livers of animals from injury caused by drug poisoning. All this properties are coincident with the Chinese uses in intoxications, food poisons, and harmonizing the adverse effects of other plants in a complex formula.

The antiulcer activity of *Radix Glycyrrhyzae* has been demonstrated both experimentally and clinically. Glycyrrhizin and its aglycone both have antiphlogistic activity and increase the rate of mucus secretion by the gastric mucosa. Glycyrrhizinic acid seems to act by raising the local concentration of prostaglandins that promote mucous secretion and cell proliferation in the stomach, leading to healing of ulcers in experimental studies. This also demonstrates a good effect on the stomach orb and the center. It is known that making stronger the center it is better for get rid of of pituita.

The spasmolytic activity of *Radix Glycyrrhyzae* has been demonstrated *in vivo* and appears to be to the flavonoids liquiritigenin and isoliquiritigenin, so its Chinese utilization in spastic pain makes sence, acting on the phase Wood.

Licorice has been used as a cough-relieving medicinal herb from ancient times. It seems that mucilage present in it or secretion produced under the influence of the active substances covers the oral and throat mucosa soothing its irritability and relieving dry cough. Choline ester of glycyrrhetinic acid can produce a central antitussive effect. After oral administration of licorice, the drug may cover the mucosa of the throat and relieve local local inflammatory irritation to control cough and promote secretion of mucus from the throat and bronchi to produce an expectorant effect. The demulcent action of the drug is due primarily to glycyrrhizin. The antitussive and expectorant properties of the drug have also been attributed to glycyrrhizin, which accelerates tracheal mucus secretion. This is very pertinent in a formula like *Ephedrae Decoctum*, and licorice contributes once again for the anti-tussic effect. Pharmacological studies showed a marked anti-inflammatory action by licorice. The similarity in structure of glycyrrhetic acid to the structure of hormones secreted by the adrenal cortex accounts for the mineralocorticoid and glucocorticoid activity of glycyrrhizic acid. Licorice constituents also exhibit steroid-like anti-inflammatory activity, similar to the action of hydrocortisone. Also the antiallergic aspect of *Radix Glycyrrhiza,* played by glycyrrhizin, 18-β-glycyrrhetinic acid and liquiritigenin can be very important to treat several respiratory diseases where this particularity plays a crucial role. Also the anti-infeccious activity revealed by *Radix Glycyrrhiza* plays an important role in a decoction as *Ephedrae Decoctum.* This decoction is used in many situations where infectious organisms are the causing factors of the disease, according to the Western point of view. *Radix Glycyrrihzae* is a very complex plant and used for so many purposes. Indeed, is almost considered a panacea. This is conniving with the fact that the *Radix Glycyrrhiza* acts in the 12 orbs and is a buffering herb.Once again these features are coincident with the with the Chinese therapeutic usage of Ephedrae Decoction, according to the Heiderberg model.

The Ephedra Decoction is just one example of thousands of constellations that belong to the rich spoil of the classic Chinese herbs. No wonder that Ephedra Decoction has been used for millennia. All its constituents seem out carefully combined to obtain successfully therapeutic results. All the properties of these plants are perfectly explicable by conventional Western methods, according to the tradicional use of this concoction.

This master thesis shows that is possible to successfully translate the effects described by the traditional language of TCM, by the Heidelberg model, into the language of Western physiology. The research of this master thesis also shows that Ephedra Decoction can be regarded as an effective medicine against symptoms related to cough, sputum, bronchitis, asthma, flu and COPD, and it may therefore be recommended to treat the symptoms above named if these cannot be controlled by Western medicine.

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