

MESTRADO INTEGRADO EM MEDICINA

# **Dietary supplements influence in the perioperative period.**

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**M**

**2021**



## **Dietary supplements influence in the perioperative period.**

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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## RESUMO

**Introdução:** Os suplementos dietéticos são descritos como fontes concentradas de nutrientes ou outras propriedades nutricionais ou fisiológicas. Não têm ação metabólica, farmacológica ou imunológica, mas podem ocorrer interações com fármacos e durante a anestesia pode ditar o futuro do doente. Existe também evidência da influência no resultado cirúrgico durante o período perioperatório. Assim sendo, este período para pessoas a usar suplementos dietéticos requer uma supervisão cautelosa e personalizada. O objetivo deste trabalho é encontrar evidências e fazer uma revisão sistemática da influência dos suplementos dietéticos durante o período perioperatório.

**Métodos:** Uma revisão da literatura com 48 artigos selecionados no PubMed, baseados em critérios de exclusão e inclusão. Os artigos foram selecionados entre 2015 e 2020.

**Resultados:** Para prevenir ocorrências adversas perioperatórias, inúmeras práticas são exploradas entre vários suplementos dietéticos. Óleo de peixe: a correlação com a fibrilhação auricular pós-operatória mostrou uma duração total média significativamente mais curta desses episódios. Bebidas com carboidratos: indicaram maior força muscular no perioperatório e melhor manutenção do estado metabólico e nutricional. Vitamina D: pode afetar a qualidade de vida e prolongar a sobrevida livre de doença, também é sugerido que a cirurgia pode reduzir abruptamente a sua concentração. Arando: pode causar diminuição na concentração sérica do antigénio específico da próstata em homens com cancro de próstata. Beta-hidroxi-beta-metilbutirato, arginina e glutamina: revelou afetar benéficamente a força muscular no perioperatório e foi sugerido que esta combinação pode aumentar os níveis séricos da hormona de crescimento. Ervas medicinais: inchinkoto pode possuir efeito hepatoprotetor, a curcuma pode ter um risco de lesão renal aguda e decocção de San Huang um efeito benéfico entre vários fatores.

**Conclusão:** Os suplementos dietéticos não são plenamente seguros para todos. Eles têm vantagens e desvantagens no que toca aos seus resultados. Muito é ainda desconhecido, portanto, é fundamental continuar a estudar estes suplementos no futuro. O papel do profissional de saúde, nesta matéria, é também bastante importante. Desde questionar os doentes sobre o consumo, a informá-los sobre potenciais efeitos e interações destes suplementos.

**Palavras-chave:** Suplementos dietéticos; Suplementos alimentares; Período perioperatório; Óleo de peixe; Bebidas com carboidratos; Vitamina D; Beta-hidroxi-beta-metilbutirato; Arginina; Glutamina; Ervas medicinais.

## **ABSTRACT**

**Introduction:** Dietary supplements are described as concentrated sources of nutrients or other properties with a nutritional or physiological effect. They have no metabolic, pharmacological, or immunological action. But interactions with other drugs can occur, and during anaesthesia it can dictate the patient's fate. There's also evidence of influence on surgical outcome during perioperative period. Therefore, this period for people with dietary supplements require a cautious and personalized management. The aim of this work is to find evidence and to systematically review dietary supplements influence in the perioperative period.

**Methods:** A literature review with 48 articles selected from PubMed, based on exclusion and inclusion criteria was conducted. The articles were selected from 2015 to 2020.

**Results:** To prevent perioperative adverse occurrences, numerous practices are explored among various dietary supplements. Fish oil: correlation with postoperative atrial fibrillation showed a significant shorter mean total duration of these episodes. Carbohydrate drinks: indicated greater muscle strength during perioperative period and better maintained metabolic and nutritional state. Vitamin D: it might impact quality of life and prolong disease free survival, also it is suggested surgery can reduce abruptly vitamin D's concentrations. Cranberry: observed decrease of serum prostate specific antigen concentrations in men with prostate cancer. Beta-hydroxy-beta-methylbutyrate, arginine, and glutamine: revealed a beneficial impact on muscle strength in the perioperative period and it was suggested this combination might increase serum growth hormone levels. Herbal: inchinkoto might indicate an hepatoprotective effect, curcumin might have a risk of acute kidney injury and San Huang decoction a beneficial effect among various factors.

**Conclusion:** Dietary supplements are not undoubtedly safe for everybody. They have advantages and disadvantages when it comes to their outcomes. A lot is still unknown, therefore, it is crucial to continue studying these supplements in the future. The role of health care providers, in this matter, is also very important. From questioning patients about their consumptions to inform them about potential effects and interactions.

**Keywords:** Dietary supplements; Food supplements; Perioperative period; Fish oil; Carbohydrate drinks; Vitamin D; Cranberry; Beta-hydroxy-beta-methylbutyrate; Arginine; Glutamine; Herbal.

## **ABBREVIATIONS**

AF - Atrial Fibrillation  
ARDS - Acute Respiratory Distress Syndrome  
Arg - Arginine  
CHO - Carbohydrate  
DFS - Disease Free Survival  
DHA - Docosahexaenoic acids  
DS - Dietary Supplements  
EC - Esophageal Cancer  
EPA - Eicosapentaenoic  
EVLWI - Extravascular Lung Water Index  
Gln - Glutamine  
HMB - Beta-hydroxy-beta-methylbutyrate  
Nrf2 - Nuclear Factor E2-related Factor 2  
NT-pro-BNP - N-terminal pro-brain natriuretic peptide  
OPERA - Prevention of Post-Operative Atrial Fibrillation  
OS - Overall Survival  
PCa - Prostate Cancer  
PiCCO<sub>2</sub> - Pulse Contour Continuous Cardiac Output  
PSA - Prostate Specific Antigen  
PUFAs - Polyunsaturated Fatty Acids  
PVPI - Pulmonary Vascular Permeability Index  
QOL - Quality of Life  
SHD - San Huang Decoction  
VD - Vitamin D  
VDD - Vitamin D Deficiency

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## INTRODUCTION

Under normal circumstances, it is known a varied diet, in recommended and established quantities, can provide a person with all nutrients necessary for a normal development and preservation of a healthy life.<sup>1,2</sup> Nevertheless, surveys indicate this ideal situation is not being done properly and therefore, there are cases of people choosing to supplement their consumption of nutrients with the help of dietary supplements (DS) because they cannot meet their energy requirements throughout oral food ingestion.<sup>2,3</sup>

DS or food supplements can be defined as concentrated sources of nutrients or other properties with a nutritional or physiological effect incorporating, vitamins, minerals, amino acids and/or enzymes, essential fatty acids, fibre, and botanical and herbal extracts.<sup>1,2,4-6</sup> They are advertised and sold in “dose” form, for instance liquids, pastilles, tablets, powders, or capsules.<sup>1,5</sup> They have no metabolic, pharmacological, or immunological action because they are not considered medicinal products. Consequently, DS are not used to prevent or treat diseases. They are normally used, not only to aid people to stay healthy, but also to avert prescription drugs, lose weight, or even to improve sports or sexual performance.<sup>2,5,6</sup>

It needs to be considered DS are usually safe due to their natural sources, but they might have some products within with the ability to cause negative effects.<sup>2,4,5,7</sup> Which means not all DS are safe for everybody to consume.<sup>5</sup> Normally, people who want to use DS have an easy way to access them, they are also low-priced and do not need a prescription.<sup>2,4</sup> Consequently, asking patients about their use becomes crucial<sup>4,5,7-9</sup>, as well as performing physical examination, and evaluating relevant diagnostic tools.<sup>9</sup> Surveys reveal only one-third of patients using DS<sup>4</sup> and three-fourth using herbal medicines<sup>10</sup> mentioned this to their health care provider without being explicitly questioned.

The high amount of consumption of DS enhances concern in a particular area such as patients who need anaesthesia, because it might occur interactions with drugs, they can cause sedation, and some DS are associated with undesirable effects such as bleeding, which can cause even bigger problems during surgery.<sup>4,5,11</sup> Hence, the importance of a meticulous pre-anaesthetic consultation. This is essential because of the side effects DS can cause, going from minor complications to higher morbidity and mortality in worst case scenario.<sup>4,5</sup>

The use of DS in perioperative can have a substantial influence on surgical outcome. It can reduce inflammation, swelling, bruising, improve immunity, stimulate healing, and reduce

oxidation created by surgery and anaesthesia,<sup>11</sup> and consequently reduce the costs of care after surgery.<sup>12</sup> Nevertheless, supplements ought to be administered cautiously.<sup>2,11,13</sup>

According to statistics the probability a surgical patient will appear with weak dietary lifestyle is fairly elevated.<sup>11</sup> So, a centred tactic to nutrition becomes important in this type of patients since the surgeon cannot change their daily life choices in limited time between scheduling the surgery and the procedure itself.<sup>11</sup>

Perioperative nutrition significance is becoming a normal practice with the increased possibility patients undergoing surgery will have higher age, obesity, or other problems.<sup>5,11</sup> Therefore, it is essential for physicians to keep patients notified of supplements with the ability to trigger perioperative complications and advise the supplements with the capability to improve patients nutrition during this period around surgery.<sup>2,4,5,11</sup>

The aim of this work is to find evidence and to systematically review dietary supplements influence in the perioperative period.

## **METHODS**

An online search was performed on PubMed, between August 2020 and December 2020. The following keywords combinations were used: "food supplements", "dietary supplements", "nutritional supplements", "herbal" and "perioperative", "preoperative", "postoperative", "anesthesia", "anaesthesia".

In this review the inclusion criteria consist of studies in humans, published in the English and Portuguese language dated between 2015 and 2020, available in full text. The number of articles resulted from this research was 83.

Subsequently, the selection of the articles was achieved by reading their abstracts and, later, by a complete reading. At this point, were excluded studies involving personal opinion articles, systematic reviews, case reports, articles in another language, trial stage investigations and studies with parenteral nutrition.

Making use of these inclusion and exclusion criteria, 13 publications were chosen for this review.

It is also important to add other articles found in bibliographic references from primarily selected articles were consulted and analysed as well as other pertinent articles about dietary supplements searched through Google. The year of their publication was not considered. At the end, this review had 48 publications analysed. (Figure 1).

## RESULTS

### Fish Oil

In a variety of studies about fish oil, a source of the long-chain omega-3 polyunsaturated fatty acids (PUFAs); eicosapentaenoic and docosahexaenoic acids (EPA and DHA), it was investigated plenty of hypotheses surrounding this DS. Among those, the correlation with postoperative atrial fibrillation (AF), perioperative bleeding, and how can this supplementation affect cognitive outcomes.<sup>14–16</sup>

A single-center, double blinded, placebo controlled randomized clinical trial study with 401 patients submitted to coronary artery bypass graft surgery was performed, they were divided into two group (PUFAs and control groups). In addition to standard care, patients took dosage of two capsules per day. This method started at least five days prior to surgery and remained until patients discharge. It was demonstrated in their study, after surgery the frequency of AF episodes between the groups was not considerable, but, and unlike several previous trials, the mean total duration of AF in PUFAs group was shorter when compared with the control group.<sup>14</sup> There was also another outcome for this study about the mean length of stay in the cardiac surgery intensive care unit and it showed a significant reduction in PUFAs group, which agrees with other studies already performed.<sup>14</sup>

At a larger proportion, Omega-3 Fatty Acids for Prevention of Post-Operative Atrial Fibrillation (OPERA) Trial was staged. It was an investigator-initiated, randomized, double-blind, placebo-controlled, clinical trial around 28 centers in the United States, Italy, and Argentina. The main objective was to ascertain if perioperative n-3-PUFA supplementation lowers the incidence of postoperative AF. This was made with 1516 patients undergoing cardiac surgery who were randomized to perioperative fish oil or placebo.<sup>17</sup>

Following this trial, Akintoye et al.<sup>15</sup> tested the effect of fish oil supplementation on perioperative bleeding, in a multinational, placebo-controlled trial involving the 1516 patients. It was observed the risk of bleeding between both groups was not significantly distinct. But the fish oil group needed fewer transfusions compared to placebo (mean = 1.61 vs 1.92,  $p < 0.001$ ) both during and after cardiac surgery. Moreover, high levels of plasma omega-3 fatty acids (achieved through normal levels plus fish oil supplementation) were associated with lower risk of perioperative bleeding. There were some minor adverse events when it came to fish oil use, such as burping, gastrointestinal upset and fish oil taste.<sup>15</sup>

Another study made, based on OPERA trial, from Jackson et al.<sup>16</sup> explored the fish oil effect on cognitive outcome, since decrease of this aspect is linked as a potential effect of cardiac surgery. The sample size was 320 because this study was limited to patients in North America in the OPERA trial and they also had to be enrolled in a United States center. The cognitive tests were made 1 day prior to surgery and at day 4 and 30 after. The results showed no indication of significant persistent cognitive decay over 30 days, therefore, according to this study, fish oil might not impact cognition after cardiac surgery. Curiously, they noticed neuropsychological test scores by day 30 were similar to those acquired before surgery, underlining the hypothesis cardiac surgery is not a source of cognitive deterioration.<sup>16</sup>

### **Carbohydrate drinks**

It has been proven carbohydrates (CHO) drinks can have the ability to maintain muscle mass and strength, decrease glucose consumption and postoperative negative nitrogen balance, as well as reducing anxiety, hunger, and thirst.<sup>18,19</sup>

In Gava et al.<sup>18</sup>, a prospective, randomized, double-blind clinical study, used handgrip strength as the way to assess each patients evolution between preoperative and postoperative period of patients submitted to cholecystectomy by laparotomy. The intake of CHO drinks 6 and 2 hours before surgery revealed the patients with supplementation had a higher handgrip strength during preoperative, immediate preoperative and postoperative periods. The most prominent difference between both hands was in the immediate preoperative period, where the control group showed lower results in handgrip strength when compared to the other two periods evaluated and when compared to the CHO group. Getting to the conclusion the patients in CHO group had greater muscle strength during the course of the perioperative period and also their metabolic and nutritional state was better maintained.<sup>18</sup>

Additionally, another study performed among patients submitted to elective colorectal surgery, where the tests used were a 2-minute and 6-minute walk tests, in which the objective was to assess if CHO would improve walking performance in postoperative.<sup>19</sup> The baseline minute walks were made during preoperative. In postoperative day 1, the median distances for the 2-minute walk test were around half of the preoperative baseline, for both groups. This distance increased on day 2 and even more on day 3. Nevertheless, the 2-minute walk test distances were not much different for both groups in all three days evaluated. The 6-minute

walk test, measured between 7-10 days after surgery, were also not significantly different among both groups.<sup>19</sup>

There were also secondary outcomes considered such as measure of serum insulin, glucose concentrations and nitrogen balance, as well as the duration of hospital stay. Among these parameters studied, this analysis showed no meaningful difference between groups, in blood sugar nor insulin concentrations in postoperative. The nitrogen balance appeared to be higher for the CHO group, mainly on postoperative days 2 and 3. The durations of hospital stay varied between groups, where the CHO group had a median of 5.5 days and the control group was 6 days.<sup>19</sup>

Therefore, the article from Mingkwan et al.<sup>19</sup> came to the conclusion preoperative CHO drinks had no significant impact on assisting postoperative healing, as it was evaluated, in this study, by walking performance.<sup>19</sup>

## **Vitamin D**

Among dietary supplementation, vitamin D (VD) is one of the most consumed. Some studies inform there is a high incidence of VD deficiency (VDD) in the critically ill patients with an association with enhanced levels of infection acute respiratory failure, acute kidney failure, sepsis, and mortality.<sup>20</sup>

The study performed by Wang et al.<sup>21</sup>, focused on the role of postoperative VD supplementation in clinical outcomes in esophageal cancer (EC) patients following surgery. It had a total of 303 patients, in which only 49 of them used VD supplementation regularly after surgery. After 2 years of follow-up only 181 EC patients survived, among those, 32 took VD. From the get-go there were several significant differences between both groups. The ones taking VD had a tendency to be younger, enrolled in some college, had a better salary, partook in more physical activity, had lower fat consumption, smoked less tobacco and were more prone to have diabetes in this study.<sup>21</sup>

The primary outcome was to assess quality of life (QOL) of EC patients at 2 years after surgery. The results showed patients using VD scored higher in physical and social functioning and global health, in addition lower scores of fatigue and appetite loss when compared with non-users. Implying VD users enjoy life more with more energy, better appetite and less fatigue. The secondary objective was to assess 3 years disease free survival (DFS) and global survival (OS). The difference between the DFS and OS was significant since patients who received VD

supplementation were more likely to have improved DFS ( $p = 0.030$ ), but when it came to OS, there was no significant association with VD supplementation ( $p = 0.303$ ). Curiously, within this results, physical activity was considered an independent prognostic factor for both OS and DFS, therefore, it was firmly underlined by this article physical activity has a protective effect on prognosis of EC.<sup>21</sup>

Overall, these results indicate VD supplementation use could improve QOL and extend DFS of EC patients. Thus, this study reinforces VD use in cancer treatment and recovery phases could help with getting better clinical outcomes.<sup>21</sup>

Another study with VD supplementation was made to investigate its role on preventing lung injury following esophagectomy, more specifically acute respiratory distress syndrome (ARDS).<sup>22</sup> In this randomized, double-blind, placebo-controlled trial, the patients received a single dose, VD supplement or placebo, between 3-14 days before surgery. The sample size was 68 patients, 33 with VD and the rest control group. There were three specific time points for assessment for the endpoints: preoperatively, within 1 hour postoperatively and 1 day postoperatively. The primary endpoint was change in extravascular lung water index (EVLWI) assessed by Pulse Contour Continuous Cardiac Output (PiCCO<sub>2</sub>) at the end of surgery. This study showed EVLWI increased significantly only between preoperative and postoperative in the placebo group, but in a general way VD treatment did not reduce the change in EVLWI during postoperative period. Also, PiCCO<sub>2</sub> derived pulmonary vascular permeability index (PVPI) was included as an outcome measure since latest data indicates it is a safer measure of alveolar-capillary permeability to distinguish nonhydrostatic edema than EVLWI. This analysis demonstrated PVPI rose significantly between preoperative and postoperative in patients with placebo, but not VD. Meaning VD supplementation did decrease the change of PVPI.<sup>22</sup>

The secondary endpoint were PaO<sub>2</sub>:FiO<sub>2</sub> ratio, which demonstrated there was no significant difference between groups; and 28 and 90 day survival, safety and tolerability of VD supplementation, revealing there were no episodes of hypercalcemia or adverse events, therefore, the trial supplementation was well tolerated. It was also discovered in the placebo group VDD appear in 58% of patients on the day of surgery and it rose to 90% by day 3 in postoperative period. For the VD supplementation group, only 5% of patients in this group had VDD at the time of surgery, rising to 49% by day 3 in postoperative period, suggesting VDD is caused by critical illness.<sup>22</sup>

In summary, a single dose of VD supplementation did not avoid the development of ARDS, and there were no changes in other outcomes. Moreover, surgical insult results in an abrupt reduction in VD concentrations.<sup>22</sup>

## **Cranberry**

Cranberry can be used in different formats, as a fruit (dry, fresh, or powder), juice or DS containing juice powder. They are utilized primarily by women with the intent of preventing recurrent urinary tract infection<sup>23</sup> but also by men with moderate to severe lower urinary tract symptoms, improving them.<sup>24</sup>

The study conducted by Student et al.<sup>25</sup> tried to evaluate the consequences of cranberry intake on prostate specific antigen (PSA) values and other indicators in men with prostate cancer (PCa) before radical prostatectomy, therefore, the patients included in this study had to have, from a prostate biopsy, a pathological diagnosis of adenocarcinoma of the prostate. It was a single-center, randomized, placebo-controlled trial with 62 patients evaluated and divided into a cranberry group and a placebo group, and they took, for at least 21 days prior to surgery, a single daily dose of 1500 mg of cranberry powder or placebo, respectively. From the start there were no significant difference between groups when it came to age, body mass index or plasma concentrations of selenium and zinc. The range of Gleason settled on an intermediate grade with a median score of 7 for both groups.

The primary outcome was to explore the effect of cranberry fruit powder supplementation on PSA response in men with PCa. Over the research period, it was observed the decrease of serum PSA concentrations by 22.5% in patients with cranberry fruit powder supplementation, while in the placebo group the concentration increased by 0.9%.<sup>25</sup>

The secondary outcome was to assess the differences between both groups when it comes to basic physiological biomarkers, chosen oxidative stress markers, urine, and prostate tissue markers. Among biomarkers, there was an inclination in the direction of increased Insulin-like growth factor-1 and decreased gamma-glutamyltranspeptidase in the cranberry group, with no significative difference in others clinical parameters. The oxidative stress markers showed high significant differences within the cranberry group for total thiol groups and catalase, for the placebo group for paraoxonase 1 and glutathione peroxidase, and both groups showed differences for erythrocyte malondialdehyde and plasma malondialdehyde. In urine there was a tendency to downregulation of beta-microseminoprotein and upregulation of prostate cancer

antigen-3 after cranberry supplementation. There were no significant discrepancies among groups when it came to prostate tissue markers.<sup>25</sup>

It was also assessed cancer staging score did not differ between before and after surgery in either group.<sup>25</sup>

### **Beta-hydroxy-beta-methylbutyrate, Arginine, and Glutamine**

A mixture containing beta-hydroxy-beta-methylbutyrate (HMB), arginine (Arg), and glutamine (Gln) has shown to have different properties, including promotion of protein synthesis and suppression of protein breakdown, contributing to an increase in muscle mass, maintenance of muscle strength and wound healing.<sup>26</sup>

In a randomized controlled study, set to see if HMB/Arg/Gln supplementation combination had an important role on the recovery of quadriceps muscle strength after total knee arthroplasty<sup>27</sup>, the investigators tried to assess the impact of said combination among 23 patients taking either placebo (orange juice) or HMB/Arg/Gln 5 days before to 28 days after surgery. These people had postoperative rehabilitation and were provided and posteriorly documented with hospital food for 3 days after surgery.

The hypothesis in this study was to see the influence of presenting a nutritional supplementation to postoperative patients whose needs for protein are elevated by the intrusive surgery and see if it could possibly enhance the recovery of quadriceps strength.<sup>27</sup>

The results included the rehabilitation, durations of hospital stay, dietary intake, body weight, amount of exercise, rectus femoris cross-sectional area where there were no significant differences between both groups. The only outcome showing significant difference was muscle strength. The investigators divided these results in operated-side knee and non-operated-side knee extension strengths. In the operated-side knee extension strength it was demonstrated a reduction of muscle strength amongst the control group between before surgery and postoperative day 14. In the HMB/Arg/Gln group there was no considerable disparities in muscle strength during that period. In the non-operated-side knee there were no considerable differences among both groups.<sup>27</sup>

In another study made with the same supplementation combination, performed by Wada et al.<sup>28</sup>, the aim was to assess the use of perioperative nutrition utilizing HMB/Arg/Gln in patients who were going to go through open abdominal surgery and see if this combination had

the power to reduce wound complications following said surgery in a randomized, double-blind, placebo-controlled trial. This study was performed in 60 eligible patients divided into HMB/Arg/Gln group and placebo group obtaining an equal quantity of isocaloric juice. Patients took the supplement daily from 3 days before to 7 days after surgery. Both groups were fairly balanced on all baseline characteristics.

The primary outcome was the prevalence of wound complications and the study showed the incidence was the same in both groups, 6 patients each. The secondary outcomes were the occurrence of postoperative complications (not including wound complications), postoperative hospital stay time, total-body skeletal muscle mass, handgrip strength and skin water content. When it came to the occurrence of postoperative complications, the number of patients affected was similar between groups (4 patients in the HMB/Arg/Gln group and 6 patients in the placebo group), among the others secondary outcomes there was no significant difference between them. Additionally, this investigation suggested HMB/Arg/Gln might increase serum growth hormone levels ( $p = 0.036$ ).<sup>28</sup>

Consequently, the investigators observed no significant advantage of HMB/Arg/Gln supplementation in either endpoints, therefore the authors would not suggest the perioperative use of this combination for the intent of boosting wound healing.<sup>28</sup>

## **Herbal**

This type of medicine can contain pharmacologically active constituents, thus can cause influence in patient's health, these can either be positive or negative.<sup>10</sup> Also, there is a lot of incomplete, uncertain, and somehow contradictory information about the majority of them, which puts herbs in an ambiguous category.<sup>10</sup>

Mizutani et al.<sup>29</sup>, investigated about inchinkoto and its hepatoprotective effects after hepatectomy. The results of this study were based in 61 patients, there was no placebo administrated. This herbal supplement was provided orally only during preoperative at least 7 days prior to surgery. There were no substantial disparities between both groups when it came to general characteristics.

The main outcome to consider was postoperative liver damage severity, which was assessed by conferring the levels of serum aspartate aminotransferase and alanine aminotransferase. This evaluation did not diverge meaningfully among the groups. The same was assessed with postoperative complications. The secondary outcome was to explore the

expression of antioxidant factors such as expression of nuclear factor E2-related factor 2 (Nrf2) and further oxygen stress-related indicators, in the liver. Among these results it was possible to see Nrf2 upregulation was enhanced in the inchinkoto group, this is the main regulator of antioxidant gene expression, so it comes to no surprise it was also possible to see the mean induction levels of antioxidant genes, like hemeoxygenase-1 and superoxide dismutase, were indeed higher within the inchinkoto group as well.<sup>29</sup>

There was also performed a subgroup analysis among the patients who underwent more severe hepatectomy. Curiously, the serum of aspartate aminotransferase and alanine aminotransferase during postoperative period were significantly lower within patients who took inchinkoto, which might indicate an hepatoprotective effect among severe hepatectomy.<sup>29</sup>

In a study lasting 3 years, Garg et al.<sup>30</sup> conducted a randomized, parallel-group, placebo-controlled trial around 10 academic hospitals with 606 suitable subjects submitted to abdominal aortic aneurysm repair. They were divided into two groups, 304 patients took curcumin, derived from a plant called turmeric, and 302 patients took placebo. The doses administrations were given during perioperative period: 4 g per day in 2 divided doses for 2 days before surgery, 2 g on the morning of surgery, other 2 g right before surgery started, 2 g 6 hours after existing the operation room and the last 2 g the morning after surgery. At baseline there were no significant difference between groups when it came to background characteristics. During this study, a total of 10 patients passed away within 30 days of surgery, 5 for each group.

Among the results, it was possible to detect curcumin metabolites in the urine and this concentration was significantly superior in the curcumin group. When it came to the primary endpoints, 4 biomarkers were analysed, the mean perioperative concentration of plasma NT-pro-BNP was 202% higher in both group and 1846% higher in plasma high-sensitivity C-reactive protein in both groups. In regard to significant differences among both groups in the primary endpoints, there were none, including plasma NT-pro-BNP and plasma high-sensitivity C-reactive protein, postoperative concentration of urine interleukin-18 and perioperative increase in the concentration of serum creatinine.<sup>30</sup>

In the secondary endpoints it was possible to see a significant higher risk of acute kidney injury within the curcumin group ( $p = 0.01$ ), but regarding hospital stay duration and the risk of a composite of clinical events, including myocardial infarction or death, there were no noteworthy differences between the groups. It was also assessed the curcumin safety documenting parameters such as diarrhea, bleeding and hypoglycemia events, and these did not differ among both groups either.<sup>30</sup>

In 2015, Zhu et al.<sup>31</sup>, investigated another herbal medicine, San Huang decoction (SHD), regarding its effect on reducing exudate in breast cancer patients. It was a study involving 30 patients and the SHD or placebo were given between 1 day before and 7 days after surgery. All of them went through a modified radical mastectomy. From the start, age, TMN stage and level of inflammatory factors did not differ substantially between both groups.

During research, many outcomes were assessed. The primary one was the quantity of fluid drained by days 1, 3 and 7 after surgery and the total volume of it by day 7 postoperatively. In this matter, the volume of fluid drained daily was always decreased among treatment group when compared to control group and this difference was only significant during day 7 ( $p = 0.012$ ) and when analysing the total volume of fluid drained ( $p = 0.001$ ). Another evaluation performed on patients was the Traditional Chinese Medicine Symptom scale, showing by day 3 after surgery the average score among SHD group was substantially decreased including symptoms like fatigue or insomnia. On the other hand, among the control group the score was increased and therefore there was a considerable difference between them ( $p = 0.002$ ). On day 7 postoperatively the difference was still significant between both groups ( $p = 0.049$ ), in the SHD group the score dropped further and the patients presented only mild fatigue. Within the control group, patients were still showing signs of insomnia and weakness, symptoms presented by SHD group by day 3 after surgery. The wound inflammation score was also documented, by day 1 both groups presented swelling, pain, and dark pink drainage fluid. There was no substantial discrepancy among the groups. By day 3 postoperatively the SHD group showed a reduction of symptoms which included a lighter drainage fluid, yet the symptoms within the control group stayed more or less the same. This revealed a significant difference between the groups ( $p = 0.02$ ). By day 7 after surgery the inflammatory symptoms decreased further, but this reduction was more prominent among the SHD group since the symptoms nearly disappeared ( $p = 0.001$ ).<sup>31</sup>

As a secondary outcome, the inflammatory factors were measured in the drained fluid. By day 3 after surgery the difference was already noteworthy among groups, but this difference was more prominent by day 7, which showed the reduction of inflammatory factors among SHD group was smaller than the level observed at 2 hours after surgery which indicated these subjects had practically recuperated from the acute inflammatory status of the radical mastectomy. The SHD safety was also analysed, showing no adverse effect in this study among subjects.<sup>31</sup>

## **DISCUSSION**

### **Fish Oil**

Several studies showed the dietary supplementation with fish oil does not have a significant impact in the perioperative period. Thus, is key to make further studies and continue researching this supplement and its mechanisms so it may be possible to know better how the perioperative administration of fish oil can influence the outcome of the patient.<sup>14–16</sup>

Indeed, the studies conducted by Akintoye et al.<sup>15</sup> and Jackson et al.<sup>16</sup> followed the protocol made for OPERA<sup>17</sup>, an older trial, considerate one of the largest to-date which studied randomized perioperative supplementation of fish oil. It included a large and varied patient population undertaking high risk cardiac surgical procedures. Among this trial there are some potential limitations such as the period of time the studies are conducted, being short-term effects of fish oil supplementation may diverge from long-term effects.<sup>15–17</sup> It is also unknown the most appropriate ratio of EPA:DHA, therefore it is still not clear what is the ideal dose of fish oil which can bring the most benefit.<sup>14,15</sup> The choice of olive oil for placebo is another prominent concern, since there is evidence showing this supplement could have impact on the cardiovascular system.<sup>14–17,32</sup> Furthermore, it has been mentioned oleic acid in olive oil can have a potential antiplatelet effect which can cause some doubts on whether olive oil is a fitting placebo or not.<sup>15</sup>

Interestingly, in the Akintoye et al.<sup>15</sup> study, it was possible to assess fish oil could reduce blood transfusion requirements in patients undergoing cardiac surgery, a theory already reported by other studies showing adults who ingest large quantities of oily fish, have a lower rate of cerebral bleed<sup>15,33</sup>, lower coronary heart disease and cardiovascular disease mortality.<sup>1,5</sup>

### **Carbohydrate drinks**

It is known long periods of starvation can lead to a higher risk of postoperative complications, by increasing catabolic pathways. Moreover, overnight fasting can lower protein synthesis and enhance nitrogen excretion.<sup>34</sup>

Studies performed with CHO drinks in the perioperative period show the intake of this type of supplements up to 2 to 3 hours before surgery is considerate safe and there is no relation with complications with anaesthesia or mortality risk. It is also suggested CHO drinks lowers

glucose consumption and metabolic disruption along with a diminished hunger, thirst and anxiety in preoperative period.<sup>35,36</sup>

Articles referred in the results had different conclusions when it came to the effect of CHO drinks in perioperative. Hence, it is essential to be critical when it comes to the used methods by each study because there are some discrepancies. For starters, the performed surgery is different (cholecystectomy by laparotomy and colorectal surgery) even though they are both considered gastrointestinal surgeries. The quantity of liquid patients consumed in both studies was different as well as the CHO drink composition. The choice of performance evaluation was also distinct, one study used handgrip strength and the other 2-minute and 6-minute walk tests to assess the results. These inconsistencies lead to no homogeneity and therefore no viable conclusion is reached. Hence, it is required further studies to evaluate, in a more consistent way, the recovery improvements in postoperative patients consuming CHO drinks.<sup>18,19</sup>

The Gava et al.<sup>18</sup> article, came to the conclusion patients consuming CHO drinks before surgery were presented with higher strength in their hands and it is safe and does not cause damage to the patients, which is supported by other studies as well. Even though this was a double-blind, randomized study, it showed some weaknesses for instance the sample size, only 27 patients were analysed. Also, the fact the control group did not receive a placebo of some sort, thus, it is not clear if the higher handgrip strength in CHO group is due to the CHO drinks or because this group had a shortened fasting period.<sup>18</sup> This is important because other studies were made with the same objective, but the control group ingested water at the same time the CHO group consumed CHO drinks, and the results presented no significant difference in the handgrip strength test between both groups.<sup>37</sup> This studies also corroborates preoperative fasting shortening benefits patients. As well as indication abbreviation of fasting decreases hospital stays, which can create a greater rotation capacity with patient hospitalization who are submitted to surgeries.<sup>38</sup>

## **Vitamin D**

In the last couple of years VD was given a lot of attention for their potential mechanisms and effects. Particularly, relation with cancer connection and their outcome. The investigation of this supplement led to the breakthrough VD has more roles than just maintaining calcium homeostasis and regulation of bone metabolism. In studies exploring other roles of VD in cancer,

it was discovered anti-angiogenesis, anti-proliferative, anti-metastasis, pro-differentiation, and pro-apoptosis activities<sup>39,40</sup> which might interfere with the outcome of cancer. Hence, there are more evidence establishing VD supplementation as an important anticancer drug and also the possibility of causing an improvement to QOL and reduction of risk of recurrence and mortality within cancer patients.<sup>39,41</sup>

The Wang et al.<sup>21</sup> was the first article trying to ascertain the connection between EC patients, VD supplementation and the outcome on QOL. It was not unexpected, considering the weak health consciousness, most of the patients did not take VD supplement on regular basis, only 49 among 303 patients did. From the start there were several substantial differences between both groups, the fact VD users tended to be younger, with higher salaries, attended some college, smoked less, had lower fat consumption and had more physical activity. This proves education in healthcare can have a positive impact among people and this education is being made amongst younger generations more.<sup>21</sup>

As limitations to this study, the sample was too small amongst VD users, only 49 patients. Also, the fact VD concentration in blood was not routinely assessed among cancer patient, thus, the relation between the level of VD and the outcome could not be reflected.<sup>21</sup>

Another restraint of this study when compared to others was in Wang et al.<sup>21</sup> it was assessed the role of postoperative VD supplementation after cancer diagnosis and the outcome on EC patients and their survival, which demonstrated a possible improvement of DFS and lower cases of recurrence. But other studies, such as Jeffreys et al.<sup>42</sup>, investigated pre-diagnostic VD supplementation and found no relation with a higher probability of survival. Consequently, there might be a significant and crucial difference when it comes to the timing of VD supplementation. The pre-diagnostic VD supplementation is more likely to have a role in reducing cancer risk, but no significant long-term results, whereas, post-diagnostic VD can help with recovery phases and might have a direct effect on improving the outcome of DFS and survival long-term.<sup>21</sup>

Physical activity was considered an individual prognostic factor for DFS and OS, which was consistent with other studies showing an increased probability of mortality and lower survival rates among people who had reduced physical activity,<sup>43</sup> so this prognostic factor was considered to have a protective effect on prognosis of EC patients.<sup>21</sup>

When it comes do VD supplementation there is a lot to be made still. The pathways exploration of this supplement is important and can bring a revolutionary change when it comes to the prevention and changing long-term results but is also vital to assess what is the optimal dose and best route of administration, so the outcomes are the best possible.

## **Cranberry**

This fruit has in its constitution numerous types of elements with the ability to bring health benefits to humans. Among them, organic and phenolic acids, saccharides, vitamins (C, E, K), anthocyanins, proanthocyanidins, triterpenoids and flavonols. These substances appear to have the power of antioxidant, anti-inflammatory, anti-bacterial, anti-viral, anti-angiogenic and anti-cancer.<sup>44</sup>

According to Student et al.<sup>25</sup> no other study has been made in humans before to assess the effects of cranberry on PCa. But the same team of investigators made a previous study, in 2010, about cranberry effects in men with lower urinary tract symptoms, increased PSA levels and non-bacterial prostatitis.<sup>45</sup> The conclusions of this study are in good concordance with the most recent one since it was documented the reduction of PSA levels in patients with cranberry supplementation as well.<sup>25,45</sup> It was also demonstrated an increase in QOL and since cranberries have diuretic effects, this might have caused a reduction in lower urinary tract symptoms in the cranberry group.<sup>45</sup>

An additional hypothesis made by Student et al.<sup>25</sup> was the decreased PSA levels might be connected with the downregulation of beta-microseminoprotein, which is known to be androgen regulated, since 6 in 9 patients with downregulation of beta-microseminoprotein also had downregulation of serum PSA.<sup>25</sup>

This study had a small sample size with 62 patients and while this is one of the first investigations in humans about the effects of cranberry on PCa, further studies are necessary to evaluate these fruits properties and its role as a prophylactic.<sup>25</sup>

## **Beta-hydroxy-beta-methylbutyrate, Arginine, and Glutamine**

Between the studies of Kanae et al.<sup>27</sup> and Wada et al.<sup>28</sup>, the endpoints ascertained revealed no significant benefit of HMB/Arg/Gln supplementation. Only in muscle strength in the operated-side knee showed a reduction of muscle strength amongst the control group and no difference in the HMB/Arg/Gln group between preoperative and postoperative period.<sup>27</sup>

Moreover, there were limitations, both studies presented small number of subjects. In Kanae et al.<sup>27</sup> the dietary intake was only supervised during 3 days after surgery, for more detailed investigations of the effects of the supplementation combination it would be necessary

an assessment of dietary intake during the whole study period, 42 days. Also, it might be informative to do a multicentre study on a larger scale, because this would imply the usage of different postoperative protocols. In Wada et al.<sup>28</sup>, the dose of HMB/Arg/Gln administered was small, which might be the reason for the negative result, but patients undergoing abdominal surgery generally cannot consume a liquid combination as much as other patients.

In this last study it was also assessed the supplementation mixture could increase serum growth hormone levels, so it would be enlightening to do a larger sample size investigation on this matter.<sup>28</sup>

## **Herbal**

Herbal medicine has been used since the beginning of time. These therapies are considered “natural” and therefore secure. The not so well explored effects, the possibility of adverse effects and drug interactions,<sup>4</sup> can cause problems on perioperative outcomes.<sup>10,46</sup>

Related to the curcumin study, the oral administration of this herbal medicine showed no beneficial effect in the outcomes analysed, which was contradictory when compared to another study in the same matter, but it must be taken into account during the other trial, the dose given to patients was higher, during a longer period of time and the capsules contained not only curcumin but also other curcumin analogues from turmeric (demethoxycurcumin and bisdemethoxycurcumin),<sup>47</sup> therefore there is no certainties if the variances between these trails have to do with any of this facts, since there is not enough evidences on the most beneficial dosage, duration or treatment composition to be administered. On top of this, still in Garg et al.<sup>30</sup>, it was documented a higher risk of presenting acute kidney injury among the patients taking curcumin, consequently there should be more exploration in this matter to assess if this finding is in fact a danger to the patients taking this type of herbal medicine.

In Zhu et al.<sup>31</sup>, the main objective of the study was to see if SHD would ameliorate inflammatory status among breast cancer patients and this because it was recognized prolongation of inflammation might have an important relation with tumour metastasis, since the number of these cells present in invasive metastases of breast cancer are high.<sup>48</sup> In this train of thought and knowing surgery causes acute inflammatory response, limiting this status postoperatively becomes very important, with the objectives of helping the wound healing and preventing tumour development.

This study showed significant responses with the treatment with SHD, reducing pain, swelling, among others, but also the amount of fluid drained volume was lower, and the inflammatory factors were almost stabilised by day 7 after surgery. These were very noteworthy results since there were a lot of improvements among the patients consuming SHD when compared to the control group.<sup>31</sup> This investigation would have had more impact if the sample size was bigger and the follow-up was made during a longer period of time, hence it would be best if such research was conducted to assess with better certainty the beneficial properties of this herbal medicine.

## KEY LEARNING POINTS

- DS are considered “natural” and therefore patients usually do not take into consideration this type of nutrition can interfere with other drugs.
- These interactions can be beneficial like reducing inflammation, improve immunity, stimulate healing, and reduce oxidation or detrimental causing problems which can go from minor complications to mortality.
- DS ought to be administered cautiously.
- The disclosure between patient-physician about DS is still minimal, so it comes to the physician to ask directly if the patient takes DS, for a better preparation and care.
- More awareness and knowledge to undesirable effects and potential interactions are required to prevent severe medical outcomes, therefore, it is crucial to investigate DS further.

## Fish Oil

- The mean total duration of AF in PUFAs group was shorter even though the frequency of AF episodes between groups was similar.
- There was a reduction in length of stay in the cardiac surgery intensive care unit in PUFAs group.
- High levels of plasma omega-3 fatty acids were associated with lower risk of perioperative bleeding.
- Adults who ingest large quantities of oily fish, have a lower rate of cerebral bleed, lower coronary heart disease and cardiovascular disease mortality.
- Fish oil can cause minor adverse events like burping, gastrointestinal upset and fish oil taste.
- Short-term and long-term fish oil supplementation may cause distinctive effects and it is still unknown which is the most beneficial dose.

## Carbohydrate drinks

- CHO drinks might help maintaining muscle mass and strength, decrease glucose consumption and postoperative negative nitrogen balance, reduce anxiety, hunger, and thirst.
- CHO drinks before surgery are safe and do not cause damage to the patients.
- Preoperative fasting shortening benefits patients and decreases hospital stays.

## **Vitamin D**

- VD in cancer can have anti-angiogenesis, anti-proliferative, anti-metastasis, pro-differentiation, and pro-apoptosis activities.
- Patients with VD supplementation might have higher physical, social functioning, and global health.
- VD use in cancer treatment and recovery phases could help with getting better clinical outcomes.
- VDD might be caused by critical illness.
- VDD in critically ill patients might be associated with enhanced levels of infection acute respiratory failure, acute kidney failure, sepsis, and mortality.
- Surgery results in an abrupt reduction in VD concentrations.

## **Cranberry**

- Cranberry appears to have antioxidant, anti-inflammatory, anti-bacterial, anti-viral, anti-angiogenic, and anti-cancer properties.
- Cranberry supplementation suggests reduction of PSA levels.
- Cranberry might reduce lower urinary tract symptoms, since cranberries have diuretic effects, and increase QOL.

## **Beta-hydroxy-beta-methylbutyrate, Arginine, and Glutamine**

- This combination suggests a promotion of protein synthesis and suppression of protein breakdown, contributing to an increase in muscle mass, maintenance of muscle strength and wound healing.
- Investigation indicates HMB/Arg/Gln might increase serum growth hormone levels.

## **Herbal**

- Information on most of this type of DS is still very incomplete, uncertain, and somehow contradictory.
- Inchinkoto might indicate an hepatoprotective effect among severe hepatectomy.
- Curcumin consumption showed significant higher risk of acute kidney injury.
- SHD revealed an important role in reducing pain, swelling, decrease the amount of fluid drained volume and inflammatory factors.

## **CONCLUSION**

The market to purchase DS and nutraceuticals, consumed to enhance health or well-being of the buyer, is massive. However, these types of supplements are not undoubtedly safe for everybody. They are known to have advantages and disadvantages when it comes to their results.

There is a lot of variety and undiscovered mechanisms when it comes to DS effects, therefore, it is crucial to continue studying these supplements in the future. It would also be important and beneficial to use similar methods during the study among each DS explored, because no homogeneity leads to discrepancies and no viable assumptions.

Health care provider's role, in this matter, is to keep their knowledge up to date and to question their patients about DS consumption, so they can inform and advise them on potential effects and interactions DS might cause.

## APPENDIX

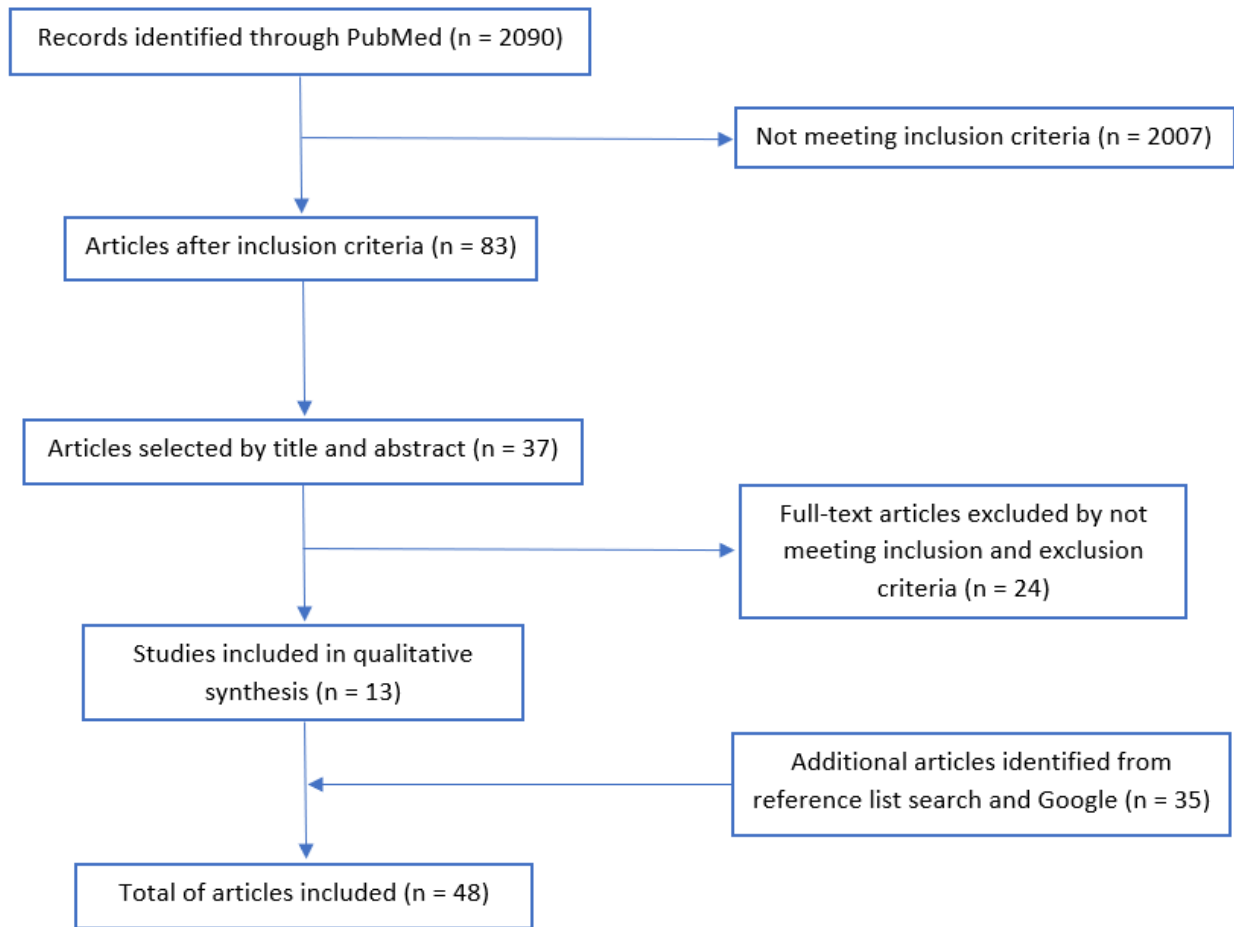


Figure 1. Articles methodology selection

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