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Review

Microbial Natural Products with Wound-Healing Properties

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Abstract: Wound healing continues to pose a challenge in clinical settings. Moreover, wound management must be performed properly and efficiently. Acute wound healing involves multiple cell divisions, a new extracellular matrix, and the process of formation, such as growth factors and cytokines, which are released at the site of the wound to regulate the process. Any changes that disrupt the healing process could cause tissue damage and prolong the healing process. Various factors, such as microbial infection, oxidation, and inflammation, can delay wound healing. In order to counter these problems, utilizing natural products with wound-healing effects has been reported to promote this process. Several natural products have been associated with wound healing, most of which are from medicinal plants. However, secondary microbial metabolites have not been extensively studied for their wound-healing properties. Further, investigations on the wound-healing control of natural microbial products are required due to a lack of studies. This review discussed the in vivo and in vitro research on the wound healing activities of natural microbial products, which may assist in the development of better wound treatments in the future.

Keywords: natural products; microbial-derived compounds; wound-healing

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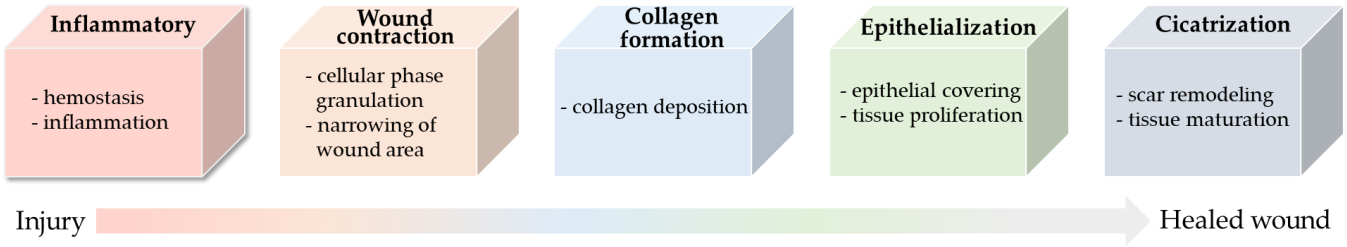
1. Introduction

The skin can be broken or opened by wounds caused by chemical, thermal, or physical injuries [1,2]. The skin is an organ that covers the external surface of the body, and it protects the bones, muscles, internal organs, and ligaments below it with multiple layers of ectodermal tissues. The skin also protects against heat, injury, light, and microbes [3–5]. Several regulatory molecules and cells must work together in order for wound re-epithelialization to occur. Within the skin layers, embedded cellular and molecular substances initiate healing at the designated phases when the cutaneous layer is damaged [6,7].

Despite a systematic process, wound healing in the human body is one of the most convoluted biological actions because the following phases overlap: inflammation, the cellular phase (granulation), contraction of the wound area (wound contraction), collagen deposition (collagen formation), epithelialization (epithelialization), and remodeling of scars (cicatrization) (Scheme 1) [3,6]. Upon successful completion of all these events, the disruption of the anatomical and the skin's functional state is restored [3]. There are several factors that can interfere with these healing processes, resulting in impaired wound healing. In the case of impaired healing, such as delayed acute and chronic wounds, the healing process generally has not progressed through the normal healing stages. The majority of chronic wounds are caused by ulcers associated with ischemia, venous causes or infection, and diabetes mellitus [2].

A natural product with medicinal properties, which contribute to alleviating these factors, can facilitate the wound-healing process and be developed as a future drug. Over the last few years, numerous research has investigated the wound-healing properties of natural products that contain antioxidant, anti-inflammatory, collagen promotion, and antibacterial properties [5]. Various phytochemicals, including alkaloids, tannins, flavonoids, terpenoids, phenolic, essential oils, and saponin compounds, may contribute to the medicinal effects. Natural products, including phytochemicals, play an important role in wound healing due

to these properties [3,7,8]. Among natural wound-healing materials, hyaluronic acid has been used in the preparation of wound bandages due to its collagen deposition enhancement, epithelialization, and wound vascularization. At present, there are many wound dressings that contain hyaluronic acid available on the market, such as Hyalo Regen from Fidia Pharma, USA, NJ, as well as Hyalofill®and Hyalosafe®from Anika Therapeutics, Bedford, MA [9].



Scheme 1. Various stages of wound healing.

Recently, natural microbial products have been reported to be an important source of drug discovery [10,11] due to their diverse chemical scaffolds [12]. However, the discovery of natural microbial products possessing wound-healing properties is still not widely investigated. The objective of this review is to highlight the use of selected microbial natural products in promoting wound-healing processes.

2. Biosurfactant

The ability of biosurfactants to interact with modifying surfaces makes them surface-active compounds (SACs). In nature and biotechnology, these biomolecules serve different functions due to their physiological roles and physicochemical properties due to their amphiphilic nature and their production by different microorganisms. The benefits of SACs over synthetic surfactants include low toxicity, increased biodegradability, low critical micelle concentrations, and environmental acceptability [13–15].

In addition, these compounds exhibit antifungal [16], antibacterial [17], antiviral [18], and antitumor [19] properties. Moreover, their antiadhesive activity and antibiofilm properties contribute to the inhibition of adhesion and colonization by pathogenic microorganisms and biofilm removal [13,20]. In chronic wounds, biofilms contribute to chronic wounds and infection, thereby causing a delay in the healing process. The most commonly found pathogens in chronic wounds are *Pseudomonas aeruginosa* and *Staphylococcus aureus*. It is difficult to identify biofilms embedded in deeper layers, such as *P. aeruginosa* biofilms, with wound smear cultures. Further, antibiotic resistance within the biofilms is a critical problem in chronic wound management [21–23]. Due to these reasons, the scientific community and physicians consider wound treatment and biofilm prevention as major priorities in the healing process. As a result, SACs have recently emerged as promising wound-healing agents that cause minimal irritation and are highly compatible with human skin [13,20]. Moreover, these bioproducts speed up the re-epithelialization process and the deposition of collagen, resulting in faster wound healing [24,25].

Surfactin A (**1**, Figure 1) isolated from *Bacillus subtilis* was reported to promote wound healing and the inhibition effects of scars. Amid the healing process, **1** upregulated expression of hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor. Moreover, it accelerated keratinocyte migration via the mitogen-activated protein kinase and factor nuclear-κB (NF-κB) signaling pathways, followed by the regulation of pro-inflammatory cytokine secretion and macrophage phenotypic exchange. In addition, **1** could heal the wound due to its antioxidant properties, with an IC_{50} = 0.55 mg/mL [25,26]. It also prevented scar tissue formation by inhibiting the expression of α-smooth muscle actin (α-SMA) and transforming growth factor (TGF-β).

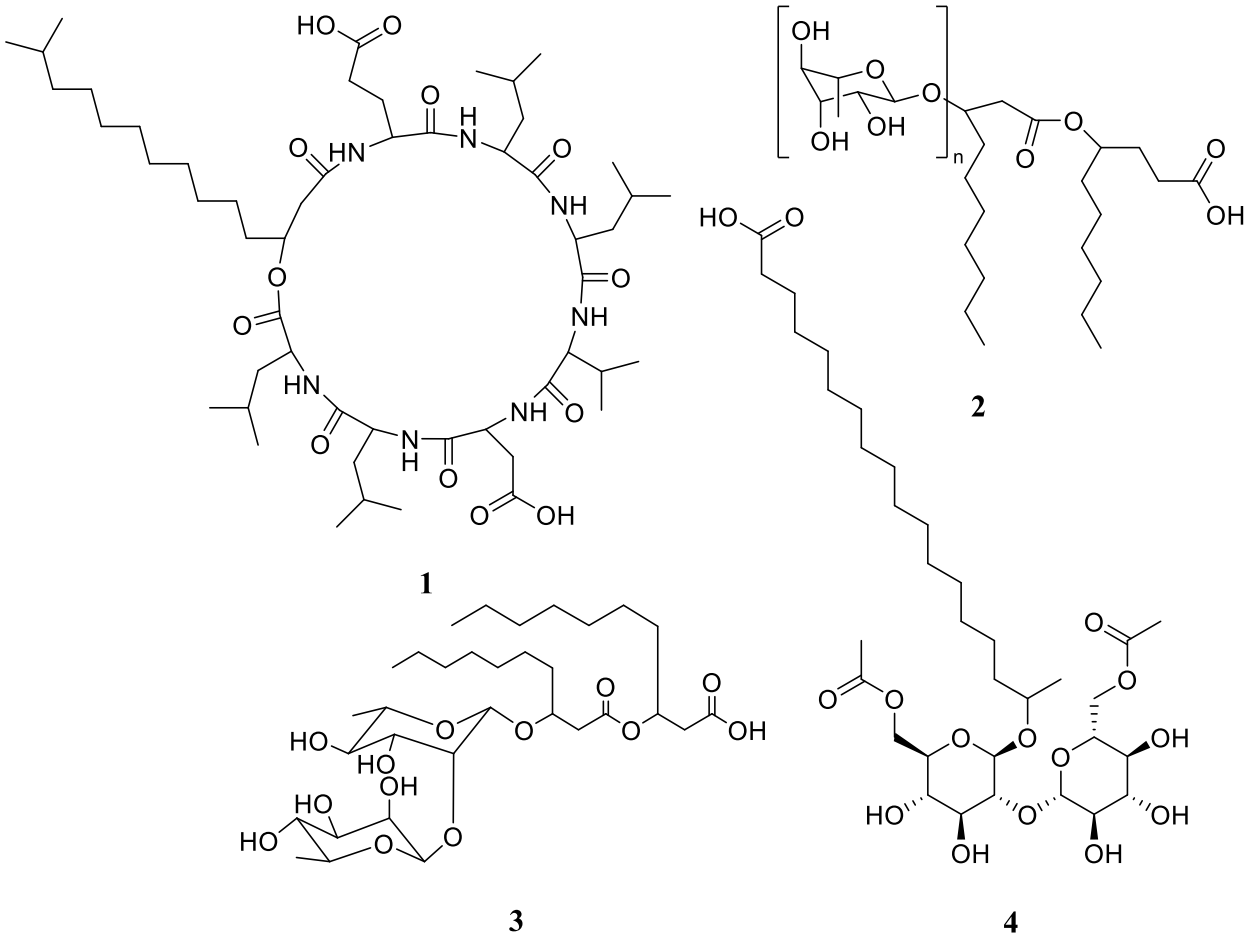


Figure 1. Chemical structures of surfactin A (**1**), BS glycolipid (**2**), rhamnolipid (**3**), and sophorolipid (**4**).

An in vitro study of a biosurfactant (BS) of a glycolipid nature (**2**, Figure 1), isolated from *Bacillus licheniformis* SV1, exhibited adequate cytocompatibility and increased 3T3/NIH fibroblast proliferation. An approach using a BS ointment in vivo stimulated re-epithelialization, fibroblast proliferation, and the faster deposition of collagen in skin excision wounds in rats, thereby demonstrating its potential to improve wound healing through transdermal delivery [27].

In a previous study, mice were treated with an ointment containing rhamnolipid (**3**, Figure 1) after creating severe wounds on their backs. The results of histopathological studies showed that **3** improved wound closure and collagenases, and it reduced inflammation by reducing the level of TNF-α without causing any negative skin reactions. There is evidence that dirhamnolipid therapy can alleviate scarring on the skin, as it has shown effects in rabbit ear hypertrophic scar models, with a depletion in α-SMA expression, type I collagen fibers, and scar elevation index scores [28].

By substituting human skin with an in vitro model of human dermal fibroblasts, a cell culture model was utilized to demonstrate the wound-healing capacity of sophorolipid (**4**, Figure 1), revealing that **4** affected the human skin fibroblast expression of elastase inhibition collagen I mRNA, with IC_{50} = 38.5 μg/mL. Additionally, an in vitro wound-healing evaluation in the human colorectal adenocarcinoma (HT-29) cell line showed a significant increase in collagenase-1 expression in HT-29 colorectal adenocarcinoma cells after treatment for 48 h with **4** [29,30].

3. Flavonoids

The flavonoid class of compounds possesses various biological functions, making them important sources of new pharmaceuticals, including those for treating skin wounds. The structure–activity relationship is one of the main factors that contributes to the pharmaceutical properties of flavonoids [31–33]. Their anti-inflammatory [34], antibacterial [35], antioxidant [36], and antifibrotic [37] properties depend largely on the presence of hydroxyl groups due to high hydroxylation.

It has already been demonstrated that flavonoids exhibit significant pharmacological activity, such as increasing epithelialization rates, modulating inflammatory cytokinases, reducing mononuclear cells in the proliferative phase, accelerating wound contraction rates, and promoting vasculogenesis and angiogenesis. Therefore, there is potential for flavonoids to be used as a treatment for various chronic diseases that lead to cutaneous lesions, including diabetes mellitus, which causes many amputations worldwide [38–41].

Baicalin (**5**, Figure 2) is a flavone glycoside with anti-inflammatory, antiviral, and photoprotective properties [42]. Compound **5** blocks the pathological keratinocyte changes in psoriatic patients [43]. An antioxidant and anti-inflammatory effect may be responsible for the wound-healing properties of the baicalin nanohydrogel preparation. Moreover, **5** inhibits nitric oxide and tumor necrosis factor-α (TNF-α), which are both important elements in the inflammatory process [44]. Finally, **5** was found to exist in the endophytic fungus *Spiropes* sp. and played a major role in the pharmacological action of *Scutellaria baicalensis* [42,45].

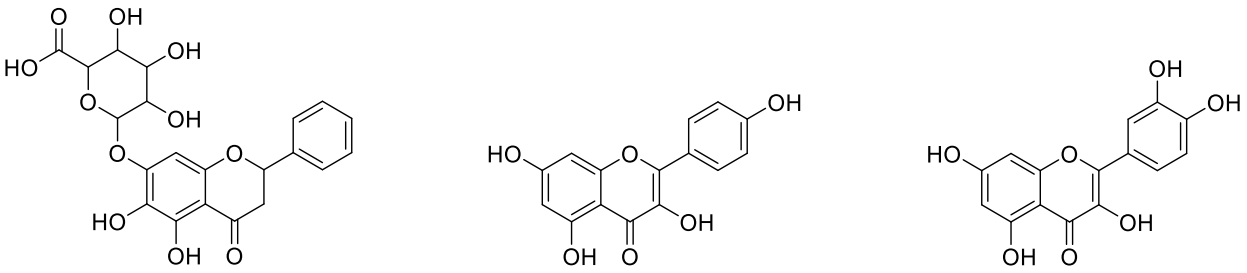


Figure 2. Chemical structures of baicalin (**5**), kaempferol (**6**), and quercetin (**7**).

Kaempferol (**6**, Figure 2) is known to inhibit cancer growth; reduce inflammation; promote antioxidant activity; and protect the heart, liver, and brain [46]. With a 1% *w*/*w* ointment concentration, **6** exhibited wound-healing activity in diabetic and non-diabetic rats. This wound-healing activity was studied utilizing incision and excision wound models [47]. According to both models, kaempferol showed crucial wound-healing activity, as indicated by the increase in the granulation tissue weight and hydroxyproline content in the incision wound model, as well as a reduction in the wound area, faster epithelialization, increased dry weight of the tissue, and increased hydroxyproline content in the excision wound model [48]. Moreover, **6** was found in many edible vegetables and the extract of the endophytic fungi *Fusarium chlamydosporum* from *Tylophora indica* [49–51].

Bioflavonoids such as quercetin (**7**, Figure 2) are known for their anti-atherosclerotic, anti-hypercholesterolemic, anti-hypertensive, anti-inflammatory, and anti-obesity properties [52]. Preclinical research has shown **7** to possess wound-healing properties [53,54]. A study by Jangde et al. evaluated quercetin's wound-healing properties in vitro and in vivo. The results indicated that wound healing was significantly accelerated, and the wound termination time significantly decreased compared to the regular dosage forms. These results suggested that connectivity tissue disorders can be treated effectively as wound-healing approaches [54]. Quercetin was found in more than 20 plants [42]. Moreover, in terms of obtaining quercetin from bacteria, it was isolated for the first time from a cyanobacterium, *Anabaena aequalis* Borge [55].

4. Quinones

Biochemical pigments called quinones are established in several living organisms, including fungi, bacteria, a few animals, and higher plants. There are many forms of quinones in nature, such as naphthoquinones, benzoquinones, polycyclic quinones, and anthraquinones. Quinones are formed when polynuclear hydrocarbons, aromatic amines, and polyhydric phenols are oxidized [56]. Quinones and their derivatives are known to be potential antioxidants. In particular, hydroxyquinones are powerful antioxidants due to their dihydroxy groups located in the ortho position. Several hydroxyquinones, including pseudopurpurin, purpurin, and alizarin, are highly effective as antioxidants. In contrast, emodin, aloe-emodin, chrysophanol, and rhein have shown lower efficacy due to the absence of the ortho-dihydroxyl groups. This indicates that the ortho-dihydroxy structure of quinone and its derivatives significantly influences its radical scavenging properties [57].

A new antibiotic, MT81 (**8**, Figure 3), was isolated and purified from *Penicillium nigricans* culture media. It was found that **8** was a polyhydroxy anthraquinone, which exhibited antibacterial properties, along with an antiprotozoal effect toward *Leishmania donovani* promastigotes in vitro. Moreover, **8** was investigated for its wound-healing effect in mice. The result exhibited the healing effects of an **8** ointment on mice infected with pathogenic organisms, and it was comparable to the positive control, nitrofurazone. This indicates that the antimicrobial effect of **8** helps to heal infected wounds by inhibiting microorganisms [58].

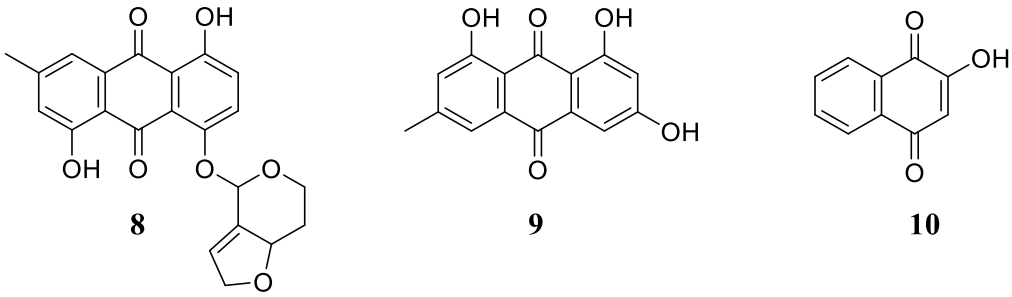


Figure 3. Chemical structures of MT81 (**8**), emodin (**9**), and hennotanic acid (**10**).

Emodin (**9**, Figure 3) is a natural anthraquinone derivative found in a wide variety of higher plants. Emodin obtained from microorganisms was first described as frangula-emodin, which was isolated from the fungus *Dermocybe sanguinea* Wulf [59–61]. In addition, **9** was identified as one of the pigmented products in the culture extracts of *Penicillium brunneum* Udagawa, *Cladosporium fulvum* Cooke, *Penicillium avellaneum*, *Penicilliopsis clavariaeformis*, *Penicillium islandicum* Sopp, *Aspergillus wentii* Wehmer, *Aspergillus ochraceus* Wilhelm, and *Aspergillus cristatus* [62–69]. Neuroprotective, anti-inflammatory, anticancer, antibacterial, anti-osteoporotic, hepatoprotective, antiviral, anti-allergic, and immunosuppressive properties are known to be associated with **9** [70]. Furthermore, the wound-healing activity of **9** using the excisional wound model in rats has been reported at dose levels of 100, 200, and 400 µg/mL [71].

Hennotannic acid (**10**, Figure 3), also known as lawsone, is an orange-red dye extracted from the leaves of *Lawsonia inermis* L., often known as the henna tree. However, Sarang et al. reported the production of 10 from an endophytic fungus, *Gibberella moniliformis*, isolated from the leaf tissues of *Lawsonia inermis* [72]. Moreover, **10** exhibited antibacterial, antifungal, antiparasitic, antitumor, and antiviral properties [73]. By using an excision and incision model, Mandawgade and Patil investigated the wound-healing effects of **10** at dose levels of 50 mg/kg (per oral) and 0.1 mg/kg (topical/ointment). Based on the result, **10** exhibited significant wound-healing activity in both models [74]. Another study on **10** also demonstrated crucial wound-healing activity in rodents [75].

5. Phenolic Acids

Polyphenol is usually found in plants and marine organisms. Since polyphenols possess antimicrobial, regenerative, and antioxidant properties, they have significant potential for application in wound treatment [76–78]. Besides their antimicrobial and antioxidant activity, polyphenols are also considered to be highly bioactive agents in wound dressings for acute wound treatment, thereby playing an important role in wound healing [76,79].

Chlorogenic acid (**11**, Figure 4) is an ester of caffeic acid with phenolic acid (quinic acid), established in twenty medicinal plants and twenty-nine fungal taxa, including *Phomopsis*, *Colleterotrichum*, *Phoma*, *Alternaria*, and *Xylariales* [42,45]. Moreover, **11** showed significant wound-healing activity in both in vivo and in vitro investigations [80,81]. A recent study demonstrated that **11** promotes wound closure and capillary tube formation, as well as enhanced wound closure with keratinocytes in vitro [80]. In addition, **11** has been shown to enhance collagen synthesis by upregulating TNF-α and TGF-β during wound healing. It may promote wound healing in excision wounds due to its antioxidative properties [81].

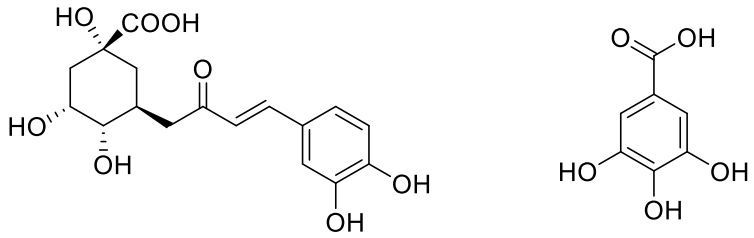


Figure 4. Chemical structures of chlorogenic acid (**11**) and gallic acid (**12**).

Gallic acid (**12**, Figure 4) is a phenolic compound that can be found in plants, as well as nineteen endophytic fungal taxa [45]; **12** exhibits strong anti-inflammatory and antioxidant properties. During in vitro experiments, **12** accelerated keratinocyte and fibroblast migration and wound healing [82]. In addition, **12** enhanced the expression of TGF-β and inhibited the nuclear factor κB (NF-κB), along with the proliferation and maturation phase of wound healing [83].

6. Peptides

Several bioactive peptides have been explored for their prospective therapeutic use in wound healing [84]. Traditional wound-healing therapies, including cytokines, growth factors, immunomodulatory factors, and plant-derived chemicals, are particularly difficult to translate into clinical practice for acute wound healing [85]. Further, research on bioactive peptides with excessive specificity, stability, and activity has attracted considerable attention compared to drugs with high costs, low activity, and delivery and safety problems [84,86,87].

Acremonamide (**13**, Figure 5), a new cyclic depsipeptide obtained from *Acremonium* sp., was isolated in an ongoing effort to discover new marine-derived natural products with wound-healing effects [88]. It is known that species of the genus *Acremonium* produce various secondary metabolites, such as hydroquinones, diterpenes, isocoumarins, sesquiterpenes, peptides, benzophenones, and butanolides [89]. These fungal strains also produce cyclic depsipeptides, an interesting bioactive natural product [89–92]. In in vivo experiments using the human wound healing RT^2 Profiler PCR array, adjustments in the wound-healing genes' expression were screened to determine the mechanisms behind the wound-healing properties of **13**. The result demonstrated, for the first time, that **13** increased keratinocyte and fibroblast motility, as well as COL1A2 and ACTC1 expression, thereby enhancing the wound-healing process [88].

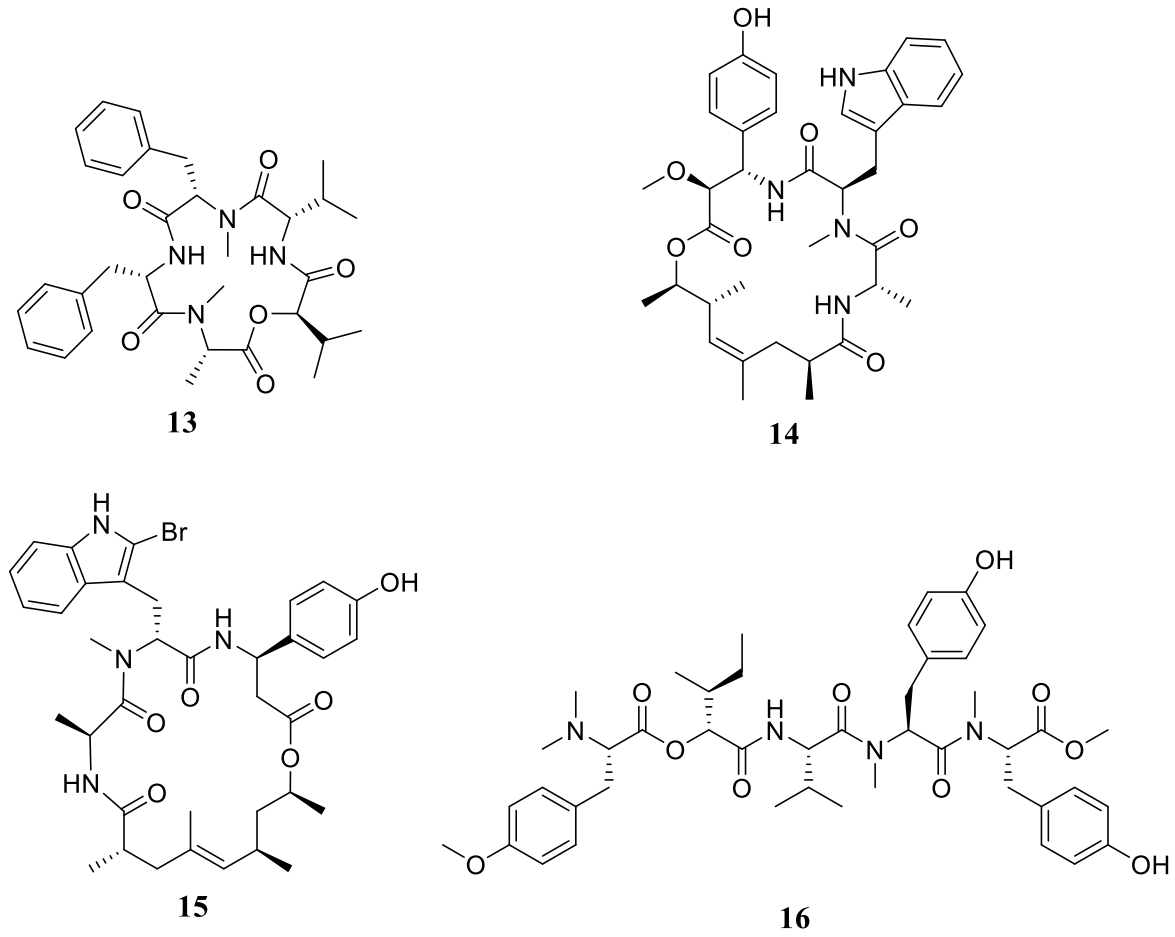


Figure 5. Chemical structures of acremonamide (**13**), chondramide A (**14**), jasplakinolide (**15**), and apratyramide (**16**).

Chondramide A (**14**, Figure 5) and its analogs isolated from a terrestrial myxobacterium, *Chondramyces crocatus*, were examined for the growth-inhibiting activity of actin cytoskeletons [93]. The actin cytoskeleton plays a significant role in wound healing—it allows actomyosin to contract, recruits repair machinery, and migrates cells [94]. By using highly purified recombinant actin from *T. gondii*, in vitro polymerization assays confirmed that both synthetic and natural products target the actin cytoskeleton, with EC_{50} values ranging from 0.3 to 1.3 μM. The results indicate that the chondramide treatment can prevent parasitic invasion and generate faster results than standard therapeutic agents such as pyrimethamine [95].

Other studies reported the wound-healing activity of jasplakinolide (**15**, Figure 5) and apratyramide (**16**, Figure 5) [96,97]. By binding to F-actin, **15** stabilized the actin filaments in vivo, leading to actin lumps and polynucleation, which are important in wound healing [96]. Moreover, **16**, a natural product isolated from a cyanobacterium, has been described to exert wound-healing effects by inducing vascular endothelial growth factor A [97].

7. Triterpenoids

Terpenoids are plant-derived phytochemicals with a large variety of chemical structures derived from isoprene and usually have polycyclic structures. They are classified into monoterpenes, diterpenes, triterpenes, tetraterpenes, sesquiterpenes, and hemiterpenes, depending on the number of isoprene units in their structures. Triterpenes either have a tetracyclic or pentacyclic structure [98–100]. Among pentacyclic triterpenes, oleanane, lupane, and ursane derivatives exhibit anti-inflammatory, anticancer, antioxidant, antivi-

ral, and cardioprotective activities. In contrast, tetracyclic triterpenes have mostly been studied for their cytotoxic and anticancer biological properties [101–104]. In recent years, systematic studies have examined the efficacy of triterpenes as wound healers. Based on the results of these studies, these phytocompounds have been displayed to promote wound healing by accelerating epithelialization and collagen formation and deposition, regardless of the wound type. Furthermore, their integration into various medicinal formulations is an effective option for wound management through their long-term delivery of active compounds. In conclusion, triterpenoids have been identified as an emerging class of wound care therapies [98,105].

Asiaticoside (**17**, Figure 6) is a triterpenoid saponin, which is found in *Centella asiatica* (L.), as well as in an endophytic fungus, *Colletotrichum gloeosporioides*, obtained from *Centella asiatica* (L.) [106,107]. Based on the ability of **17** to induce the development of granulation tissue and collagenase-induced epithelialization in rabbits, it was proven that **17** exhibits wound-healing properties [108]. In addition, **17** also induces type I collagen synthesis in human dermal fibroblast cells [109].

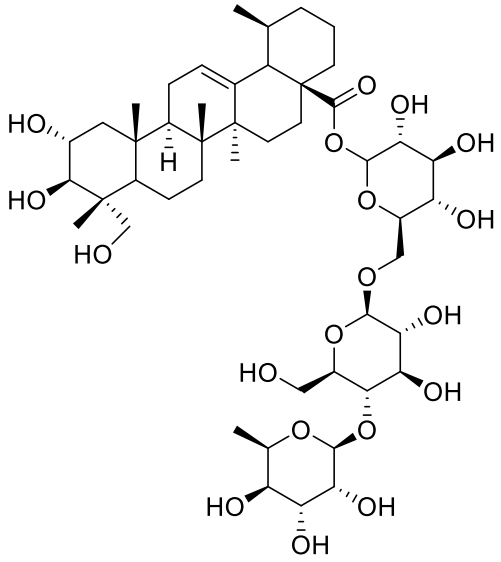


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Figure 6. Chemical structures of asiaticoside (**17**).

8. Others

In addition to their skin-rejuvenating properties, probiotics have also been described to ease atopic eczema, atopic dermatitis, wound healing, and the innate immunity of the skin. It has been demonstrated that non-viable cultures of lactic acid bacteria can exert antimicrobial and immunomodulatory effects. Several studies have shown that lactic acid bacteria compounds, such as cell wall fragments and metabolites, can enhance the skin barrier function and elicit particular immune responses [110–112].

Lipoteichoic acid (**18**, Figure 7) is an immune-stimulating systemic component in the cell walls of both pathogenic and non-pathogenic Gram-positive bacteria. It plays a crucial role in the growth and physiology of bacteria [113]. Previous research has revealed that **18** could distribute as a crucial pathogen-associated molecular motif, resulting in nitric oxide (NO) production and the stimulation of NF-kB, along with the construction of pro-inflammatory mediators and cytokines [114,115]. In addition, lipoteichoic acid from beneficial probiotics has been reported to induce tolerance by protecting against the production of the pro-inflammatory cytokines related to TNF-α sepsis and increasing the resistance to microbial infection among dermal cells [110]. Furthermore, upon the topical application of **18**, it was found to promote skin protection against microbial infections by

triggering toll-like receptors and displayed skin-wound-healing capabilities by activating human β-defensin mechanisms, in addition to its antimicrobial properties [116,117].

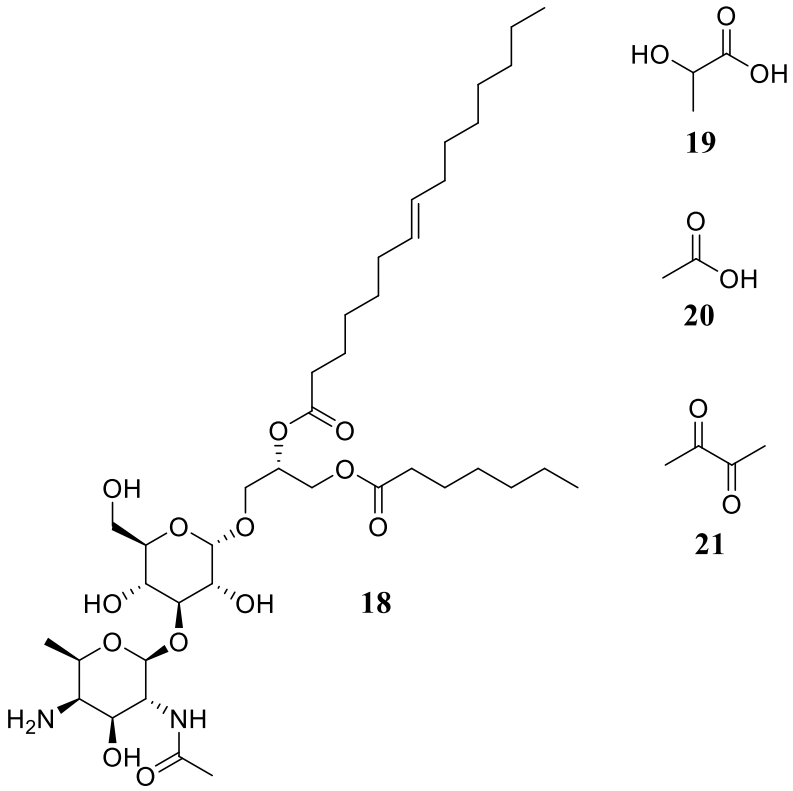

Figure 7. Chemical structures of lipoteichoic acid (**18**), lactic acid (**19**), acetic acid (**20**), and diacetyl (**21**).

In chemical synthesis or microbial fermentation, lactic acid (**19**, Figure 7) is constructed as one of the α-hydroxy acids, which appear in the alpha position of the acid and comprise one hydroxyl group attached to the alpha position [118,119]. The use of lactic acid has been widespread for many years in skin-care products and cosmetic regimens, and it is known to show antibacterial properties that are effective against most pathogenic microbes [120,121]. In addition to its antimicrobial properties, **19** is considered a preventative remedy for acne vulgaris [122]. Further, because of its ability to improve the function of the stratum corneum barrier, **19** has shown potential for numerous skin applications, and it improved ceramide production by keratinocytes [123].

In heterofermentative lactic acid bacteria, acetic acid (**20**, Figure 7) can be produced from the hexose monophosphate or pentose pathway [124]. In particular, **20** has been used in treating microbial infections and superficial infections, as well as burns, on various occasions [125]. It has been shown to display antibacterial activity against many microbes, including *P. aeruginosa* and *S. aureus* [110]. When various antibiotic-resistant strains cause inflammation, and therapeutic options are inadequate, acetic acid has been recommended as the greatest treatment option [125].

Diacetyl (**21**, Figure 7), also known as 2,3-butanedione, can be produced by certain strains of *Streptococcus*, *Leuconostoc*, *Pediococcus*, and *Lactobacillus*, and **21** has shown possible antimicrobial dermal properties, with the highest sensitivity against Gram-negative bacteria and fungi rather than Gram-positive bacteria [121]. In addition, at a very low concentration of 100 ppm, **21** has been established to exert bactericidal activity against *S. aureus* and *Escherichia coli*. Although the antimicrobial activity of **21** has been proven thoroughly, there is little research on its topical function, and extensive investigation is required to determine how it affects the skin and other tissues [41,126–128].

9. Conclusions

This review highlighted several microbial natural products with antibacterial, anti-inflammatory, antioxidant, and actin cytoskeleton growth-inhibitory activities that are important in promoting wound-healing activities. Successful wound-healing treatment is crucial for the better quality of life of patients. Identifying the active compounds responsible for the wound-healing properties and their mechanism is currently challenging. There is a high demand for wound-healing agents; therefore, the upscaling of their production needs to be investigated. Several reviews have reported the wound-healing properties of plants and bioactive compounds derived from plants [3,129–132]. In addition, the antioxidant, antimicrobial, anticancer, and anti-inflammatory properties of microbial compounds have also been widely reviewed [11,133–136]. However, research on the wound-healing properties of microbial compounds is still lacking; therefore, further investigations on the wound-healing control of natural microbial products are required. This information may help to develop better treatments for wound healing.

Based on the reported results, compounds **1**, **12**, **13**, **14**, **15**, **16**, and **19** exert their wound-healing properties by accelerating keratinocyte migration to enhance wound closure. Moreover, compounds **8**, **9**, **10**, **18**, **19**, **20**, and **21** show antibacterial activity; the bioactive minimum inhibitory concentration (MIC) values of **9** were 28.9 µm for *Bacillus subtilis* and 14.4 µm for *Staphylococcus aureus*. However, **9** was not active against two Gram-negative bacteria (*Klebsiella pneumoniae* and *Escherichia coli*) at the highest concentration (1851.9 µm) tested [137]. Similarly, **9** has been reported to exhibit antimycobacterial and broad-spectrum antibacterial activity, particularly against *M. tuberculosis* (lowest MIC = 0.9 µm) and Gram-positive bacteria (lowest MIC < 14.8 µm) [69]. A broad range of MIC values of **10** was reported for *Fusarium oxysporum* (574 mmol/L), *Aspergillus niger* (861 mmol/L), *A. flavus* (287 mmol/L), and *Candida albicans* (2.933 mmol/L) [138]. In addition, compounds **1** and **3** prevented scar tissue formation, with a reduction in α-SMA expression. Compounds **3**, **5**, **11,** and **18** reduced inflammation by decreasing the level of TNF-α, while compounds **1**, **11**, and **12** led to enhanced TGF-β expression. In the case of compound 11, it has been shown to enhance collagen synthesis by upregulating TNF-α and TGF-β during wound healing. Furthermore, compound **2** from *Bacillus licheniformis* increased 3T3/NIH fibroblast proliferation, compound **4** showed a significant increase in collagenase-1 expression in HT-29 colorectal adenocarcinoma cells, and compounds **6** and **7** are well known for their anti-inflammatory activity, which can significantly accelerate the increase in the granulation tissue weight. These results prove that all compounds can be used effectively as wound-healing treatments.

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