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REVIEW

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Recent advances and future prospects in topical creams from medicinal plants to expedite wound healing: a review

Iliyasu Datti Gwarzo[a,b], Siti Pauliena Mohd Bohari[a,f], Roswanira Abdul Wahab[b,c,d] and Arifullah Zia[a,e]

[a]Department of Bioscience, Faculty of Science, Universiti Teknologi Malaysia, UTM Johor, Malaysia; [b]Department of Chemistry, Faculty of Science, Universiti Teknologi Malaysia, UTM Johor, Malaysia; [c]Enzyme Technology and Green Synthesis Research Group, Department of Chemistry, Faculty of Science, Universiti Teknologi Malaysia, UTM Johor, Malaysia; [d]Advance Membrane Technology Research Centre, School of Chemical and Energy Engineering, Faculty of Engineering, Universiti Teknologi Malaysia, UTM Johor Bahru, Johor, Malaysia; [e]Department of Biology, Faculty of Science, Nangarhar University, Darunta, Jalalabad, Afghanistan; [f]Cosmetic and Fragrance Laboratory, Institute of Bioproduct Development, Universiti Teknologi Malaysia, UTM Johor, Malaysia

ABSTRACT
Wound healing is a complex process driven by a series of stages that require a suitable wound closure environment, attributable to many factors. However, several factors contribute to delay in healing processes, including infection and the presence of certain diseases. Under unfortunate circumstances, an inadequate wound healing process could lead to amputation. Gauze is the traditional dressing to cover up wounds but tends to dry the wound bed. Therefore, a moist dressing may prove helpful in providing a suitable environment, preventing skin dryness, and enhancing angiogenesis of the wound area. The application of topical cream could expedite wound healing better than a moist dressing, as the former facilitates the repair process by maintaining the hydration levels of the affected skin. The issues mentioned above are discussed in detail in this review paper, focusing on recent advances, advantages and drawbacks of topical creams for wound treatment. In addition, the article includes suggestions to improve topical cream formulations for effective delivery of the needed therapeutic agents to assist in wound repair. Crucially, topical creams could play a key role in personal wound care and facilitate regenerative medicine. Novel strategies for speedy wound healing are in demand to alleviate the healthcare financial burden.

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Introduction

Wound healing is a dynamic and complex mechanism influenced by a series of cascades and factors that mutually lead to wound closure [1]. Skin recovery success depends on the sequence of events involved in cellular, biochemical and molecular responses. For this reason, the wound healing process of the extracellular matrix goes through three overlapping processes: the inflammatory phase, proliferative phase and remodeling phase [2]. These interdependent stages occur in a well-ordered fashion, overlapping each other in a well-connected cascade. Promoting these stages hinges on the wound type, its related pathological conditions, and the condition and type of dressing material. An unusual delay in the wound healing stages may have profound consequences on patients, especially those with diabetes, venous, arterial diseases. Other diseases that complicate wound repair include hypotension, hypovolemia, edema, anemia, altered hormonal responses, nutritional deficiencies and poor hydration. Microbial infections would also delay the wound repair process and ultimately lead to chronic wound infection alongside recurrence issues [2, 3]. Bacterial growth, which leads to wound bed colonization, could trigger a non-noticeable immune response that extends the inflammatory phase [4]. A high bacterial population indicates critical colonization or infection, which would further hinder the healing processes. Most often, improper handling of chronic wounds could lead to amputation or death [5]. Therefore, developing better strategies and therapeutic agents is necessary to expedite wound healing, especially that of chronic wounds.

The traditional bandaging of wounds using gauze is ineffective to accelerate the healing process as the technique desiccates the wound base [3]. Dry gauze

CONTACT Siti Pauliena Mohd Bohari pauliena@utm.my Department of Bioscience, Faculty of Science, Universiti Teknologi Malaysia, 81310 UTM Johor Bahru, Johor, Malaysia; Roswanira Abdul Wahab roswanira@kimia.fs.utm.my Department of Chemistry, Faculty of Science, Universiti Teknologi Malaysia, 81310 UTM Johor Bahru, Johor, Malaysia.
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dressing usually sticks to the wound's surface, which becomes a painful affair for the patient upon removal [6, 7]. This undesirable outcome is inevitable as the gauze dressing compresses the wound to initiate the treatment. However, the dressing must be regularly changed to prevent maceration and other health issues [8]. Besides gauze, film dressing is another option of a multifunctional and adhesive dressing. The thin layer and semi-permeable membrane over the wound provides good oxygen and water vapor exchange while preventing microbial colonization [7]. Similarly, a transparent film structure facilitates wound inspection without dressing removal.

Film dressing has the following advantages, namely, easy handling of the wounds, providing a barrier from external contamination, and reducing pain. However, the disadvantages of the technique include being traumatic upon removal and possible excessive exudate pooling [9]. For traditional practitioners, natural remedies such as honey may prove promising to enhance the healing of different wound types such as surgical- and infected surgical wounds and burns [10]. Recent studies have shown that wounds treated with honey generally heal faster than untreated wounds [8, 10]. Modernization has also inspired advancements in wound-healing strategies, for instance, the use of medicated topical creams [11–13].

Topical applications such as creams formulated with therapeutic ingredients can substitute wound dressing to accelerate the healing process, mitigate inflammatory reactions [14], and reduce bacterial infections commonly associated with severe wound injury [15]. Hence, there is a need to find a clear formulation containing active ingredients to promote optimal conditions for an effective regeneration process. Furthermore, a topical cream formulation is suited for delivering therapeutic ingredients on the skin, an outer layer of the body. Creams are semi-solid emulsions with an opaque appearance similar to translucent ointments. However, ointments have a higher oil content than creams, whereas creams have an equal amount of water and oil [13]. Creams are better absorbed into the skin than ointment [13]. In cream production, the type of formulation is either water-in-oil or oil-in-water to effectively deliver the active ingredients to affected sites such as skin, muscles and bones [14]. Studies have shown that the ideal formulation for creams used in wound treatment is that from natural sources. However, further investigations are necessary to substantiate this claim [16–18].

Herein, this review highlights the development of different topical cream formulations as part of wound-healing strategies in regenerative medicine. The paper also summarizes the advantages and the drawbacks of novel topical cream formulations to enhance healing and skin regeneration. Topical formulations of creams for chronic wound healing are also discussed.

Wound

A wound is a disorder that occurs from the environmental interruption of the typical anatomic structure of the skin, which affects normal tissue functions [19]. Wounds could occur incidentally, such as an animal bite, accident fall, or deliberately such as gunshots or surgical interventions [4, 20]. The damaged skin encourages organisms and other foreign entities to invade the tissues or internal organs and lead to unwanted infections [21]. Untreated or poorly healing wounds can profoundly influence the health system [22, 23]. Notably, wounds are classified based on the nature of the healing process, the number of skin layers, and the locality of infected skin. According to the natural healing process, wounds can be classified into acute and chronic wounds [24], discussed in detail in the section below.

Classification of wounds

Acute wound

An acute wound is a superficial mechanical injury from burns or trauma, and clean penetrating wounds from knife cuts or surgical incisions. Tissue injury from such a would usually heals completely, with minimal scarring within a short duration [24]. Wound repair is relatively quick if the proper treatment, such as dressing and medication, is given [25]. Care must be taken to avoid pathogens that could exacerbate the wound into a chronic one [26]. Characteristics of an acute wound include normal bleeding, redness, swelling and pus production at the wound site [27]. However, symptoms of an acute wound may also vary from one patient to another [4]. For example, a diabetic patient has an impaired wound healing mechanism triggered by hyperglycemia, chronic inflammation, micro-, macro-circulatory dysfunction, hypoxia, autonomic and sensory neuropathy [28]. In contrast, wounds on patients with venous or arterial disease take substantially longer to heal. Reoccurrence due to venous valve incompetence and calf muscle pump insufficiency is highly possible. Both complications could lead to venous stasis and hypertension, and eventually tissue ischemia [29].

Understanding the wound features is essential to aid in the speedy repair of an acute wound. Figure 1 illustrates the structure of acute wounds,

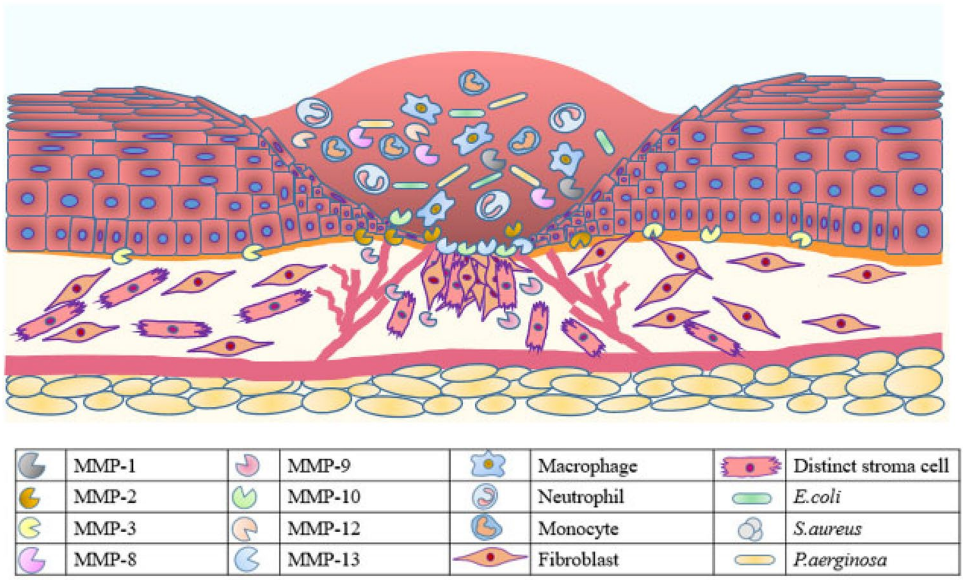

Figure 1. Schematic of an acute wound.

including the neutrophil, macrophages, monocytes, fibroblast, distinct stroma cells and some pathogenic bacteria. The structure of acute wounds includes the high concentration of matrix metalloproteinase (MMPs), contributing to wound healing [30]. Acute wounds also have unusually high numbers of neutrophils and macrophages, which play a key role in digesting the invading microbe to avoid colonization [30].

Chronic wound

A chronic wound is a type of wound that fails to heal through the normal healing process due to overlapping inflammatory, proliferative phase and remodeling phases [26]. Statistics have shown that 30% of chronic wounds require one month to heal because of the wounds' location or complications of diseases or infection [26]. In contrast to acute wounds, the structure of chronic wounds (Figure 2) has higher bacterial colonies leading to different types of infection compared to an acute wound [31]. In addition, the inflammatory stage is prolonged in chronic wounds without any progressive healing. Factors contributing to this include poor circulation and neuropathy, which causes loss of protective sensation, risk of infection, unresolved inflammation, etc [32].. At this stage, the inflammatory and physiological reactions continue to decrease with a profound impact on membrane basement degeneration and collagen production [4]. Among others, chronic wounds undergo uncontrolled protease activity with epithelial layer disruptions, which promotes bacterial colonization [33]. As a matter of fact, bacterial colonization is the hallmark of a chronic wound and poses a major problem in wound repair [34].

Wound infection

Wound infection happens when pathogenic bacteria grow within the damaged skin [4], in which the chronic wound stimulates their colonization at the wound bed [4]. Dowd *et al.*, (2008) [35] and Mihai *et al.* (2018) [1] reported that most pathogenic bacteria found in chronic wounds are gram-positive bacteria, for example, *Staphylococcus aureus, S. epidermidis, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Finegoldia magna* and *Enterococcus faecalis* [1, 35]. Wong *et al.* (2015) [36] also reported that the population of each bacterial species tends to vary in acute or chronic wounds. Chronic wounds have a higher concentration of pathogenic bacteria because of existing diseases in the patient. The diseases effectively reduce the neutrophil population in the body and other crucial substances that aid in wound healing. Nonetheless, the exact contribution of bacteria in delaying wound healing remains controversial because of the different organisms inhabiting the wound [36].

Similarly, differences in the gram-positive and gram-negative bacterial cell membrane pose additional challenges in selecting the correct antibiotic or medication to cure wounds. This is because the thicker but chemically simpler peptidoglycan architecture in gram-positive bacteria is distinct from the more chemically complex gram-negative bacterial cell wall [1]. Likewise, the ability of pathogenic organisms to form

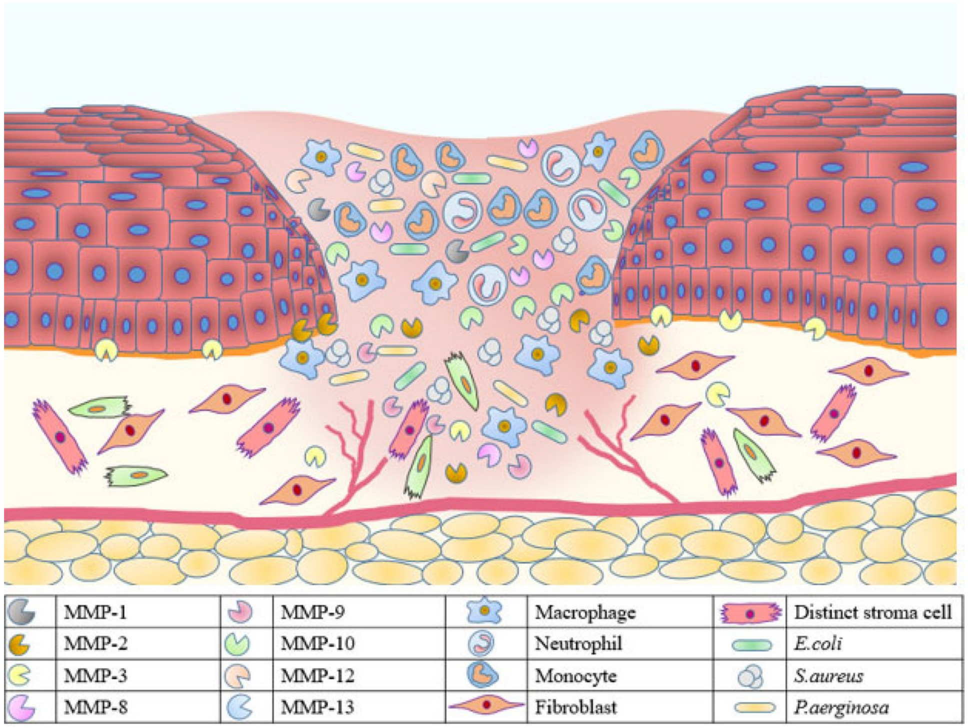

Figure 2. Schematic of a chronic wound.

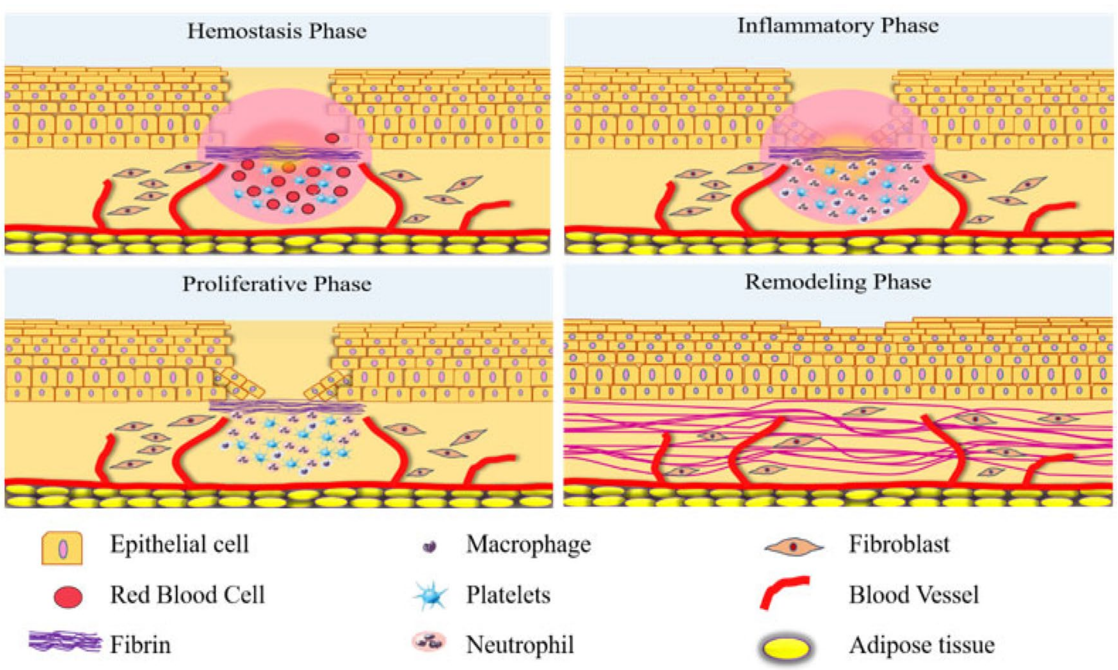

Figure 3. Schematic of the wound healing process.

biofilm further increases the likelihood of chronic wounds [1]. Hence, regular cleaning and debriding of the wound surface is highly recommended in chronic wounds. Such conditions could deteriorate critically and eventually lead to amputation.

Mechanism of wound healing

The wound healing mechanism kick starts when the skin surface is broken and a wound is formed. The healing process occurs in three successive phases

(Figure 3) involving inflammation, proliferation and remodeling [37]. The healing process begins with homeostasis and monitoring blood loss to prevent microbes from entering the wounded area [37]. The above changes are immediately followed by hemostasis, an inflammatory phase characterized by an increased number of pro-inflammatory cells, neutrophils and is regulated by macrophages [37]. The macrophages' role is to remove debris and pathogens to aid growth factors such as fibroblast growth factor and cytokine [24]. The proliferative phase immediately overlaps with the inflammatory phase. New tissue and new blood vessels develop in this phase, and the body matrix fills the wounded site [24]. The next phase is the remodeling phase, in which tissue is produced to increase the tensile strength and reduce blood supply to the wounded area [24]. Optimally healed wounds show minimal tissue damage with adequate tissue perfusion. Basically, the structure and function of the affected area are fully restored [22, 38].

Topical application

A topical application describes medicated admission on the body surface such as skin or mucous membrane to treat certain ailments using certain substances, for instance, creams, foams, gels, ointment and others [39]. Previously, several topical applications were used in conventional wound healing, including topical liquid, semi-solid formulations, and traditional dry dressings such as silver and povidone-iodine [40]. Though the solutions are not widely used now, some such as povidone-iodine have clinical importance in reducing the microbial load in wound management. This chemical base solution has been improved by changing the concentrations of certain components and incorporating gelling substances such as paraffin wax. The additives are useful to extend the adherence duration of the dressing on the wound. Certain bioactive or therapeutic components are also added in the cream formulation to facilitate the process of wound repair [41, 42].

Conventional carrier systems have been employed to transport numerous chemicals to the skin topically. Due to the complex structure of the skin, these devices are ineffective for skin administration of large molecular structures and highly lipophilic substances. To circumvent these drawbacks, researchers have developed novel carrier systems such as vesicular systems, microemulsions and nanoparticles [43]. For example, microemulsions are being investigated extensively to improve ceramides penetration through the stratum corneum [44].

Moreover, ceramic particles that can be used as nanocarriers in macromolecular therapies are developing as a new area of research in nanotechnology because of their ultra-small size (less than 50 nm), porous nature, and lack of swelling or changes in porosity with pH. These nanoparticles can encapsulate biomacromolecules and protect them against denaturation caused by external pH and temperature fluctuations. Silica and other inert elements are commonly used for obtaining nanoparticles and are highly compatible with biological systems [45]. There are various examples where ceramic nanoparticles based on silica and their derivatives, such as hydroxyapatite and calcium salts, can be used to treat wounds. Collagen-ca nanoparticles were created, and they can manage the pH of the environment as well as calcium homeostasis, allowing for faster wound healing [46].

Bioactive plant components with antibacterial and wound-healing capabilities have also been delivered *via* nanotechnology. Curcumin, one of turmeric's most well-known active ingredients, has antimicrobial, anti-inflammatory and antioxidant properties [47]. Gaseous molecules, natural products, bioactive plant chemicals and growth factors can all be delivered directly to the necessary location using nanotechnology. Topical cream treatment could significantly reduce infection and microbial burden, and reduce the time for wound healing [27].

The self-adapting hydrogel may alter shape to better match the structure of containers or irregular surfaces than typical hydrogel due to its unusual mobility. As a result, when used as a drug carrier, a self-adapting hydrogel can change shape in response to the constantly changing environment of living tissues, allowing it to seamlessly adhere to irregular tissue surfaces, potentially leading to significantly improved drug delivery and therapeutic outcomes compared to traditional treatments [48]. In an early *in vitro* test, the hydrogel was employed as a wound dressing model. L929 cells were grown on a Petri dish, then scratched with a 200 L pipette tip to generate an artificial wound. The experimental wounds were coated with hydrogel and the wound recovered, implying that the hydrogel might be used as a wound dressing [49].

Additionally, chitosan hydrogel was used for topical application in wound healing [49]. Because of their biodegradable, biocompatible, non-toxic, antibacterial, biologically adhesive, biologically active and hemostatic characteristics, chitosan-based hydrogels are regarded as ideal materials for improving wound healing. Chitosan-based hydrogels have been shown to stimulate wound healing at various phases of healing, as well as to reduce wound-healing variables (such as excessive inflammatory and chronic wound infection) [49]. A the unique biological features of the chitosan-based hydrogel allow it to be used as a wound dressing as well as a drug delivery system (DDS) to carry antibacterial agents, growth factors, stem cells and other therapeutic agents, potentially speeding up wound healing. By altering or combining with other polymers and carrying various types of active ingredients, chitosan-based hydrogels can improve the effectiveness of wound healing for a variety of wounds [49].

Current wound dressing strategies

Current wound dressing strategies include the use of anti-microbial agents, absorbents, occlusive, adherence material and debridement dressings which are graded based on clinical results [50]. A dressing material can be made physically from different sources such as animal, herbal or synthetic. Traditionally, dressing wounds includes bandage dressing that comprises cotton, natural or synthetic fibers bandage [40, 51]. This is followed by gauze dressing, which slightly differs from the formulation of bandage dressing. However, all the above strategies fail to provide a moist environment to the wound and increase soreness during removal [40]. Nowadays, therapeutic agents such as antibiotics, alongside moisturizers, are incorporated into bandage dressing to maintain the hydration levels of the affected skin area, boost the wound healing process and avert microbial infection [50]. Among others, hydrocolloids, hydrogels, alginates and polyurethane films/foams are commonplace materials for delivering therapeutic agents.

Traditional topical formulation

Traditionally, a topical formulation for wound treatment contains povidone-iodine prepared in liquid and/or semi-solid formulation or bandage dressing [40, 52]. Povidone-iodine solutions play an essential part in reducing the bacterial load in the wound [40]. Literature has shown that other bioactive compounds such as aloe vera extract are combined with povidone-iodine or sliver and then incorporated into the dressing. This combination has been effective in preventing infections and enhancing the healing process [40, 42]. Likewise, a saline solution is used to clean wounds and remove dead tissues [52]. However, the major problem with the liquid dosage form is the ability of the therapeutic ingredient to remain on the wound site for an extended duration to impart its beneficial effects on the damaged skin fully.

On the other hand, the semi-liquid formulations include silver sulfadiazine cream and silver nitrate ointment [53] and are used for treating bacterial infections. The cream and ointment can remain on the wound surfaces for a more extended duration than liquid formulations [53]. However, semi-solid such creams are ineffective on highly exuding wounds because the wound will absorb the fluid and cream. This causes the semi-solid cream to lose its rheological characteristics [40, 54]. Natural resources in the form of topical formulations have been introduced as therapeutic agents for treating wounds. For example, *Aloe vera* is a popular natural substance in wound treatment because it contains anti-microbial, anti-inflammatory substances and immune stimulants [42].

Current formulations

Traditional applications for wound healing have been replaced or improved to meet the desired application. Table 1 enlists the natural substances used to expedite wound healing, namely extracts of *Spathodea campanulata* (stem bark), *Daucus carota Linn aloe vera, Hibiscus sabdariffa, Eupatorium glandulosum* (Asteraceae), *Cissus quadrangularis* (Vitaceae), *Pistacia atlantica, Lantana camara* leaves extract, *Withania*, *Allium sativum* (garlic) and *Curcuma longa* (Tumeric).

Ofori-Kwakye *et al.* (2011) [51] formulated a cream containing a concentrated *Spathodea campanulata* extract, which accelerated the wound closure because of the high flavonoid content. The formulated cream successfully healed the wounds with ~95% and total closure after 20 and 24 days of application, respectively (Table 1). The enhanced healing activities were due to reduced peroxidation by the flavonoids and prevented cell necrosis [51]. Another study by Patil *et al.* (2012) [55] prepared a cream comprising flavonoids extracted from the *Daucus carota Linn*. plant. The formulated cream showed promising application for wound healing given the absence of skin irritation and substantially contributed to wound repair compared to the control [55] (Table 1).

Similarly, Builders *et al.* (2013) [56] formulate a cream from *Hibiscus sabdariffa* Linn mixed with the antibiotic gentamicin. They described that the wound was completely closed in less than 20 days of application [56], presumably from the synergistic action of gentamicin and flavonoids that averted wound infection, aside from accelerating the wound repair process [56]. M. Sellappan and T. Praveen [57] prepared a

Table 1. Different formulation and delivery methods of various topical creams from some plant sources for wound healing.

Source	Formulation	Delivery method	Remarks	References
Spathodea campanulata (stem bark)	10%/20% of *Spathodea campanulata*	Applied twice daily on the wound surface	The 20% cream enhanced the wound healing activities	[44]
Daucus carota Linn.	4% ethanolic extract	Applied on the wound surface	The wound healing may be attributed to potential, but other physiological properties are needed	[48]
Hibiscus sabdariffa extract and Gentamicin	10% *Hibiscus sabdariffa* and 10% gentamicin	Apply the cream directly to the wound	Shows progressive closure of the wound within the shortest time	[49]
Eupatorium glandulosum (Asteraceae) and *Cissus quadrangularis* (Vitaceae)	10% of the sources	Applied on the wound surface	Shows significance contraction to wound healing	[50]
Eucalyptus oil	16.66% oil, 66.68% water and 16.66% surfactant	Apply on the wound surface	Significant increase in wound healing activity compared to control drug	[55]
Aloe vera	The powder was dissolved in 0.9% saline solution	The Aloe vera gel was applied to the wound surface	Improved the biochemical and morphological characteristics of a cutaneous wound in the rat; this practice may be valuable in a clinical trial	[51]
Pistacia atlantica	10% of the source	Applied on the surface of the wound	There is much improvement in the re-epithelization, which led to enhance wound healing	[52]
Lantana camara leaves extract	10% of the extract	Applied on the wound surface	The cream has maximum wound healing activity	[18]
Withania, garlic, and curcuma	1% of the source	Each cream was applied to the surface of the wound	Each of the sources shows a clear wound healing activity	[53]
Honey and Aloe vera	70% honey, 20% aloe vera and 10% peppermint	Applied on the wound site during dressing	Significant enhancement of wound healing and protection against infection	[54]
Coconut oil and simvastatin	22.5% oil, 55% water and 22.5% surfactant	Applied in the burn surface	Enhanced the healing of normal and chronic burns	[56]

topical cream containing extracts of *Eupatorium glandulosum* (*Asteraceae*) and *Cissus quadrangularis* (Vitaceae) as active ingredients. They discovered that a 10% cream composition of the *Eupatorium glandulosum* led to a significant contraction in the wound area on the 8th-day post-application. The healing rate was comparable to the standard drug used for the experiment, as tests showed that a high concentration of the mixed active ingredients showed appreciable anti-microbial activity. The wounds healed and contracted more rapidly than formulations containing lower concentrations of mixed plant extract [57]. Moreover, according to Pazyar *et al.* (2014) and Artem *et al.* (2018), rosemary is one of the most often utilised herbs in cutaneous wound healing. They examined the aqueous extract and essential oil efficacy in alloxan-induced diabetic BALB/c mice [58]. Different aspects of the diabetic wound healing process, such as a reduction in inflammation and an enhancement in wound contraction, re-epithelialization, regeneration of granulation tissue, angiogenesis, and collagen deposition, were observed in the treated wounds, with significant differences (p.01) between the treated and control groups [59].

An *aloe vera* cream formulated by Oryan *et al.* (2016) [60] improved its efficacy to expedite the would repair process following the addition of saline solution. Compared to the controls, treatment with high dosages of *A. vera* and saline increased the rate and quality of inflammation and fibroplasia, resulting in more granulation tissue developing and filling the wound area in the short-term (day 10) test [60]. Hamidi *et al.* (2017) [61] used a *Pistacia atlantica* extract in their formulation based on the well-reported antioxidant properties of the plant. The optimized cream formulation was seen to profoundly shorten the healing process [61]. Vijayalakshmi *et al.* (2018) [18] also developed a 10% *Lantana camara* leaf extract cream. The formulation was exceptional and resulted in a 98% total closure of the wound surface on the 12th day and total wound healing on the 15th day. In another study by Alawdi (2019) [62], the combined extract of *Withania*, garlic and *Curcuma* substantially accelerated the healing rate of surgically induced wounds on rabbits, at a healing rate of 97% on the 12th day with total closure on the 14th day [62]. Afterward, Abbasi *et al.* (2020) [63] experimented with integrated *Aloe vera*, honey and peppermint as bioactive ingredients in their prepared formulation. They reported that the synergistic effect of the components yielded quicker and better wound repair than formulations with the individual components (Table 1) [63].

Baidoo *et al.* (2020) performed an experiment with the leaf and stem bark of *Entada africana*. When compared to the negative control group, leaf and stem bark extracts dramatically increased wound contraction, re-epithelialization and granulation tissue development, all of which indicate a significant treatment response. Exudate and unpleasant odors were not produced in any of the treated groups, indicating that infection was not present [64]. The ternary active ingredient cream also significantly healed wounds faster, prevented infection and scarring, and relieved pain [63].

Water-in-oil or oil-in-water nanoemulsions prepared by high-energy or low-energy homogenization have been used to formulate topical creams containing extracts of medicinal plants to ameliorate the wound healing process. The high-energy homogenization method (ultra-sonication) was employed to prepare an oil-in-water nanoemulsion with eucalyptus oil which exhibits anti-inflammatory and anti-microbial bioactivity (Table 1) [65]. The nanoemulsion resulted in total wound closure in Wistar rats in less than 20 days [65]. Another study that prepared an oil-in-water nanoemulsion from coconut oil and simvastatin as the bioactive compound (Table 1) demonstrated remarkable wound-healing qualities. The outcome has to do with coconut oil's anti-inflammatory and antibacterial qualities, while simvastatin promotes the synthesis of vascular endothelial growth factors at the injury site [66]. Moreover, another study explored cream formulations using sea cucumber extract and different types of oil phases, such as olive oil, tea tree oil, and lemongrass oil, to see how the oil affected the physicochemical qualities and wound healing efficacy of the creams [67]. Even when the creams were maintained at severe temperatures, the created creams showed good physicochemical parameters such as homogeneity, spreadability, theology and pH, and no evidence of phase separation. Using Franz diffusion cells, the *ex vivo* release profile of sea cucumber extract from the prepared creams was determined.

In comparison to the control group, topical treatment of the prepared creams on the excision wound in rats revealed a considerable wound healing efficacy. The ability of the oils to promote skin penetration for the release of sea cucumber extract had no bearing on the wound healing efficiency of the prepared creams. Lemongrass oil was a good skin penetration enhancer for the release of sea cucumber extract, while olive oil worked more synergistically with sea cucumber extract to promote wound healing in this investigation [67]. The rosmarinic acid (RA) group showed a significant reduction in wound size according to [68]. On day 3, there was a statistically significant difference in the wound area decrease between the control group and the rosmarinic acid group. This disparity is most likely due to RA's anti-inflammatory properties [68]. Aramwit and Sangcakul [69] used rosmarinic acid with sericin lotion and saw a 90% improvement on day 11, with full recovery on day 15. Another research with rosmarinic acid with topical recombinant human epidermal growth factor treatment showed 90% improvement on day 10 and full closure on day 14 [70]. Based on the considerable statistical findings (about 90% on day 14; > 95% improvement on day 21), the clinical benefit of rosmarinic acid would be apparent after day 7 and RA should be used for at least 3 weeks for best effect.

Percolation was used to extract apigenin-rich chamomile flower extract (CFE). Liposomes were made using 1:2 mixtures of Ratermann phospholipid and apigenin and then integrated into oil in water cream with several topical excipients. Compared to a non-liposomal cream containing plain CFE apigenin, an *in vitro* dissolution investigation revealed enhanced release. The *in vivo* trial with apigenin cream demonstrated considerable anti-inflammatory effect in 19 human volunteers between 24 and 65 years [71]. Apigenin liposomal cream worked well, was well tolerated and had fewer side effects than corticosteroids [71]. Moreover, natural polymers (e.g. collagen, chitosan and hyaluronic acid) hydrogels can induce anti-inflammatory responses in chronic wounds, promoting healing [72]. According to several studies, cellulose promotes wound healing by releasing and maintaining therapeutic levels of a variety of growth factors (e.g. PDGF, EGF and FGF) at the wound site, as well as increasing dermal fibroblast migration and proliferation and suppressing bacterial proliferation in wounds [73–75]. Table 1 summarizes the above-described formulated creams to assist in the process of wound repair.

Future formulations

The reviewed studies indicated that most wound-healing enhancing formulations were made from natural resources containing flavonoids, alkaloids and saponins. These phytochemicals have good reputations for exhibiting good anti-microbial, anti-inflammatory, anti-oxidative properties. Hence, their synergistic effects could facilitate the process of wound repair and skin regenerative properties. All reviewed literature indicated that increasing the concentration of the biochemical substances enhances the healing activities in each formulation. Therefore, concerted efforts of the scientific community are needed to isolate different kinds of flavonoids, alkaloids and saponins. In this way, more structures of the beneficial phytochemicals could be elucidated for further synthesis by chemists, possibly in large quantities to facilitate scale-up production. Sourcing bioactive ingredients purely from plant extracts may not be adequate or sustainable for the large commercial market. On another note, formulators should consider using higher concentrations of penetration enhancers to boost the delivery of the therapeutic agents into the wound.

Delivery method

Drug delivery systems have been developed to ensure that the incorporated drugs in the formulation are absorbed into the body and delivered to targeted locations [76]. Skin being the largest organ and the outermost layer of the human body is very much suited to targeted delivery of therapeutic agents through topical delivery [76]. This is because the human skin suffers from common diseases such as acne, wound, and other skin disorders [77]. The correct combination of active ingredients and base components would allow for a wide range of topical preparations suitable for delivering the active ingredients [76]. The methods to prepare the topical formulations are classified based on physical properties such as suspension or composition such as cream or ointments and their intended uses, such as liniment. Table 2 summarizes the various types of topical applications to deliver bioactive ingredients through the skin. Most important, topical delivery of these ingredients aids in enhancing skin tolerability and the drug's anti-inflammatory activity in the body [78].

Limitation of topical cream

There are many challenges to address when developing topical drugs for wound healing, as shown in Table 3. Hence, such treatment (cream) must withstand the proteolytic wound environment to accelerate the wound healing activity. This factor is crucial to ensure the active substances reach the targeted sites in the skin [79]. Meanwhile, the ineffectiveness of the cream on exuding wounds has to do with the dilution of the cream in the exudes, which altered the physicochemical properties of the cream [40]. However, the topical application of creams in the wound-treatment regime may not always work for all diseases. This approach tends to be time-consuming, and the regime becomes complicated when several formulations must be prescribed [80, 81]. There are issues of the lower permeability of certain topical creams and their tendency to irritate the skin, associated with diverse compositions of anti-inflammatory agents used in the cream [81]. Care must be taken to choose the right combination of active ingredients in a formulation, as certain components can invalidate the therapeutic action of another component and vice versa.

Competitors to topical creams

The technology in developing topical creams has been around for over three decades. Such cream offers a good alternative to bandaging dressing. These creams, if formulated correctly, can simultaneously provide a moist environment for the wound while accelerating the healing rate. There are over 100 patents of topical creams globally for diseases related to the skin [82]. The technology that developed topical creams has considerably advanced, with numerous versatile formulation strategies to meet the demands of a highly competitive dermatological and nutraceutical market [82]. The following substances, active agents, propellants, surface-active agents, solvents, co-solvents and viscosity-modifying agents, are needed to achieve an optimum formulation for efficacious delivery of the wound healing active ingredients through the skin. While corticosteroids are used in most commercial topical foams, the active ingredients may also include antibacterial, antifungal, antiviral agents, anti-inflammatory agents, local anesthetic agents, skin emollients, and

Table 2. Different delivery methods for topical application of wound healing treatments.

Forms	Description
Cream	The cream is the semi-solid emulsion formulation for skin or wound application, which is less greasy and has good spreadability.
Gel	The gel is a transparent semi-solid preparation for one or more active ingredients suitable for hydrophilic or hydrophobic bases.
Ointment	It is also a greasy semi-solid preparation of the dissolved drug.
Paste	It is a stiff preparation containing a high proportion of fine powder; this is less greasy than cream and ointment.

Table 3. Advantages and disadvantages of topical creams for wound healing.

Advantages of topical creams	Disadvantages of topical creams
The simplest way to deliver a drug	Very slow in absorption
The drug can be delivered simply.	Slow absorption rate.
The application can be terminated when needed	Due to the drug excipient, skin irritation may occur.
Avoid gastro-intestinal incompatibility.	Can only be used for a specific medication
Non-invasive	Some have high molecular weight; therefore, these cannot penetrate through the skin

protectants; depending on the skin conditions being treated [81]. A pressurized dosage makes a topical cream unique, which is also self-generating.

The occurrence of nanofibers will also compete with the topical cream in the treatment of wounds. All-natural and man-made polymers have been used. Nanofiber technology can substantially improve the development of novel wound-healing solutions. Nanofiber scaffolds have mechanical integrity, good adhesion to an injury, and the ability to maintain temperature homeostasis, allow gas exchange and absorb exudates without becoming occlusive [83].

Furthermore, the current trending knowledge of molecular biology, such as microRNAs, will also compete with topical applications for wound healing activities [84]. MicroRNAs (miRs) are non-coding RNAs with approximately 22 nucleotides that bind to the 3-untranslated regions (3-UTR) of target messenger RNA (mRNA) and regulate gene expression post-transcriptionally [85]. Reportedly they regulate a wide range of cellular and physiological functions in health and disease. Several pieces of evidence suggest that miRs control signaling during wound healing. MiR-146a and miR-155 control macrophages during the inflammatory phase, promoting the production of cytokines and growth factors required for monocyte differentiation into macrophages [84,86].

Wound-healing activity has been discovered in synthetic antimicrobial peptides (s-AMPs), developed to enhance structural stability and high antibacterial activity under physiological conditions [87]. This shows that it will compete with topical application for wound healing activity in the future. Some AMPs are regarded as prospective wound care agents because, in addition to their inherent anti-microbial action, they can alter several wound-healing systems such as inflammation, epithelialization, tissue granulation and remodeling. Even though some wound-healing peptides lack anti-microbial characteristics, some have significant therapeutic potential in treating persistently infected wounds, such as diabetic foot ulcers [88].

Moreover, the development of Toll-like receptors provides an avenue to compete with topical application [84]. Toll-like receptors (TLRs) are a family of highly conserved pattern recognition receptors (PRRs) that signal the presence of various pathogen-associated molecular patterns (PAMPs) to immune cellular system elements. TLRs trigger immunological responses *via* NF-κB-dependent and interferon regulatory factor (IRF-) dependent processes after attaching to distinct biochemical components of protozoa, bacteria and viruses [84, 89]. TLRs are also activated by endogenous ligands known as damage-associated molecular patterns (DAMPs), which are unavailable to the immune system under normal settings or change in response to injury, allowing PRRs to recognize them. Following tissue damage, these patterns are unmasked or released from damaged cells, thus triggering inflammation by TLRs and other PRRs. As a result, TLRs are thought to be master protectors of tissue structural integrity, activated by molecular indications of infection or injury and play a critical role in wound healing [89].

Conclusions

It is apparent that the rate- and mechanism of wound healing are interlinked; thus, not all wounds can be treated in the same. In this regard, nature is a good source of phytochemicals that could positively and profoundly impact the wound healing process. There is much evidence that naturally derived bioactive chemicals have healing characteristics, which has sparked great interest among researchers in their possible application in wound healing. Scientists have proven that incorporating plant-based bioactive molecules in the formula of topical creams would substantially improve the bioavailability and biological properties of the plant ingredients, guaranteeing a better healing process. Also, with more complex natural-based and advanced cream formulations being developed for wound treatment, these products can be used effectively to expedite skin regeneration with minimal scarring. Hence, the advancement of wound healing techniques paves new opportunities for designing newer, better, and cost-effective treatment options.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

Disclosure statement

The authors have no conflicts of interest to declare.

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ORCID

Roswanira Abdul Wahab http://orcid.org/0000-0002-9982-6587

References

[1] Mihai MM, Preda M, Lungu I, et al. Nanocoatings for chronic wound repair—modulation of microbial colonization and biofilm formation. IJMS. 2018;19(4):1179.
[2] Morin C, Roumegous A, Carpentier G, et al. Modulation of inflammation by cicaderma ointment accelerates skin wound healing. J Pharmacol Exp Ther. 2012;343(1):115–124.
[3] Han G, Ceilley R. Chronic wound healing: a review of current management and treatments. Adv Ther. 2017;34(3):599–610.
[4] Rahim K, Saleha S, Zhu X, et al. Bacterial contribution in chronicity of wounds. Microb Ecol. 2017;73(3):710–721.
[5] Zheng Y, Ji S, Wu H, et al. Topical administration of cryopreserved living micronized amnion accelerates wound healing in diabetic mice by modulating local microenvironment. Biomaterials. 2017;113:56–67.
[6] Fonder MA, Lazarus GS, Cowan DA, et al. Treating the chronic wound: a practical approach to the care of nonhealing wounds and wound care dressings. J Am Acad Dermatol. 2008;58(2):185–206.
[7] Mulholland EJ, Dunne N, McCarthy HO. MicroRNA as therapeutic targets for chronic wound healing. Mol Ther Nucleic Acids. 2017;8:46–55.
[8] Krishnan K A, Thomas S. Recent advances on herb-derived constituents-incorporated wound-dressing materials: a review. Polym Adv Technol. 2019;30(4):823–838.
[9] Vowden K, Vowden P. Wound dressings: principles and practice. Surgery (Oxford). 2017;35(9):489–494.
[10] Ibrahim N, Wong S, Mohamed I, et al. Wound healing properties of selected natural products. IJERPH. 2018;15(11):2360.
[11] Mohanty C, Sahoo SK. Curcumin and its topical formulations for wound healing applications. Drug Discov Today. 2017;22(10):1582–1592.
[12] Datta HS, Mitra SK, Patwardhan B. Wound healing activity of topical application forms based on ayurveda. Evid Based Complement Alternat Med. 2011;2011:1–10.
[13] Kaur J, Kaur J, Jaiswal S, et al. Recent advances in topical drug delivery system. Pharm Res. 2016;6(07):6353–6369.
[14] Sarabahi S. Recent advances in topical wound care. Indian J Plast Surg. 2012;45(2):379–387.
[15] Bhatia N, Kaur G, Soni V, et al. Evaluation of the wound healing potential of isoquercetin-based cream on scald burn injury in rats. Burns Trauma. 2016;4:1–8.
[16] Thapa RK, Diep DB, Tønnesen HH. Topical antimicrobial peptide formulations for wound healing: current developments and future prospects. Acta Biomater. 2020;103:52–67.
[17] Nagula RL, Wairkar S. Recent advances in topical delivery of flavonoids: a review. J Control Release. 2019;296:190–201.
[18] Vijayalakshmi A, Sangeetha S, Ranjith N. Formulation and evaluation of herbal shampoo. Asian J Pharm Clin Res. 2018;11(4):121–124.
[19] Mohandas A, Anisha B, Chennazhi K, et al . Chitosan-hyaluronic acid/VEGF loaded fibrin nanoparticles composite sponges for enhancing angiogenesis in wounds . Colloids Surf B Biointerfaces. 2015;127:105–113.
[20] Fallouh HB, Venugopal PS, Newton A. Occult gunshot wounds in the emergency department. The Lancet. 2009;373(9664):631–632.
[21] Dombrádi Z, Bodnár F, Orosi P, et al. A case report of vancomycin-resistant Enterococcus faecalis colonization of a femoral wound in Central europe. Cent Eur J Med. 2009;4(2):259–261.
[22] Oguntibeju OO. Medicinal plants and their effects on diabetic wound healing. Vet World. 2019;12(5):653–663.
[23] Zuarez-Easton S, Zafran N, Garmi G, et al. Postcesarean wound infection: prevalence, impact, prevention, and management challenges. Int J Womens Health. 2017;9:81–88.
[24] Patel S, Srivastava S, Singh MR, et al. Mechanistic insight into diabetic wounds: Pathogenesis, molecular targets and treatment strategies to pace wound healing. Biomed Pharmacother. 2019;112:108615.
[25] Dorai AA. Wound care with traditional, complementary and alternative medicine. Indian J Plast Surg. 2012;45(2):418–424.
[26] Mahmoudi M, Gould LJ. Opportunities and challenges of the management of chronic wounds: a multidisciplinary viewpoint. CWCMR. 2020;7:27–36.
[27] Rajendran NK, Kumar SSD, Houreld NN, et al. A review on nanoparticle based treatment for wound healing. J Drug Delivery Sci Technol. 2018;44:421–430.
[28] Baltzis D, Eleftheriadou I, Veves A. Pathogenesis and treatment of impaired wound healing in diabetes mellitus: New insights. Adv Ther. 2014;31(8):817–836.
[29] Andriessen A, Apelqvist J, Mosti G, et al. Compression therapy for venous leg ulcers: risk factors for adverse events and complications, contraindications—a review of present guidelines. J Eur Acad Dermatol Venereol. 2017;31(9):1562–1568.
[30] Krishnaswamy VR, Mintz D, Sagi I. Matrix metalloproteinases: the sculptors of chronic cutaneous wounds. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 1864;2017(11):2220–2227.
[31] Sen CK. "Advances in wound care," 2019.
[32] Stone RC, Stojadinovic O, Rosa AM, et al. A bioengineered living cell construct activates an acute wound healing response in venous leg ulcers. Sci. Transl. Med. 2017;9(371):eaaf8611.
[33] Chauhan N, Wrobel A, Skurnik M, et al. Yersinia adhesins: an arsenal for infection. Proteomics Clin Appl. 2016;10(9–10):949–963.
[34] McMenemy K. Skin and soft tissue infections. Physician Assistant Clinics. 2017;2(2):165–176.
[35] Dowd SE, Wolcott RD, Sun Y, et al. Polymicrobial nature of chronic diabetic foot ulcer biofilm infections determined using bacterial tag encoded FLX amplicon pyrosequencing (bTEFAP). PLoS One. 2008;3(10):e3326.
[36] Wong SY, Manikam R, Muniandy S. Prevalence and antibiotic susceptibility of bacteria from acute and chronic wounds in malaysian subjects. J Infect Dev Ctries. 2015;9(9):936–944.
[37] Mahgoub HA, Elnaggar A, Sadeyen J-R. Implementation of tissue histopathology and parasitic morphometric analysis in the diagnosis of myxobolus fomenai infec-

tion in the skeletal muscles Nile tilapia. AJIDM. 2017;5(4):137–142.
[38] Karodi R, Jadhav M, Rub R, et al. Evaluation of the wound healing activity of a crude extract of rubia cordifolia L.(indian madder) in mice. Int J Appl Res Nat Prod. 2009;2(2):12–18.
[39] Simões A, Veiga F, Vitorino C, et al. A tutorial for developing a topical cream formulation based on the quality by design approach. J Pharm Sci. 2018;107(10):2653–2662.
[40] Boateng JS, Matthews KH, Stevens HNE, et al . Wound healing dressings and drug delivery systems: a review. J Pharm Sci. 2008;97(8):2892–2923.
[41] Calixto LS, Infante VHP, Campos PMM. Design and characterization of topical formulations: correlations between instrumental and sensorial measurements. AAPS Pharm Sci Tech. 2018;19(4):1512–1519.
[42] Farstvedt E, Stashak TS, Othic A. Update on topical wound medications. Clin Tech Equine Pract. 2004;3(2): 164–172.
[43] Tessema EN, Gebre-Mariam T, Neubert RH, et al. Potential applications of phyto-derived ceramides in improving epidermal barrier function. Skin Pharmacol Physiol. 2017;30(3):115–138.
[44] Školová B, Janůšová B, Zbytovská J, et al. Ceramides in the skin lipid membranes: length matters. Langmuir. 2013;29(50):15624–15633.
[45] Roy P, Berger S, Schmuki P. TiO2 nanotubes: synthesis and applications. Angew Chem Int Ed Engl. 2011;50(13):2904–2939.
[46] Shanmugapriya K, Kang HW. Engineering pharmaceutical nanocarriers for photodynamic therapy on wound healing: Review. Mater Sci Eng C. 2019;105:110110.
[47] Hussain Z, Thu HE, Ng S-F, et al. Nanoencapsulation, an efficient and promising approach to maximize wound healing efficacy of curcumin: a review of new trends and state-of-the-art. Colloids Surf B Biointerfaces. 2017;150:223–241.
[48] Decker CG, Wang Y, Paluck SJ, et al . Fibroblast growth factor 2 dimer with superagonist in vitro activity improves granulation tissue formation during wound healing. Biomaterials. 2016;81:157–168.
[49] Li Y, Wang X, Fu Y-N, et al. Self-Adapting hydrogel to improve the therapeutic effect in Wound-Healing. ACS Appl Mater Interfaces. 2018;10(31):26046–26055.
[50] Rezvani Ghomi E, Khalili S, Nouri Khorasani S, et al. Wound dressings: Current advances and future directions. J Appl Polym Sci. 2019;136(27):47738.
[51] Ofori-Kwakye K, Kwapong AA, Bayor MT. Wound healing potential of methanol extract of spathodea campanulata stem bark forumlated into a topical preparation. Afr J Trad Compl. Alt. Med. 2011;8(3):218–223.
[52] Saghazadeh S, Rinoldi C, Schot M, et al. Drug delivery systems and materials for wound healing applications. Adv Drug Deliv Rev. 2018;127:138–166.
[53] Jewo PI, Fadeyibi IO, Babalola OS, et al. A comparative study of the wound healing properties of moist exposed burn ointment (MEBO) and silver sulphadiazine. Ann Burns Fire Disasters. 2009;22(2):79–82.
[54] Hudspith J, Rayatt S. Treatment of minor burns: Authors' reply. BMJ. 2004;329(7460):292.
[55] Patil MVK, Kandhare AD, Bhise SD. Pharmacological evaluation of ethanolic extract of daucus carota linn root formulated cream on wound healing using excision and incision wound model. Asian Pac J Trop Biomed. 2012;2(2):S646–S655.
[56] Builders P, Kabele-Toge B, Builders M, et al. Wound healing potential of formulated extract from hibiscus sabdariffa calyx. Indian J Pharm Sci. 2013;75(1):45.
[57] Sellappan M, Praveen T. Effect of topical herbal formulations on antimicrobial and wound healing activity. Open Conf Proceed J. 2013;4(1).
[58] Artem Ataide J, Caramori Cefali L, Machado Croisfelt F, et al. Natural actives for wound healing: a review. Phytother Res. 2018;32(9):1664–1674.
[59] Pazyar N, Yaghoobi R, Rafiee E, et al. Skin wound healing and phytomedicine: a review. Skin Pharmacol Physiol. 2014;27(6):303–310.
[60] Oryan A, Mohammadalipour A, Moshiri A, et al. Topical application of aloe vera accelerated wound healing, modeling, and remodeling: an experimental study. Ann Plastic Surg. 2016;77(1):37–46.
[61] Hamidi SA, Naeini AT, Oryan A, et al. Cutaneous wound healing after topical application of pistacia atlantica gel formulation in rats. Turk J Pharm Sci. 2017;14(1): 65–74.
[62] Alawdi SH, Shehab M, Al-Mekhlafi AG. Formulation of herbal gel preparations from medicinal plants and evaluation of their wound healing activities. Saudi J Biomed Res. 2019;4(8):279–284.
[63] Abbasi MS, Rahmati J, Ehsani AH, et al. Efficacy of a natural topical skin ointment for managing Split-Thickness skin graft donor sites: a pilot double-blind randomized controlled trial. Adv Skin Wound Care. 2020;33(7):1–5.
[64] Baidoo MF, Mensah AY, Ossei PPS, et al. Wound healing, antimicrobial and antioxidant properties of the leaf and stem bark of entada Africana Guill. & Perr. S Afr J Bot. 2021;137:52–59.
[65] Sugumar S, Ghosh V, Nirmala MJ, et al. Ultrasonic emulsification of eucalyptus oil nanoemulsion: Antibacterial activity against Staphylococcus aureus and wound healing activity in wistar rats. Ultrason Sonochem. 2014;21(3): 1044–1049.
[66] Hosny KM, Alhakamy NA, Sindi AM, et al. Coconut oil nanoemulsion loaded with a statin hypolipidemic drug for management of burns: Formulation and in vivo evaluation. Pharmaceutics. 2020;12(11):1061.
[67] Sunmugam THIVIYA, Azhari HANISAH, Ng S-F, and FAZREN, et al. Influence of the oil phase on the wound healing activity of sea cucumber Extract-Based cream formulations. JSM. 2021;50(3):839–847.
[68] Küba MC, Türkoğlu A, Oğuz A, et al. Comparison of local rosmarinic acid and topical dexpanthenol applications on wound healing in a rat experimental wound model. Folia Morphol (Warsz). 2021;80(3):618–624.
[69] Aramwit P, Sangcakul A. The effects of sericin cream on wound healing in rats. Biosci Biotechnol Biochem. 2007;71(10):2473–2477.
[70] Kwon Y-B, Kim H-W, Roh D-H, et al. Topical application of epidermal growth factor accelerates wound healing by myofibroblast proliferation and collagen synthesis in rat. J Vet Sci. 2006;7(2):105–109.
[71] Arsić I, Tadić V, Vlaović D, et al . Preparation of novel apigenin-enriched, liposomal and non-liposomal, antiin-

flammatory topical formulations as substitutes for corticosteroid therapy. Phytother Res. 2011;25(2):228–233.
[72] Sánchez-Sánchez R, Martínez-Arredondo E, Martínez-López V, et al. Development of hydrogel with anti-inflammatory properties permissive for the growth of human adipose mesenchymal stem cells. J Nanomater. 2016;2016:1–8. vol
[73] Jung R, Kim Y, Kim H-S, et al. Antimicrobial properties of hydrated cellulose membranes with silver nanoparticles. J Biomater Sci Polym Ed. 2009;20(3):311–324.
[74] Cullen BM, Silcock DW, Boyle C. "Wound dressings comprising oxidized cellulose and human recombinant collagen," ed: Google Patents 2010.
[75] Moura LIF, Dias AMA, Carvalho E, et al . Recent advances on the development of wound dressings for diabetic foot ulcer treatment—a review. Acta Biomater. 2013;9(7):7093–7114.
[76] Bhowmik D. Recent advances in novel topical drug delivery system. Pharma Innovat. 2012;1(9):12–31.
[77] Garg T, Rath G, Goyal AK. Comprehensive review on additives of topical dosage forms for drug delivery. Drug Deliv. 2015;22(8):969–987.
[78] Herman A, Herman AP. Topically used herbal products for the treatment of hair loss: preclinical and clinical studies. Arch Dermatol Res. 2017;309(8):595–610.
[79] Öhnstedt E, Lofton Tomenius H, Vågesjö E, et al. The discovery and development of topical medicines for wound healing. Expert Opin Drug Discov. 2019;14(5):485–497.
[80] Dayan N. Delivery system design in topically applied formulations: an overview. Deliv Syst Handbook Personal Care Cosmetic Prod. 2005;101–118.
[81] Sobhan M, Hojati M, Vafaie S-Y, et al. The efficacy of colloidal oatmeal cream 1% as add-on therapy in the management of chronic irritant hand eczema: a Double-Blind study. CCID. 2020;13:241–251.
[82] Zhao Y, Jones SA, Brown MB. Dynamic foams in topical drug delivery. J Pharm Pharmacol. 2010;62(6):678–684.
[83] Jing X, Mi H-Y, Peng J, et al . Electrospun aligned poly(propylene carbonate) microfibers with chitosan nanofibers as tissue engineering scaffolds. Carbohydr Polym. 2015;117:941–949.
[84] Serra MB, Barroso WA, Silva NNd, et al. From inflammation to current and alternative therapies involved in wound healing. Int J Inflammation. 2017;2017:1–17.
[85] Wilczynska A, Bushell M. The complexity of miRNA-mediated repression. Cell Death Differ. 2015;22(1):22–33.
[86] Park H, Huang X, Lu C, et al. MicroRNA-146a and microRNA-146b regulate human dendritic cell apoptosis and cytokine production by targeting TRAF6 and IRAK1 proteins. J Biol Chem. 2015;290(5):2831–2841.
[87] Pfalzgraff A, Heinbockel L, Su Q, et al. Synthetic antimicrobial and LPS-neutralising peptides suppress inflammatory and immune responses in skin cells and promote keratinocyte migration. Sci Rep. 2016;6(1):31577.
[88] Gomes A, Teixeira C, Ferraz R, et al. Wound-healing peptides for treatment of chronic diabetic foot ulcers and other infected skin injuries. Molecules. 2017;22(10):1743.
[89] Huebener P, Schwabe RF. Regulation of wound healing and organ fibrosis by toll-like receptors. Biochim Biophys Acta (BBA)-Mol Basis Disease. 2013;1832(7):1005–1017.