

Exploring innovative adhesive approaches to manage medical adhesive-related skin injuries (MARSI)

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ABSTRACT

Medical adhesives are essential to secure wound care dressings and medical devices to the skin, to bind wound edges, track vital signs, or even provide local drug delivery. Despite several options in the market, most medical adhesives are composed of acrylate, hydrocolloid, and silicone, materials that are associated with the development of Medical Adhesive-Related Skin Injury (MARSI). Moreover, these injuries reduce skin integrity, causing pain, delaying wound healing, and increasing the risk of infection, consequently extending the treatment time, and impairing the quality of life and health of the patients. To prevent MARSI, a new generation of adhesives is being investigated based on the use of natural biomaterials (bio-adhesives) and/or on alterations of the adhesion mechanism that mimic the adhesion that occurs in nature, such as adhesion by hydrogen bonds and van der Waals interactions (nature-inspired adhesives). This review focuses on the advanced medical adhesives, both available and under development, to prevent the MARSI problem and to treat consequent health problems, such as skin infection and late skin regeneration.

1. Introduction

Medical adhesives are fundamental in several clinical procedures and treatments, predominantly for the attachment of an external medical device (e.g., dressings, catheters, ostomy bags, nasogastric tubes, drains, and monitoring devices) to the skin, to bind wound edges, to track vital signs or even to provide local drug delivery. Therefore, good skin adhesion is fundamental to firmly hold the devices and protect the site of injury or device placement from external factors, such as bacterial infection, moisture-associated damage, sun radiation, and pollution [1, 2]. Most of the adhesives in the market are chemical-based viscous materials that fill skin irregularities to increase the contact area and improve adhesion. However, these properties are correlated with a higher risk of injury and skin damage, both at the time of adhesive placement and removal [1,3], a problem known as Medical Adhesive-Related Skin Injuries (MARSI). MARSI not only affect the integrity of the skin, but also cause pain, increase the risk of infection,

and delay the healing process. These complications are common in all care settings, from healthy outpatients to acute or critically ill patients, yet they are commonly unrecognized and underreported [1].

This review provides a detailed classification of which injuries are provoked by medical adhesives, as well as a description of the existing solutions in the adhesive market that attempt to prevent or even treat these injuries. This document highlights innovative adhesives that aim to reduce this burden and skin injuries when MARSI are not treated adequately.

2. Medical adhesive-related skin injury - MARSI

MARSI were defined by McNichol *et al.* in 2013 as “an occurrence in which erythema and/or other manifestation of cutaneous abnormality (including, but not limited to, vesicle, bulla, erosion, or tear) persists 30 min or more after removal of the adhesive” [1]. More recently (2020), Fumarola *et al.* redefined MARSI as “skin damage related to the use of

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medical adhesive products or devices such as tapes, wound dressings, stoma products, electrodes, medication patches and wound closure strips” [4]. These skin injuries occur when layers of epidermal cells are partially or completely removed by the medical adhesive upon its removal or react to the adhesive compounds, causing erythema, laceration, trauma, and/or irritation which persist for at least 30 min [5].

There are three main categories of MARSIs, Fig. 1 [1,6–8].

- Mechanical (related to the separation of skin layers and resulting in peeling friction, blunt force, or strain injuries);
- Dermatitis (related to inflammation, chemical irritation, or allergy, caused by direct contact with the adhesive compounds);
- Others, such as maceration (related to prolonged retention of moisture or exudates) and folliculitis (related to inflammation of the hair follicles).

Although MARSIs are still a neglected health condition [9], the truth is that for every 100 patients who use an adhesive, 55 develop skin-related problems [10]. These injuries reduce skin integrity and cause pain and distress, contributing to longer hospital stays and treatment time, increased adhesive usage and patient morbidity, delay wound healing, and raise the risk of complications, including infections [1,4]. Additionally, the treatment of MARSIs is costly, representing a very sizable portion of the budget of hospitals and healthcare facilities. These are not only due to direct costs related to the treatment of injuries but also due to the extension of the treatments, which require both human resources and hospital beds when hospitalization is required [10]. In 2016, it was estimated that the care and management of MARSIs costs ranged from £1.10 to £7.90 per patient per treatment [11]. The rise in life expectancy, better healthcare access, and an increase in the number of surgeries (such as ostomies), were responsible for an exponential growth in the market of medical adhesives, reaching an annual consumption of € 10 thousand million, in 2019 [12]. In fact, the multinational company 3 M reported in 2016, in its market studies, that the annual treatment cost of MARSIs exceeded €10 million, considering the USA alone [13,14].

The most vulnerable groups to develop MARSIs are newborns, children, the elderly, cancer patients, orthopedic surgery patients, and ostomy patients [15]. For instance, 1 in every 10 newborns and hospitalized children [16], 2 out of 10 patients in long-term care [17], 4 in every 10 hip surgery patients [18], and 8 out of 10 ostomy patients [15,19] will suffer from MARSIs. The skin of newborns, babies, and children is more sensitive, as well as thinner and more fragile, with similar properties to the skin of the elderly, which is additionally rougher, making it more difficult to remove adhesives without causing

damage [15,20]. However, the group with the highest risk of developing MARSIs are patients who use continuous and frequent medical devices attached to the skin, such as ostomates [21]. An ostomy is a surgical procedure that allows body waste to pass through a surgically created stoma on the abdomen into a prosthetic known as a “pouch” or “ostomy bag” on the outside of the body, or an internal surgically created pouch for continent diversion surgeries. Due to the recurrent use of adhesives to secure ostomy bags or cannulas in place, these patients often develop serious skin injuries and/or infections due to skin exposure to urine, feces, moisture, or external agents. In addition, when considering intestinal stomas, ostomy bag displacement, and content leakage often leads to adhesive failure [19,21–23]. Nevertheless, in addition to these vulnerable groups, a patient who requires the use of a simple dressing or the attachment of a more complex medical device is also susceptible to developing MARSIs.

Although MARSIs are underestimated and underreported (such as in the specific case of ostomates), Bernatchez *et al.* [6] have recently reported a summary of the prevalence/incidence of the different medical scenarios of patients with MARSIs (Fig. 2).

Besides the patients, MARSIs also affect the healthcare staff. Recently, Wei *et al.* [24] reported results from a cross-sectional survey revealing that, in China, 41.9 % of medical personnel who were encouraged to use protective adhesive dressings under personal protective equipment (PPE) during the infectious coronavirus disease (COVID-19) pandemic, suffered from MARSIs, reporting severe pain and skin damage upon dressing removal.

2.1. MARSIs-associated infection

The use of medical adhesives is also related to an increase in the number of microorganisms (bacteria and fungi) in the region of the skin in contact with the adhesive, which becomes a reservoir of pathogenic microorganisms [1]. It was reported that 11 out of 21 samples (52 %) of surgical adhesive tapes collected in various sectors of three Australian hospitals were contaminated with multidrug-resistant organisms (methicillin-resistant *Staphylococcus aureus* (MRSA) and/or vancomycin-resistant *enterococci*) [25]. When MARSIs occur, as in any skin lesion, there is a risk of localized or systemic infection, particularly in the aforementioned risk groups, and also in patients with comorbidities that compromise the immune system, such as diabetes, renal failure, cancer, organ transplantation, etc. [21].

Improving medical adhesives to irradiate MARSIs and related infection problems is crucial. MARSIs inhibition decreases both direct and indirect costs, by improving the health condition of the patient and by reducing hospitalization, treatment duration, and recovery time [13, 26].

3. Medical adhesives in healthcare applications

Medical adhesives can be classified into two main categories when considering their mode of application and their shear modulus before application: *in situ* forming adhesives or preformed adhesives (Fig. 3) [27].

3.1. *In situ* forming adhesives

In situ forming adhesives, also called tissue glues, are a specific type of medical adhesives mainly used to close skin wounds or seal surgical sites, as an alternative to sutures or staples. They are used when the preformed adhesive is not able to be applied to irregular surfaces or the skin tissue is too sensitive to be compressed [27]. These adhesives are fluid precursors that when applied to wounds or defects, after filling the site, solidify over time or after specific stimuli (e.g., humidity, temperature, pH, and light exposure). The delivery approach defines the different types of *in situ* adhesives. Fluid precursors with a low viscosity are delivered as aerosol sprays to cover irregular and large tissue

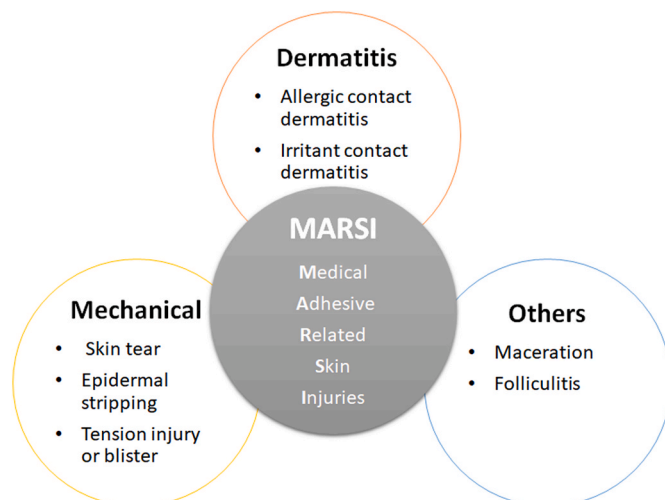


Fig. 1. Types of MARSIs.

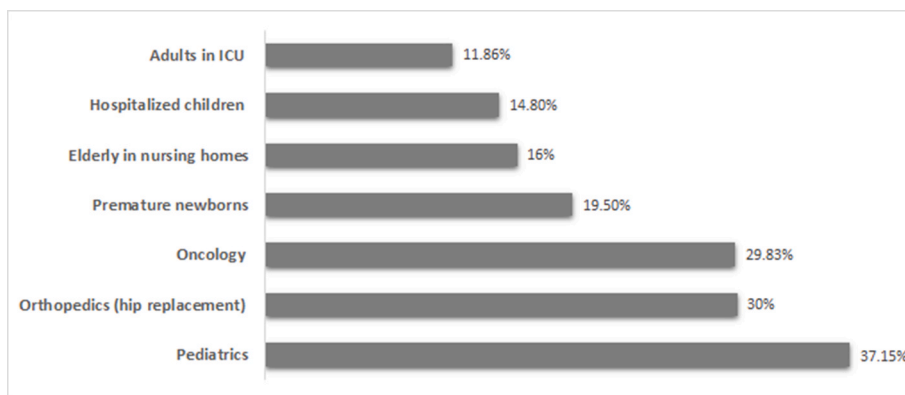


Fig. 2. Examples of prevalence/incidence of MARS in the literature. Source [6].

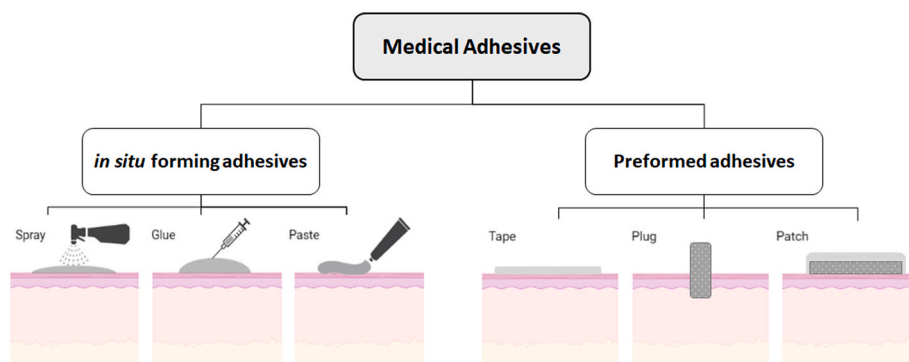


Fig. 3. Classification by physical form of medical tissue adhesives. Preformed adhesives: light grey – thin adhesive film; dark grey with white spots – elastic matrix. Icons from Biorender.

surfaces, while the viscous liquid is pasted on the tissue site. The injectable tissue adhesive glue (low-to-medium viscose fluids) is the most common approach used in limited tissue sites requiring no compression.

Tissue adhesive sprays are mostly used in topical applications with a short duration, being also attractive for hemostatic use, such as the reinforcement of suture lines in vascular repair and tissue reconstruction. These adhesives should show an instant adhesion to ensure acceptable retention when applied onto the tissue substrate, although the homogeneity of the adhesive and its intrinsic defects are not easy to control. Polymeric materials have been used as sprayable adhesives which hinder an effective cleaning of the spray gun after each application, blocking the spray nozzle. Adhesive glues are compatible with several delivery routes (e.g., syringes, catheters, endoscopes, and trocars), and are used in minimally invasive procedures characterized by limited surgical sites or in scenarios of unfeasible suturing/stapling. Most of the glues are composed of a mixture of at least two compounds which can require external stimuli to trigger the adhesive matrix formation. Paste adhesives are injected into the target tissue through a syringe or a tube-like route due to the high viscosity of the precursor. These adhesives exhibit a finite yielding stress providing shape stability and application in dynamic surfaces, in opposite to spray and glue adhesives, where their precursors would flow away. The main advantages and drawbacks of each type of *in situ* forming adhesives are summarized in Table 1.

The *in situ* forming adhesives can be classified based on their chemical composition: cyanoacrylates (known as super glue), protein adhesives, or polysaccharides [28]. Applications of these adhesives as fixers for small and lightweight medical devices (e.g., catheters) have also been considered [29,30].

Nevertheless, this type of medical adhesives, due to their lack of

certain mechanical properties cannot be widely used in several clinical procedures, such as the attachment of more complex and heavier medical devices. Despite their process of removal consisting of the dissolution of the material [27], and thus, they do not damage the skin during removal, some of these adhesives have been associated with contact dermatitis [31], i.e., with MARS.

3.2. Preformed adhesives

Preformed adhesives are composed of a solid matrix with a defined geometry and are very commonly used in everyday life, both in and out of healthcare facilities. These adhesives are mainly used when there is a large treatment site, such as skin lesions, open surgeries, or traumatic events. In addition, they are easy to apply. These adhesives are produced in several shapes and sizes and can be adjusted to cover the wound or incision [32,33]. They are available in one of three formats with different aspect ratios: tapes, plugs, and patches (Fig. 3), each with its advantages and disadvantages (Table 1).

Adhesive tapes are thin and lengthy films, devised to attach medical devices to tissues/organs, to seal small incisions and prevent fluid leakage [32], or to support external medical devices, like bandages and tubes [34]. They can adapt to irregular or rough tissues but have the downside of limiting movement or functionality and are not ideal when considering large defects.

Adhesive plugs are usually composed of an elastic matrix designed to fill cavities or defects in tissues. They are commonly used in first-aid practices of traumatic events, mainly to stop bleeding and prevent further damage to the site [33]. These adhesives are simple and easy to use, even in first-aid scenarios, but sometimes are not the best fit for the geometry of the wound. However, they can lead to complications, such as severe inflammations when used in large quantities and if not

Table 1

Advantages and drawbacks of the different types of *in situ* forming adhesives and preformed adhesives. Based on [27].

Medical adhesives		Advantages	Drawbacks
<i>in situ</i> forming adhesives	Spray	<ul style="list-style-type: none"> Fast coverage of large tissue surface. Hemostatic application. 	<ul style="list-style-type: none"> Poor control of adhesive homogeneity over the adhesion region. Can flow away from the site. Blockage of the spray nozzle.
	Glue	<ul style="list-style-type: none"> Several delivery routes. Wide range of materials. Easily applied to limited and non-compressible tissue surfaces. 	<ul style="list-style-type: none"> Matrix-forming triggers can be required. Can flow away from the site.
	Paste	<ul style="list-style-type: none"> Does not flow away from the site. Appropriate for special control of adhesion. 	<ul style="list-style-type: none"> Limited choices. Large access routes.
Preformed adhesives	Tape	<ul style="list-style-type: none"> Flexible to adapt to irregular tissue surfaces. Good mechanical strength and permeability. 	<ul style="list-style-type: none"> Unsuitable for large tissue sites. Lack of functionality.
	Plug	<ul style="list-style-type: none"> Quick and easy use as first-aid. 	<ul style="list-style-type: none"> Potential incompatibility to wound geometry. Possible excessive swelling. Can cause inflammation.
	Patch	<ul style="list-style-type: none"> Large wound dressing. Customizable functional matrix. 	<ul style="list-style-type: none"> Unsuitable for irregular tissue surfaces. Need for compressive forces.

removed/replaced in adequate time [27].

Adhesive patches are a compromise between tapes and plugs, as they usually consist of an elastic matrix covered by a thin film that reaches beyond the edge of the matrix. They are composed of hydrogels or elastomers and are intended to be applied on injuries where the wound area is capable of remodeling or reshaping [33], and on smooth and flat tissue surfaces [27]. Patches are a popular choice for open wound scenarios, such as large chronic wounds or ulcers. They have the advantage of possessing a shape design that improves customizable functions (e.g., retain moisture, avoid leakage, provide local drug delivery system), but are not adequate for use in irregular skin defects and require compressive forces to be conformable to the skin tissue [27].

Preformed adhesives are also classified regarding adhesion methods.

- **Pressure-sensitive adhesives (PSAs)** – chemically inert materials typically composed of elastomers that adhere to dry and moist skin through Van der Waals forces when moderate pressure is applied [35]. PSAs are commonly used as medical tapes to fix medical devices to the body and as skin bandages for wound care [27];
- **Contact adhesives** – hydrogels where adhesion occurs due to strong interfacial bonding between the hydrogel matrix and a wet tissue [36]. These hydrogel-based adhesives bond firmly with metals and elastomers being suitable for fixing wearable electronics for mobile health [27];
- **Stimuli-sensitive adhesives** - temporary adhesives where adhesion can be activated on-demand through external triggers such as UV light, heat, electric, or magnetic stimuli [37,38]. These adhesives are not yet used in clinical practice.

The advantages and disadvantages of the preformed adhesives for adhesion applications are displayed in Table 2.

Table 2

Advantages and drawbacks of the preformed adhesives for adhesion applications.

Preformed adhesives: adhesion methods	Advantages	Drawbacks	Ref.
Pressure-sensitive adhesives (PSAs)	<ul style="list-style-type: none"> Can be applied to dry and wet skin. 	<ul style="list-style-type: none"> Moderate adhesion energy. Skin stripping (<i>stratum corneum</i> damage) caused by repeated changing of PSAs at the same site. 	[27]
Contact adhesives	<ul style="list-style-type: none"> High adhesion energy. Quick adhesion. 	<ul style="list-style-type: none"> Only applied on wet skin. Can cause irritant contact dermatitis. 	[27, 39]
Stimuli-sensitive adhesives	<ul style="list-style-type: none"> Strong adhesion. Weak adhesion when peeled off. 	<ul style="list-style-type: none"> Stimuli can be harmful to patients. 	[37]

Nowadays, the most widely used medical adhesives are acrylate, silicone, or hydrocolloid-based. Acrylate adhesives dominate the PSAs market as they can achieve strong binding to the skin, being suitable to secure a variety of medical devices to the latter [40]. Furthermore, acrylate formulations can be easily modified to adapt their adhesion strength. However, they are difficult to apply on large wounds and are often associated with allergic reactions, being the main cause of MARSIS [41]. Acrylate adhesives are not repositionable, cause more skin trauma during removal, and have poor adhesion stability over time [4]. Additionally, as a petroleum-derived product, its environmental impact must also be taken into consideration [42]. Silicone adhesives are the newest class of medical adhesives and offer advantages over acrylates, including biocompatibility, high flexibility, and moisture permeability [43]. They are also less aggressive on the skin than other types of adhesives, having a lower prevalence of MARSIS [3,44]. However, these types of medical adhesives are more expensive [4] and are not able to secure critical tubing (like ventricular assist devices (VAD), drains, and catheters) or heavy devices (such as ostomy bags), often leading to leakage-related issues. Additionally, most silicones are obtained from unsustainable fossil fuels and have a reduced rate of biodegradability [45]. Hydrocolloid adhesives strongly adhere to the periphery of the wound, forming a soft gel in the moist wound due to the presence of the exudate [43]. Comparative studies have shown that these adhesives can have higher adhesive strength than even acrylate adhesives. However, they lead to a higher pain intensity upon removal from the skin [4,46].

Overall, most of the above-mentioned preformed adhesives are associated with mechanical and dermatitis skin damage, i.e., MARSIS.

4. Medical adhesives with additive properties: Commercialized

The number of commercially available advanced adhesives with additive properties is still relatively small, particularly when considering the medical adhesive market. As seen in Table 3, all the described drug delivery adhesives are focused on the prevention/treatment of infection and the induction of skin regeneration, problems that can be associated with MARSIS, and not with its prevention. Advanced adhesives to prevent MARSIS require more innovation in their chemical composition and in the process of adhesion to the skin which will be discussed below.

5. Medical adhesives for MARSIS-related problems: under investigation

To overcome the limitations of the medical adhesives described above, there has been an increase in the number of medical adhesives being researched to prevent MARSIS and prevent/treat associated

Table 3

Examples of commercially available advanced medical adhesives with additive properties to avoid MARS-associated infections and/or induce skin regeneration.

Product name	Manufacturer	Composition	Description	Limitations	Reference
Silverlon®	Argentum Medical, LLC	Nylon and silver	Medical adhesive tape that enables the passage of wound fluids and creates a non-adherent antimicrobial barrier.	The amount of silver in the skin. The dressings reduced viability, induced oxidative stress and DNA damage in skin cells, and induced the production of pro-inflammatory IL-6 by monocytes [47].	[48]
TRIOMED™	I3BIOMEDICAL	Triiodide and ethoxylated fatty acids	Medical adhesive with antibacterial properties.	Not recommended for pregnant women, people with thyroid problems, or for use over more than a few months [49].	[50]
Non-specified	NADCO®	Silver ions and zeolite	Adhesive, which has been applied in medical and non-medical scenarios, with antibacterial properties.	Raised concerns for human health and the environment (Repr. 2, Skin Irrit. 2, Eye Dam. 1 and as Aquatic acute [51]).	[52]
Non-specified	Pikdare S.p.A.	Chlorhexidine	Medical patch with antibacterial properties.	Not described.	[53]
PolyMem Silver®	Ferris Mfg. Corp.	Dressing with silver	Cloth Adhesive Border with an interactive, multifunctional, antimicrobial silver-containing dressing and a comfortable cloth border.	The incorporation of metals (silver).	[54]
Tegaderm™ Ag Mesh	3 M™	Silver sulfate, 8 mg/g in nonwoven gauze	Porous, non-occlusive dressing that conforms to the wound base and wicks drainage into the dressing with silver ions, adding antimicrobial properties.	The incorporation of metals (silver).	[55]
OPSITE POST-OP VISIBLE®	Smith&Nephew	0.2 µm Gore™ expanded PTFE from the MMT range, PALL Versapore™ 200 R, and Donaldson™ TX6628	Waterproof and antibacterial dressing with a see-through absorbent pad that helps to reduce unnecessary dressing changes and disrupt the healing process, with low pain upon removal.	Not described.	[56–59]
OXY® 3-in-1 Maximum Strength Acne Treatment Pads	OXY® Skin Care	Salicylic acid	Acne treatment patch with regenerative properties.	Gastrointestinal upset ranging from gastritis to gastrointestinal bleeding [60].	[61]
HydroClean® Advance	PAUL HARTMANN Lda	Ringer solution (ex.	Medical adhesive with both antibacterial and regenerative properties.	High-volume infusion must be used under specific monitoring in patients with cardiac or pulmonary failure [62].	[63]
A-Clear AID Soothing Spot Patch	NEOGEN DERMALOGY	Hydrocolloid with salicylic acid	Acne treatment patch that presents both antibacterial and regenerative properties.	Focuses only on Acne.	[64]

complications, such as infection and delayed tissue healing.

5.1. Functional medical adhesives: strategies and approaches

Several strategies have been proposed to develop functional tissue

adhesives as illustrated in Fig. 4.

These can be classified as.

- **Bio-inspired:** synthetic adhesives with similar properties to those found in nature, such as non-toxicity, quick and high strength

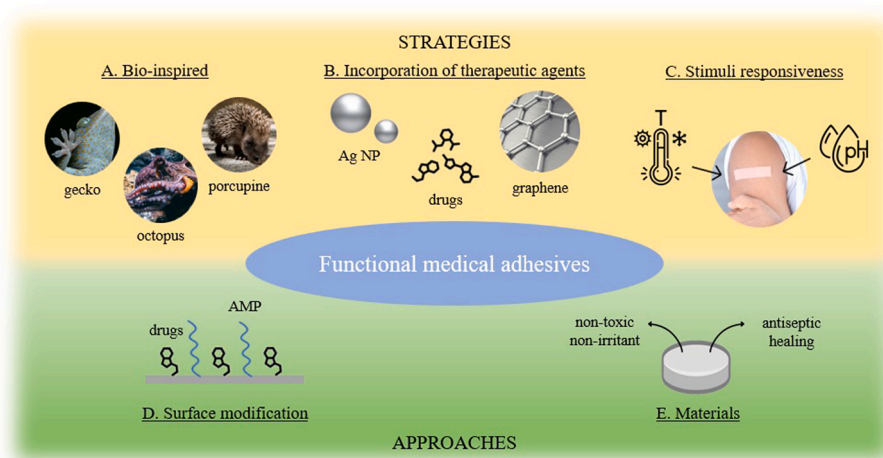


Fig. 4. Strategies and approaches for functional medical adhesives: A) Bio-inspired adhesives try to replicate characteristics found in nature, for example in animals such as the gecko [65,66], the octopus [67] and the porcupine [68], among others; B) Incorporation of therapeutic agents, such as silver nanoparticles (Ag NP) [69], drugs [70] and graphene-based nanomaterials [71], allows for a targeted sustained and controlled release over time; C) Stimuli responsiveness can enable the assessment of wound conditions or adhesive reaction, for example through exposure to temperature (T) [72] or pH changes [73]; D) Surface modification is an approach that alters the adhesive interface with the tissue by the addition of different moieties such as drugs [68] and antimicrobial peptides (AMP) [74]; E) Material selection influences greatly the final properties of the adhesive such as being non-toxic and non-irritant, as well as antiseptic [69,75,76] and/or healing [76,77]. Photographs from Unsplash. Icons from Flaticon and Biorender.

adhesion, retention of adhesive properties after repeated usage, and underwater adherence, among others [78];

- **Incorporation of therapeutic agents:** the most investigated strategy [79], which consists of developing painless transdermal drug administration adhesives that solely target the treatment site and are capable of a sustained and controlled release over time [80]. Thus making it possible to overcome the limitations of some medicines, which have poor solubility, require multiple doses, and can have toxic side effects on non-target organs, usually associated with the systemic administration routes [80].
- **Stimuli responsiveness:** conferring additional properties to medical adhesives such as enabling a reliable assessment of wound conditions, for instance, temperature, hydration, and pH (intrinsic stimuli) [27], or enabling a reaction from the adhesive (e. g. drug release, attachment/detachment) through exposure to external elements (extrinsic stimuli).

To achieve the above-mentioned strategies, different approaches can be followed (Fig. 4), these are described as.

- **Surface modification:** altering the adhesive interface between the chemical moieties or bioactive molecules and tissues. Due to the nature of this strategy, it is commonly used to provide contact-killing coatings/surfaces [81].
- **Materials:** the selection of non-irritant/non-toxic materials for the adhesive plays a crucial role in the final properties of the adhesive itself.

5.2. Functional medical adhesives: properties

The goal of these approaches is to modify the adhesion and functional properties of adhesives as shown in Fig. 5.

5.2.1. Safe adhesion

The main constraint of conventional adhesives is their strong adhesion to the skin which results in detachment of superficial cell layers

during the adhesive removal, compromising the integrity of the skin barrier.

Liu *et al.* demonstrated that a hydrogel formed by polyacrylamide-polydopamine/Cu²⁺ displays a strong adhesion to the wrist joint at different angles and it prevents infection at the wound site (Fig. 6-A) [68]. A chitosan and dextran-based hydrogel presented high transparency, exhibiting high light transmission rates, and a good adhesiveness on human skin (Fig. 6-B), resulting from hydrogen bonds, and hydrophobic and electrostatic interactions between chitosan and the skin tissue surface [75]. Despite these promising results, the authors did not evaluate the effect of the removal of the hydrogels on the skin surface, i.e., if the adhesive take-off can or not be related to MARSIs.

Up to now, the prevention of MARSIs is based on recommendations in the healthcare practice, including good skincare, medical adhesive remover usage, and appropriate selection of medical adhesive to maintain skin integrity and avoid associated complications [9].

BestHealth4U is the first company that design an adhesive to exclusively prevent and eliminate MARSIs [66]. The Bio2Skin is a sustainable and biocompatible polymeric adhesive that firmly adheres to the skin by establishing hydrogen bonds between skin water molecules and the adhesive matrix, mimicking the unique adhesion structure of the gecko lizard. The strong glue-less Bio2Skin adhesive avoids pain and skin damage upon its removal and under continuous use, without causing irritation and allergic reactions thanks to its low stripping.

5.2.2. Antimicrobial effects

Considering the applications of medical adhesives and their vulnerability to contamination with microorganisms, one of the most desirable additional features is antimicrobial activity.

A hyaluronic acid and dopamine-based hydrogel, loaded with doxycycline, with multifunctions including adhesiveness and a controlled release, inhibited the growth of both *E. coli* and *S. aureus* (Fig. 6-C) [70]. The *in situ* incorporation of Baicalein did not improve the antibacterial ability of the chitosan and dextran-based hydrogel, nonetheless, it increased its antioxidant ability [75].

Considering the rise of antibiotic-resistant organisms, physical

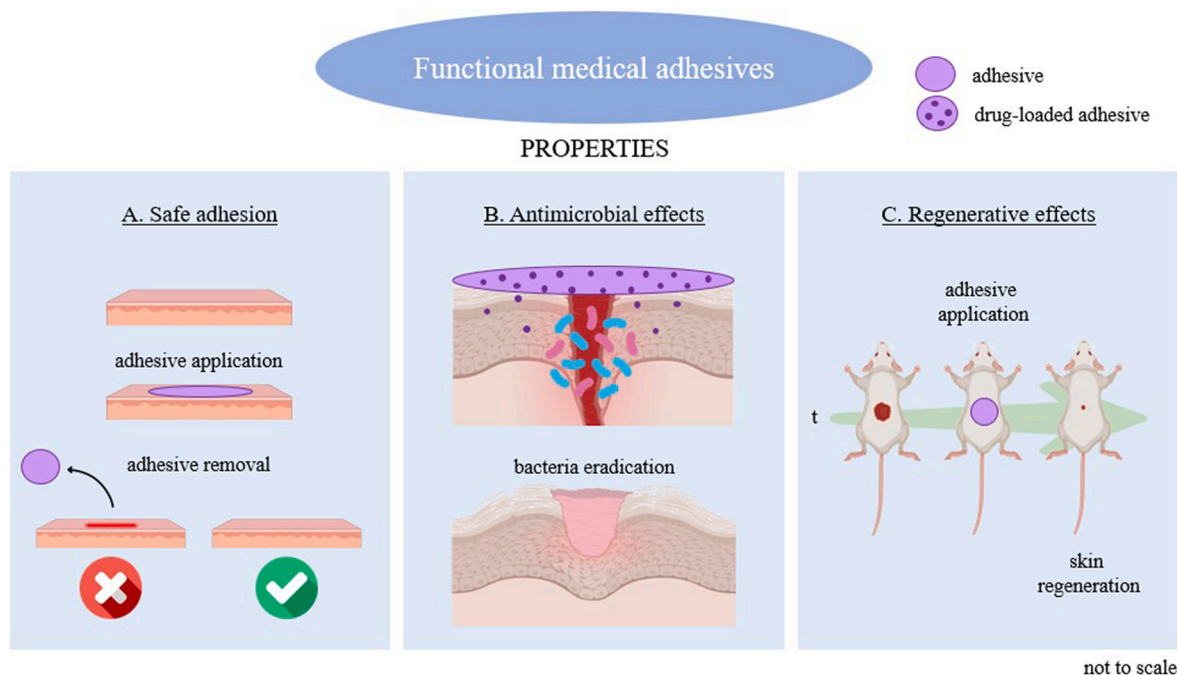


Fig. 5. Properties of functional medical adhesives: A) Safe adhesion describes adhesives with strong adhesion but which avoid pain and skin damage upon removal and after continuous use [66]; B) Antimicrobial effects involve the incorporation and/or release of compounds such as drugs [70] or nanomaterials [82] which fight infection by microorganisms; C) Regenerative effects lead to the reparation of the skin barrier with restoration of the proper structure and function of the skin over time (t) [77]. Icons from Flaticon and Biorender.

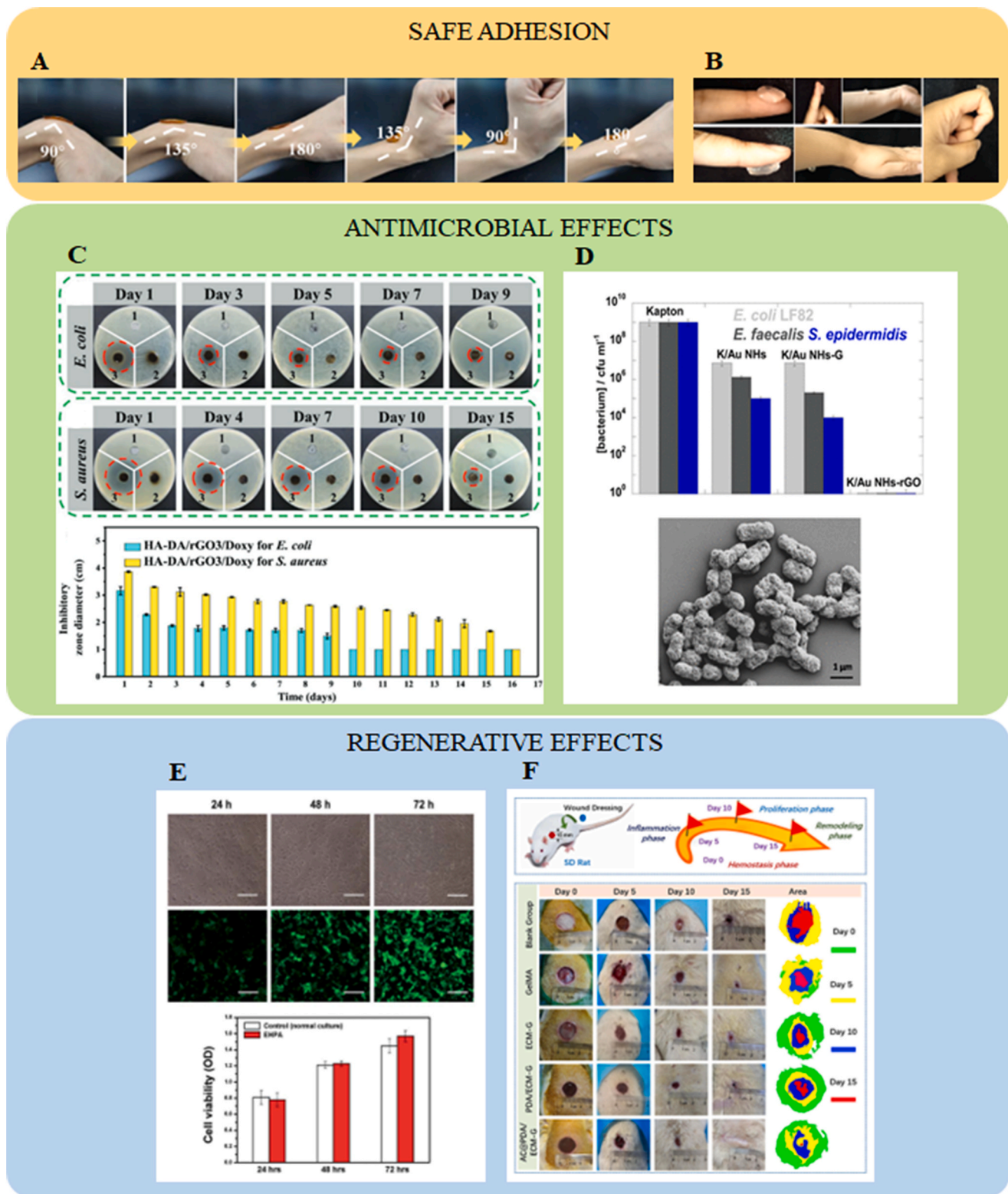


Fig. 6. Medical adhesives under investigation and their properties. A) PPC hydrogel adhesion on a human wrist during exercise. Adapted with permission from Ref. [68]. Copyright © 2023 Elsevier. B) QCS2-ODex-31 hydrogel adhesion on a finger, arm, and joint skin. Adapted with permission from Ref. [75]. Copyright © 2023 Elsevier. C) Zone of inhibition testing of 1-blank, 2-HA-DA/rGO3 hydrogel, and 3-HA-DA/rGO3/Doxy hydrogel against *E. coli* and *S. aureus*. Adapted with permission from Ref. [70]. Copyright © 2020 John Wiley and Sons. D) Photothermal killing of bacteria shown by CFU reduction and SEM imaging (*E. coli*). Reprinted (adapted) with permission from Li, C. *et al.*, Flexible Nanoholey Patches for Antibiotic-Free Treatments of Skin Infections. *ACS Appl Mater Interfaces*, 2017. 9 (42): p. 36,665–36674, [71]. Copyright © 2017 American Chemical Society. E) Fibroblast proliferation in contact with ϵ -polylysine hydrogel. Reproduced with permission from Ref. [83]. Copyright © 2016 Royal Society of Chemistry. F) AC@PDA/ECM-G hydrogel wound healing performance on a mice wound model. Adapted with permission from Ref. [77]. Copyright © 2023 Elsevier.

Table 4
Examples of advanced medical adhesives for MARS-related complications currently under investigation.

Strategy	Approach	Functional Properties	Examples
Bio-inspired	Surface modification	<ul style="list-style-type: none"> • Strong adhesion 	<ul style="list-style-type: none"> • Based on the footpads of gecko lizards, a skin adhesive patch with high-density micropillars and bulged tips made up of poly (dimethylhexane) (PDMS) was developed and shown to avoid common medical adhesive side effects such as redness, allergic reaction, and pain upon removal [65]. • Octopus-inspired adhesive patches with 3D microtips demonstrated high dry/wet adhesion performance and stable attachment and detachment to/from moist, hairy, and rough skin without any observable chemical residues. Due to the variety of surfaces these patches attach to, they could be used both for wound healing and attachable medical devices [67].
	Substrate Materials		<ul style="list-style-type: none"> • A mussel-inspired polydopamine-polyacrylamide (PDA-PAM) hydrogel was created, having exceptional tissue adhesiveness that provided adhesion without skin tissue irritation or inflammatory response, as well as sustaining several attachment and detachment cycles without loss of adhesion strength [87]. • Bio2Skin is a gecko-inspired polymeric adhesive that provides simultaneously a strong adhesion and low stripping thanks to the hydrogen bonds between the water molecules on the skin and the adhesive [66].
Incorporation of therapeutic agents	Substrate Materials	<ul style="list-style-type: none"> • Strong adhesion • Antiseptic • Healing 	<ul style="list-style-type: none"> • Tissue adhesive polyacrylamide/polydopamine (PAM/PDA) hydrogels embedded with extra-large pore mesoporous silica nanoparticles (XL-MSNs) featuring significantly strong adhesion for transdermal drug delivery through swelling of the hydrogel. The adhesive hydrogels did not exhibit <i>in vitro</i> cytotoxicity or skin irritation and inflammation in an <i>in vivo</i> mice model [88]. • Decellularized ECM and GelMA hydrogel with the incorporation of polydopamine-loaded asiaticoside nanoparticles showed good physicochemical properties and biocompatibility <i>in vitro</i>, while a fast wound closure without scarring and the highest-formed hair follicles after 15 days of treatment [77]. • The encapsulation of Baicalein improved the oxidative effects of the chitosan and dextran-based hydrogel, not affecting the inherent antibacterial properties of the hydrogel. The hydrogel exhibited suitable adhesion to the skin, transmission property (transparency), good self-healing, and biocompatibility [75]. • Incorporation of bioactive agents, such as drugs [70], metallic [71,82] or metallic oxide nanoparticles [85], chitosan [86], and antimicrobial peptides (AMPs) [83] have been explored to prevent skin infections and to promote wound healing.
Stimuli responsiveness	Substrate Materials	<ul style="list-style-type: none"> • Strong adhesion 	<ul style="list-style-type: none"> • A thermo-responsive hydrogel patch of poly (gallic acid) complexed with gelatin methacrylate GelMA showed body temperature-triggered adhesion to the skin and ice-induced painless detachment. Findings justified that this hydrogel was friendly to fragile skin [72].
Bio-inspired + Incorporation of therapeutic agents	Surface modification	<ul style="list-style-type: none"> • Antiseptic • Healing • Strong adhesion 	<ul style="list-style-type: none"> • Grafting of silver nanoparticles (AgNPs) onto sericin (from silkworm silk)/poly (vinyl alcohol) hydrogels with excellent biocompatibility, antimicrobial activity, and biofilm inhibition, as well as facilitating re-epithelialization and collagen deposition to promote wound healing [69]. • Bio2Skin Advanced is a bio-based product inspired by a gecko lizard, that binds to the skin through hydrogen and van der Waals bonds, creating a mild adhesion to the skin, a protective barrier against infection, and prompt skin recovery from MARS [76].
Incorporation of therapeutic agents + Stimuli responsiveness	Substrate Materials	<ul style="list-style-type: none"> • Strong adhesion 	<ul style="list-style-type: none"> • Encapsulation of doxorubicin hydrochloride within a poly (N-isopropylacrylamide) hydrogel modified with graphene oxide nanosheets and quadruple hydrogen bonding ureido-pyrimidinone moieties to achieve a thermo- and pH-responsive adhesive, paving the way toward on-demand drug release from adhesive materials [73]. • Carbon nanotubes, graphene-based materials, and gold nanoparticles are photothermal-sensitive materials able to convert radiation into heat, promoting the bactericidal effect by raising the temperature [71,89].
Bio-inspired + Incorporation of therapeutic agents + Stimuli responsiveness	Surface modification	<ul style="list-style-type: none"> • Strong adhesion • Antiseptic • Healing 	<ul style="list-style-type: none"> • Inspired by the barb hangnail microstructure of porcupine quill, microneedles of polycaprolactone with a polymeric adhesive back patch (composed of polyacrylamide-polydopamine/Cu²⁺) are loaded with sodium hyaluronate-modified CaO₂ nanoparticles and metformin [68]. The back patch could not be peeled off from the application site. The bio-inspired multilayer structure of microneedle patches under NIR irradiation shows an efficient antibacterial effect, inhibiting the inflammation of the wound while promoting angiogenesis [68].

applications have also been proposed, such as the incorporation of alternative antibacterial agents, such as metallic nanoparticles onto adhesive matrices. The incorporation of silver nanoparticles in hydrogel matrices [82] has been investigated, with results showing significant antibacterial activity. An adhesive film composed of highly aromatic polyimide resins (Kapton®) was combined with gold nanoparticle arrays to develop a medical patch capable of killing bacteria (*E. coli*, *E. faecalis*, and *S. epidermidis*) upon exposure to near-infrared (NIR) radiation. This type of therapy relies on the capability of such materials to convert radiation into heat, thus raising the surrounding temperature and killing pathogens on the site upon incidence of NIR radiation (Fig. 6-D) [71].

5.2.3. Regenerative effects

The tissue of wounds should be repaired as quickly as possible for the restoration of the proper structure and function of the skin [84]. Skin disrupted by MARS is also of consequence, since besides the wound site

itself, the surrounding skin is also detrimental to the healing of the wound, delaying injury resolution when left untreated [84]. Therefore, the development of medical adhesives that help in the regeneration of the skin tissue, could bring a significant advantage to the healing process.

Wang *et al.* developed enzyme-induced dual-network *in situ* forming bio-adhesive hydrogel based on ϵ -polylysine. Besides the proven antimicrobial properties, these hydrogels lead to fibroblast proliferation, and increased survival period (Fig. 6-E) [83]. A bioactive composite hydrogel (AC@PDA/ECM-G), composed of decellularized extracellular matrix (ECM) and gelatin methacrylate (GelMA) incorporating polydopamine-loaded asiaticoside nanoparticles, exhibited an outstanding wound healing performance on a full-thickness excisional wound model in mice (Fig. 6-F) [77]. After 15 days of treatment with AC@PDA/ECM-G hydrogel, the wound was completely healed without leaving a scar. The control (blank) group still had a large wound area,

while the GelMA, ECM with GelMA hydrogel (ECM-G), and the hydrogel loading polydopamine nanoparticles (PDA/ECM-G) groups were almost healed showing black scars. This model demonstrated the active role of asiaticoside in promoting angiogenesis, new collagen, and new hair follicle synthesis, thus effectively accelerating scarless skin regeneration [77].

Other types of adhesives besides hydrogels have been studied with the intent of improving wound healing and regeneration. Hydrocolloids are one such example. A hydrocolloid patch covered with zinc oxide nanoparticles was able to stimulate the wound healing rate in an *in vivo* rat model, reducing pro-inflammatory cytokines and increasing fibroblast proliferation [85]. Another example of this type of adhesive is a chitosan-embedded patch, which showed an increase in the rate of wound reconstruction in the skin of rats [86].

A safe and effective multifunctional strategy in transdermal drug delivery consisted of a multilayer bioinspired adhesive composed of microneedles (polycaprolactone tips) encapsulating sodium hyaluronate-modified CaO₂ nanoparticles and metformin (antidiabetic agent), and with a composite hydrogel as adhesive back patching was designed for diabetic wound healing [68]. The combination of the hydrogel with the loaded microneedles under NIR irradiation significantly promotes the antibacterial ability and biocompatibility, as well as allows the regulation of blood glucose levels and generation of oxygen species, improving the wound healing process and inhibiting the inflammation at the wound site [68].

Bio2Skin Advanced adhesive, devised by the BestHealth4U company, revolutionizes the current concept of medical adhesives as it is a glue-less adhesive with in-built wound healing properties, i.e., it combines antiseptic and regenerative properties with mild adhesion to the skin, respecting the skin and allowing a better wound healing [76]. This innovative adhesive consists of the incorporation of antiseptic and regenerative compounds into the Bio2Skin adhesive during the production process. These compounds will be released in the injury site, creating a protective barrier against infections, and promoting skin recovery from MARSII.

The described approaches, strategies, and properties, as well as some examples that apply them are provided in Table 4.

6. Conclusions

Medical adhesives are essential to attach a wide variety of medical devices that monitor or maintain the functions of organs or tissues. As the medical treatment is completed or if the adhesive has to be changed, the medical adhesive has to be removed. This constant contact of skin with adhesives often leads to the development of skin damage, such as MARSII, especially if the adhesives are not adequately chosen or applied/removed. A quick, easy, and damage-free removal (i.e., on-demand detachment) is fundamental, however, the current adhesives do not meet these requirements.

Several advances have been made, from new nature-inspired materials to the incorporation of therapeutic agents with/without a stimuli effectiveness, enhancing strong adhesion without skin damage and pain, improving wound healing and skin regeneration, and preventing skin infections. However, no study reported the effect of the novel adhesives on the skin surface upon its removal. Thus, despite these promising advances, several improvements are still needed to develop superior medical adhesives capable of maintaining adequate adhesion capability, reducing skin injuries, being easy to peel off, and reducing the overall healing time.

This literature revision allows the conclusion that the field of medical adhesives still has a long way to go before all the associated limitations and obstacles are overcome. However, it also shows that despite still being somewhat experimental, natural and nature-mimicking materials will most likely bring great benefits both regarding adhesion properties and skin care.

Health education and medical records about injuries related to

medical adhesives are essential. The prevention of medical adhesive-related skin injury should be done by adopting multifactorial measures, which range from identifying risk factors and correct handling of adhesives to the process of educating professionals, patients, and communities about these injuries.

To summarize, bioinspired adhesives composed of biocompatible materials with outstanding functional properties have been achieved, though no evidence of this new generation of multifunctional adhesives with the ability to prevent and/or minimize MARSII has been reported so far. Although the significant and promising improvements in novel multifunctional adhesives carried by the scientific and medical community, the importance of this topic has to be highlighted and discussed, and thus its investigation has to be encouraged.

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Luísa Fialho: Writing – original draft. **João Albuquerque:** Writing – original draft. **A. Sofia Pinho:** Writing – original draft. **Ana Margarida Pereira:** Writing – original draft. **Cláudia Monteiro:** Writing – review & editing. **Nelson Oliveira:** Writing – review & editing. **Sónia Ferreira:** Funding acquisition, Writing – review & editing. **M. Cristina L. Martins:** Funding acquisition, Writing – review & editing.

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Data availability

No data was used for the research described in the article.

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