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# Stingless Bee Honey, the Natural Wound Healer: A Review

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**Keywords**
Antioxidant · Anti-inflammation · Moisturizing properties · Stingless bee honey · Wound healing

**Abstract**
***Background:*** The stingless bee is a natural type of bee that exists in almost every continent. The honey produced by this bee has been widely used across time and space. The distinctive feature of this honey is that it is stored naturally in the pot (cerumen), thus contributing to its beneficial properties, especially in the wound healing process. ***Methods:*** In this article, several studies on stingless bee honey that pointed out the numerous therapeutic profiles of this honey in terms of its antioxidant, antimicrobial, anti-inflammatory, as well as moisturizing properties are reviewed. All of these therapeutic properties are related to wound healing properties. ***Results:*** Antioxidant in stingless bee honey could break the chain of free radicals that cause a detrimental effect to the wounded area. Furthermore, the antimicrobial properties of stingless bee honey could overcome the bacterial contamination and thus improve the healing rate. Moreover, the anti-inflammatory attribute in this honey could protect the tissue from highly toxic inflammatory mediators. The moisturizing properties of the honey could improve wound healing by promoting angiogenesis and oxygen circulation. ***Conclusion:*** The application of honey to the wound has been widely used since ancient times. As a result, it is essential to understand the pharmacological mechanism of the honey towards the physiology of the wounded skin in order to optimize the healing rate in the future.



## Introduction

*Stingless Bees*

There are approximately 500 species within the stingless bee genus, with the majority of these species being located in Latin America, the mainland of Australia, Africa, and Eastern and Southern Asia [1]. Stingless bees can be classified into 2 genera, namely, the *Melipona* and the *Trigona.* The *Melipona* genus is numerically large, even larger than that of the common honey bee (*Apis mellifera* Linnaeus) [2]. Stingless bees also play an important role in the ecology, economy, and culture. They act as the main pollinators for many wild and cultivated tropical plants [3]. Their products such as honey, pollen, and cerumen have been used as a source of income for generations. In addition, stingless bees are attached to the cul-



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**Fig. 1.** Stingless bee honey.

ture of indigenous people, especially the Mayan, in rural areas of America [4].

According to a research officer in the Malaysian Agricultural Research and Development Institute (MARDI), the specialty of the stingless bees is the ability to pollinate small-sized flowers due to their diminutive figure which cannot be achieved by the relatively big honey bee. Besides, the stingless bees are not choosey in building a colony hive. As a result, it is easier to build an artificial hive to manipulate the colony and increase the honey production. As the name suggests, the stingless bees do not sting; thus, it is easier to extract the honey, pollen, and propolis frequently. Furthermore, stingless bees are easier to handle compared to honey bees that are often lost, always abandon their hive, and are vulnerable to disease [5]. Likewise, stingless bee honey is unique as it originates from the rich vegetation in native environments. It has a distinctive sweetness mixed with a sour and acidic taste. The appearance of stingless bee honey is displayed in Figure 1. In contrast to the stingless bee population, the distribution of this honey is lower compared to that of the common honeybee. This is due to the limited knowledge about this honey, which has resulted in it being less popular in terms of its industrial production, shelf life, and quality standard [6]. Therefore, stingless bee honey should be further explored due to its mass production and convenience of management.

*Cerumen and Honey Production in the Pot*

Another beneficial product from the stingless bee is "propolis," geopropolis, or cerumen, as it is exclusively known, in order to avoid confusion with *A. mellifera* propolis. Propolis is a natural resinous and waxy product that is produced by mixing beeswax and resins collected from a variety of plant parts by *A. mellifera* bees [7]. On the other hand, cerumen is a mixture that is similar to propolis but with the addition of the mandibular secretion of the stingless bee during its construction [8, 9]. The functions of these products are slightly different, where the cerumen is used as a storage pot for the honey and to mummify trespassers as well as to ensure that the environment in the hive is sterile, while the propolis is used as an internal layer and for sealing the extra space surrounding the hexagon-shaped nest combs. Consequently, due to the storage of honey in the cerumen pots, the quality of the stingless bee honey is influenced by the infiltration of phytochemicals from the cerumen [10, 11].

In the cerumen pots, the nectars have to go through 3 different transformation processes before turning into honey. The first transformation is a physical change, where a large part of water evaporates from the nectar. Then, a biological transformation takes place, which is mainly a fermentation process by yeast and bacteria. These microorganisms originate from a suitable microenvironment chosen by the bee and play a symbiotic role with the colony [12, 13]. Lastly, a chemical transformation occurs when the worker bees secrete the enzymes from their cephalic glands that are able to hydrolyse the nectar's sucrose into fructose and glucose [12, 14]. Although it is hard to refute that the characteristics of honey vary depending on the bee species, nectar sources, and climate, the noteworthy similarity in stingless bee honey is the water content that is commonly higher than in other types of honey [15, 16]. As a result, the rich water condition invites the microorganism to inhabit and thrive inside the honey. Most of these microorganisms are probiotics with their beneficial enzyme secretion that works along with the enzymes from the stingless bees to enrich and conserve the quality of the honey [12, 17].

*Wound Healing*

Wound healing is an outstanding biological process for the restoration of the integrity of the skin after injury. It can be divided into 4 overlapping phases, which are haemostasis, inflammation, proliferation, and remodelling [18]. Figure 2 summarizes the main phases in the wound healing process. Wounds that fail to progress into the normal stage of healing are recognized as delayed

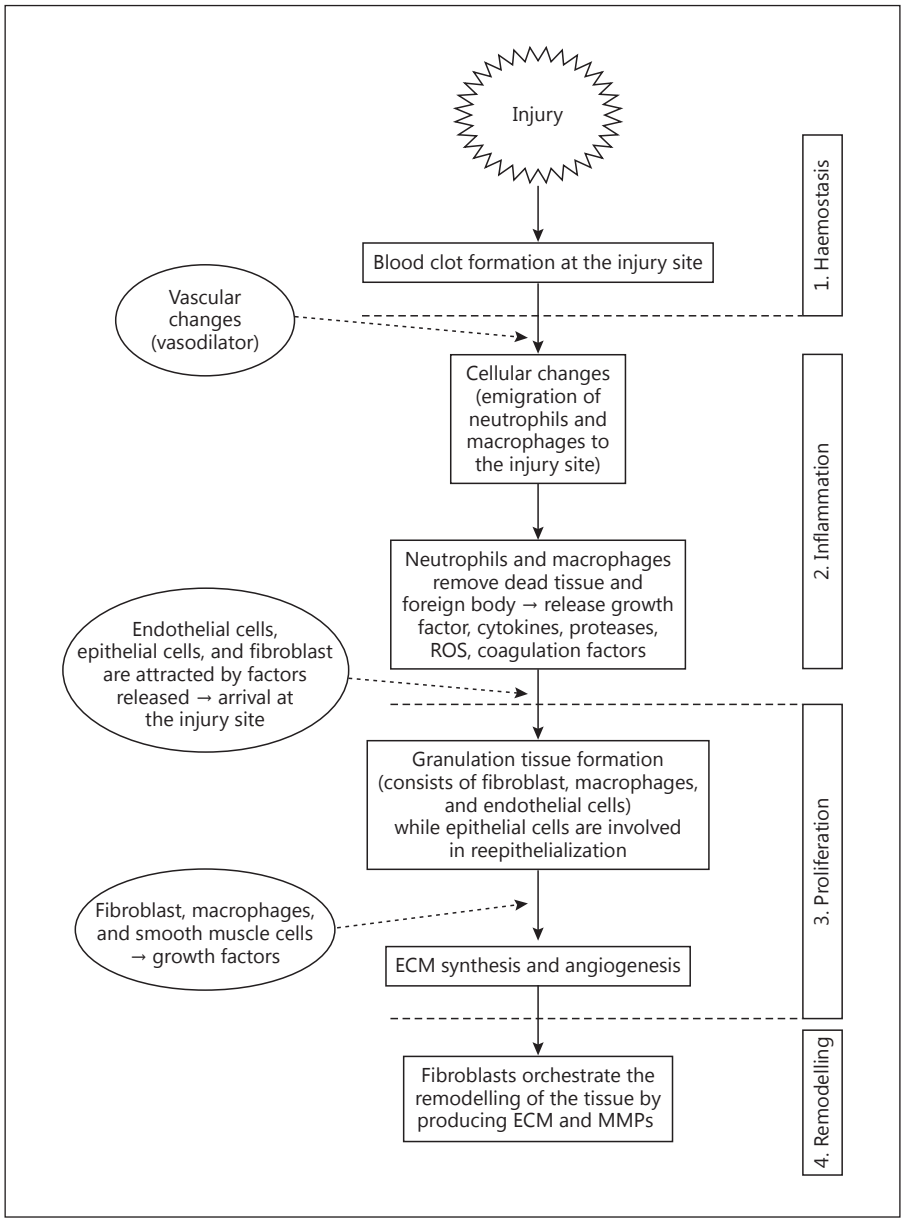


**Fig. 2.** Main phases in the wound healing process. ROS, reactive oxygen species; ECM, extracellular matrix; MMP, matrix metalloproteinase.



acute wounds and chronic wounds. This impaired healing of a wound occurs due to a postponed, incomplete, or uncoordinated healing process. The factors that significantly cause an abnormal progression in wound healing are oxygenation, infection, age and sex hormones, stress, diabetes, obesity, medications, alcoholism, smoking, and nutrition [19].

*Mechanism of Wound Healing by Honey*

As mentioned before, surgeons from the ancient Egyptian era used honey for the treatment of open wounds. However, although they did not understand the mechanism of cellular biology and microbiological theory, they believed in the use of natural antiseptics and antibiotics like honey to dress wounds in order to prevent infection as well as to increase the rate of healing [20]. Honey is blessed with several wound healing properties that make it an ideal active element in formulations for the dressing of wounds. Firstly, since honey is a natural agent, it is aesthetically pleasing. Furthermore, honey is able to keep a wound in a sanitary condition by means of the wound debridement process, thus creating good deodorization

**Table 1.** The components of stingless bee honey that can enhance the wound healing rate

| | Ref. No. |
|---|---|
| Sugars: mainly glucose and fructose | 6 |
| Proteins, vitamins, and minerals | 6 |
| Peroxide component: glucose oxidase for the production of hydrogen peroxide and D-gluconic acid | 44 |
| Non-peroxide components (flavonoids, polyphenols) | 104 |
| High acidity | 15, 105 |
| High water content | 44 |

for the wound [21, 22]. In addition to these properties, honey promotes angiogenic activity, which is important in wound healing mechanisms, and also induces the formation of granulation tissue as well as skin reepithelialization [23, 24]. Several studies have indicated other fascinating bioactivities of honey such as antinociceptive [25, 26], immunomodulatory [27, 28], and nematicidal activities [29, 30]. The main active mechanisms of honey that are involved in the healing of wounds are its antioxidant, antibacterial, and anti-inflammatory properties. All of these properties will be explained in greater detail later in this paper. Table 1 reveals the components of stingless bee honey that may contribute to the enhancement of wound healing.

## Stingless Bee Honey as Antioxidant

### *Effects of Reactive Oxygen Species on Wounds*

Antioxidants are agents that save cells from the harmful effects of reactive oxygen species (ROS). Examples of ROS are singlet oxygen, superoxide, peroxyl, and hydroxyl radicals. These ruthless free radicals originate from endogenous stressors, resulting from natural by-products of cellular metabolism, or exogenous stressors such as UV light, pollutants, drugs, smoke, or radiation [31, 32]. As their name suggests, these reactive molecules provoke the deterioration of membranes, lipids, amino acids, and DNA [33]. The damage to the DNA can lead to the breakdown of collagen, thus disrupting the proliferation stage in the wound healing process.

In the haemostasis stage at the beginning of the wound healing process, vasodilation takes place around the wounded tissue. However, overstimulation of vasodilation caused by inducible nitric oxide synthase (iNOS) may lead to the production of hydrogen peroxide and other ROS [34, 35]. These free radicals can generate oxidative stress and further worsen the condition of the wounded tissue. The accumulation of ROS will not only harm the wounded site but also spread it across other organs in the body. ROS can activate various humoral and cellular mediators to initiate the inflammation process at the distant organs [36, 37].

### *Role of Antioxidants in Enhancing the Wound Healing Process*

Antioxidants act as a saviour to the structure of cells by neutralizing ROS and thus terminating the damaging chain reaction in the body. Antioxidants can be categorized into 2 types, namely, enzymatic and non-enzymatic antioxidants [38, 39]. Enzymatic antioxidants transform a free radical into a stable molecule that is less harmful to the body. These antioxidants can be further classified into several classes, which are ascorbate peroxidases, catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase, and glutathione S-transferase [40–42]. On the other hand, the non-enzymatic antioxidants block and cut the damaging chain reaction caused by ROS or even inhibit the formation of free radicals. Examples of these antioxidants are ascorbic acid, tocopherol, carotenoids, and phenolic compounds [42].

### *Antioxidant Properties of Stingless Bee Honey*

The major therapeutic action of honey in improving the wound healing process comes through its antioxidant activity since it can prevent the detrimental effects on the wounded site caused by oxidative stress [43]. It can be postulated that the antioxidant effects of stingless bee honey can also be applied to the treatment of wounds since its antioxidant content is higher or similar to that of other types of honey. Research on the stingless bee (Meliponini tribe) in Australia indicated that the honey produced contains a higher level of flavonoids than the honey produced by *A. mellifera*. The total antioxidant activity in the *Tetragonula carbonaria* (stingless bee) honey was proven to be higher than that of the European floral honey, while its radical scavenging activity is equal to that of the European floral honey [44]. These findings are supported by

another research study on the *Melipona fasciculate* (another stingless bee species), where the content of polyphenol in this stingless bee honey is the highest in comparison with other South American honey bees [45]. In Malaysia, the researchers from MARDI have revealed that the major free phenolic acid in stingless bee honey consists of protocatechuic acid (PCA) and 4-hydroxyphenylacetic acid [46]. PCA is a strong antioxidant that can improve cell proliferation in the wound healing process [47], whereas 4-hydroxyphenylacetic acid is able to scavenge the reactive oxygen and nitrogen species [48, 49].

As a matter of fact, another product generated from stingless bees, such as cerumen, also has antioxidant properties [50, 51]. In an in vitro study using 5-lipoxygenase (5-LOX) cell-free assays, the polar extract of cerumen has shown the ability to suppress the catabolism of linoleic acid, thus displaying a potent antioxidant effect that can prevent lipid peroxidation and protect the integrity of the cell membranes [11]. In addition, it has been shown that the ethanol extract of cerumen possesses antioxidant properties that reduce the number of ROS and protect human erythrocytes from lipid peroxidation in an antioxidant assay by using a human erythrocyte model [39]. This action is attributed to phenolic compounds, which are important antioxidant components that inhibit haemolysis in erythrocytes [52]. The high antioxidant content in stingless bee honey may provoke interest in the application of this honey in wound healing research.

## Antimicrobial Role of Stingless Bee Honey

### *The Presence of Microorganisms Could Delay the Healing Process*

Microorganisms exist inside all wounds but the majority of them do not infect the wound, and the wound will heal eventually. This situation happens when the host's immune system and the bioburden of the wound are in a state of equilibrium. Bioburden is a condition where an object is contaminated by a number of bacteria [53]. Nevertheless, if the bioburden overcomes this balance, or there is impairment in the wound healing process, the bacteria will proliferate and occupy the host's tissues [54, 55]. The invasion of foreign bodies into a wound could hinder the healing process and may eventually cause the formation of a granuloma or an abscess. If no action is taken, another problem will arise later, where the leftover collagen produced during the prolonged wound healing process will build up keloid scars [56, 57].

As previously mentioned, there are several microorganisms present in the cerumen during honey production. There is some conundrum whether this may impact the healing process when applying honey to the wound. These microorganisms cannot hinder the healing process since most of them have been identified as non-pathogenic which are from the *Bacillus* genus [58, 59] and actinomycete *Streptomyces* [60]. In contrast, several notorious bacteria like *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Clostridium*, and *Coliform species* tend to disturb the healing process [61, 62]. As a consequence, a prolonged and abnormal inflammatory response will occur together with tissue damage and delayed healing. If this situation is prolonged, it may worsen and can lead to systemic illness. Therefore, an intervention should be introduced immediately after the injury as a precautionary measure [53]. A nursing approach to wound healing focuses on preventing pathogenic colonization and eradicating these foreign invaders that are causing the wound healing process to remain at a stagnant phase [63].

### *Antimicrobial Mechanism of Stingless Bee Honey against Infection*

The main point of antimicrobial or antibacterial applications is to prevent or confront infections, especially during the injury period. Stingless bee honey can be used as an antibacterial ingredient in pharmaceutical formulations since it possesses antimicrobial and antiseptic properties. The antimicrobial activity of stingless bee honey was validated by using the Kirby-Bauer antibiotic test, the agar dilution test, broth microdilution, and time-kill viability assays [10, 64, 65]. This study was supported by researchers from Brazil where they found that stingless bee honey has the ability to inhibit the growth of gram-positive and gram-negative bacteria [66]. A unique feature of stingless bee honey is that it is stored in cerumen pots made of wax and propolis. Choudhari et al. [67] found that propolis from India has a compelling antimicrobial property. Similarly, Campos et al. [39] also discovered that propolis samples in Brazil contain broad antimicrobial properties. Therefore, the quality of the honey stored in the propolis-infused cells is influenced by its beneficial content.

The antibacterial effect of honey can be divided into peroxide and non-peroxide components [68]. The peroxide component is based on the activity of hydrogen peroxide. Hydrogen peroxide is regulated by 2 important enzymes in honey, namely, glucose oxidase and catalase. Glucose oxidase induces the production of hydrogen peroxide, while

catalase will destroy the hydrogen peroxide in order to preserve the nutritional content of the honey [69, 70]. Hydrogen peroxide will enhance the production of cytokines for the inflammatory response to kill the bacteria [22, 71]. The non-peroxide components are based on phytochemicals, high sugar content, and the acidity of the honey. The phytochemical components in honey that contribute to the antibacterial effects are flavonoids, phenolic substances, and antibacterial peptides [72]. These components may act by directly inhibiting phagocytosis, thus preventing the superoxide free radicals from damaging the tissues. The last non-peroxide component is the acidity in the honey caused by organic acids. These acids, which make up 0.57% of the honey itself, will suppress the majority of the microorganisms that grow in a pH of between 7.2 and 7.4 [73].

In stingless bee honey, the antibacterial effect is influenced by non-peroxide activity. It is uncommon to observe non-peroxide activity in *A. mellifera* honeys, but Temaru et al. [10] have demonstrated strong non-peroxide activity in a variety of samples of stingless bee honey across the world. An entomological study by Stow et al. [74] has indicated that cuticular antimicrobial compounds that have been secreted from stingless bee honey are responsible for preventing microbial growth. From this finding, Irish et al. [64] have postulated that the non-peroxide activity of stingless bee honey has a connection with the anatomical structure itself of the stingless bee. The non-peroxide activity has a more significant and substantial mechanism in antimicrobial action. Since there is a limitation of its counterpart; the peroxide activity is limited by the presence of catalase in the human body [75]. Therefore, with these coveted antibacterial properties, the application of stingless bee honey on the wounded area may decrease microbial infection and thus rapidly initiate the healing process.

## Anti-Inflammatory Role of Stingless Bee Honey

### *The Inflammation Effect on Wound Healing*

Initially, inflammation is a beneficial biological response of the blood vessels to any potentially dangerous threat. It is a complex protective effort by the body to remove the harmful agent and to immediately instigate the healing process. Macrophages play an important role in this defence mechanism by increasing the production of proinflammatory cytokines, nitric oxide (NO), and prostaglandin E2 ($PGE_2$). All of these inflammation mediators are highly cytotoxic and are involved in the innate response by killing the target cells [76, 77]. In spite of their beneficial effects, the overproduction of these mediators by the activated macrophages may cause tissue damage that can lead to chronic diseases and impaired wound healing [78]. The introduction of an anti-inflammatory agent can control the activated macrophages as well as the production of the inflammatory mediators.

The bad news is that most of the anti-inflammatory pharmaceuticals are not compatible with wound healing. For instance, non-steroidal anti-inflammatory drugs (NSAIDS) are cytotoxic to the tissues, while corticosteroids can inhibit the development of epithelial tissues. In several animal studies, the use of NSAIDS, such as ibuprofen, has a negative impact such as an antiproliferative effect that can cause a numerical decline in fibroblasts, minimized wound contraction, deferred epithelialization, and most importantly, impaired blood vessel formation [19, 79, 80]. As a result, wound care products make little reference to anti-inflammatory action, even though inflammation is still the main cause of delays in the healing of chronic wounds [81]. Inflammation results in fibrosis, which can be a source of hypertrophic scars in cutaneous wounds [82].

### *Anti-Inflammatory Mechanism of Stingless Bee Honey*

In contrast to most anti-inflammatory drugs, honey, which possesses anti-inflammatory properties, results in less scarring from the healing of wounds caused by burns [83]. The anti-inflammatory effect in stingless bee honey is more prominent in the cerumen. In the in vitro study along with the antioxidant test, Massaro et al. [11] reported that the anti-inflammatory mechanism in the cerumen extract in stingless bee products inhibits the 5-LOX enzyme that is responsible for the synthesis of proinflammatory mediators. Similarly, Franchin et al. [84] found that the ethanolic extract of geopropolis (another name for cerumen) significantly reduces the level of proinflammatory cytokines.

The anti-inflammatory property in honey is contributed by phenolic compounds. Several studies have proven that phenolic compounds can inhibit the overproduction of inflammatory mediators such as NO [78], TNF-α [85], and $PGE_2$ [86]. Besides, phenolic compounds act as free radical scavengers that can protect cells from cytotoxicity induced by proinflammatory mediators [87, 88]. Therefore, this will reduce the inflammation period in the wound healing stage and thus enhance the rate of healing. Furthermore, honey can also reduce oedema, thus eventually lowering the microvascular hydrostatic pressure on the wound tissue. Oedema constrains the access to oxygen and nutrients that are essential for tissue growth in wound healing [89]. The anti-inflammatory agents have a similar correlation with antioxidants in terms of dealing

with ROS. Stingless bee honey contains both of these elements, which strengthens its ability to counteract all of the detrimental effects in the inflammation process.

## Stingless Bee Honey as a Natural Moisturizer for Wound Healing Treatment

*Moisturizer as Wound Healing Enhancement*

In an earlier period, the emphasis of wound care management was on covering the wound to preserve dryness around the wound. This was achieved by removing excess exudates and by protecting the wound against infection [90]. However, since 2003, clinicians and researchers have introduced the concept of "tissue, infection/inflammation, moisture, and edge," which goes by the acronym of TIME [91, 92]. This moisture-friendly approach has become the standard in wound care strategy.

A moist surrounding for the wound can prevent secondary infections and create effective oxygen circulation [93]. Besides that, a moist condition can impede desiccation and necrosis, enhance the formation of blood vessels and connective tissues, as well as rehydrate dried out tissues [55, 90]. In fact, the application of a moisturizer to the wound can not only relieve the pain but also reduce the possibility of the appearance of scars later on [94]. On the other hand, it is essential to avoid wound dryness because a dry environment can delay the migration of epidermal cells and slow down autolysis and the proteolytic action for tissue regeneration [95].

*Moisturizing Effect of Stingless Bee Honey*

Like other types of honey, stingless bee honey also has a high moisture content. A physicochemical analysis by Oddo et al. [44] revealed that the moisture content in stingless bee (*T. carbonaria*) honey is relatively higher than that in *A. mellifera* honey. Honey has good moisturizing properties due to the presence of hydroxyl groups. The basic components of honey, which are sugars, proteins, and lactic acid, can act as moisturizers [96]. In addition, the presence of glycerine, propylene glycol, and sorbitol, which are frequently applied as solvents in cosmetics, can enhance the moisturizing properties of the honey [97, 98]. Several studies have suggested that ingredients such as vitamins B, E, and K, together with several good minerals like potassium, phosphorus, and calcium that are present almost in all honeys, contribute to the hydrating attributes of honey [99–101].

The high water content in stingless bee honey prevents dehydration to the wound because of the osmotic effect that gradually delivers fluid to the wound tissue [88, 102]. This will maintain a moist environment around the wound tissue and, as mentioned before, will accelerate the healing, even though a continuous moist condition can develop into a wet condition leading to maceration of the wound [103]. Fortunately, the high osmolarity of the honey can protect the skin from maceration and continuously maintain the moist surrounding [102].

## Conclusion

In conclusion, it is important to take a serious note concerning wound care and healing agents due to the nature of the wound healing process, which is highly complex and highly exposed to external infection. Phytochemical and pharmacological evidence has supported the ethnopharmacological use of stingless bee honey in wound care. All of these beneficial effects could enhance the stingless bee honey profile as a wound healing agent. Historically, the application of honey to the wound has been used since ancient times; therefore, it is essential to understand its pharmacological action towards the physiology of the wounded skin in order to optimize the healing rate. Stingless bee honey has a lot of similarities with other honeys in terms of its bioactive components, but the efficacy of the components has yet to be discovered. As a result, more systematic research is needed to provide comprehensive scientific evidence for its use as well as to clarify any doubt and false acclaim. The potent biological activities of stingless bee honey may create a new therapeutic choice from the current honey and represent an interesting advance in the search for promising applications in the pharmaceutical industry for the wound healing area.

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## Disclosure Statement

There is no conflict of interest.

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