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Review

Applications of Beehive Products for Wound Repair and Skin Care

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Abstract: There is a long and interesting history between honeybees and humans. From the beginning, honey has been utilized not only as a sweetener, but also as an ointment and a drug to treat several diseases. Until the discovery of antibiotics, honey was a very popular product used to protect and preserve skin and promote wound healing, to counteract gastrointestinal pains and disorders of the oral cavity, and for other diseases. After the development of antibiotic resistance, honey again gained interest for its use in wound management. Subsequently, more recently, in vitro and in vivo studies have displayed antimicrobial, antioxidant, and other effects of honey and honeybee products, as well as protection of cardiovascular, respiratory, nervous, and gastrointestinal systems. Moreover, recent studies have demonstrated that beehive products are also able to influence the phenotype of skin cells, such as keratinocytes, fibroblasts, and endothelial cells, involved in correct wound healing. This review will characterize the great potential of honeybee products in the field of health and skin care, considering that honey is a virtually inexhaustible natural resource which people, as bees have been domesticated over the centuries, can freely access.

Keywords: aquaporin-3; honey; H_2O_2; honeydew honey; propolis; royal jelly

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1. Introduction

Honey plays a significant role in the history of humankind. Humans have been harvesting honey from the beginning, and honey has been utilized for its sweet taste, nutritional benefits, and medicinal properties [1].

In fact, honey is an important part of the diet and has continued to be used as a natural sweetener. Moreover, bee domestication, including beekeeping or apiculture, had a noteworthy impact on agriculture and food production [2].

Furthermore, honey has been utilized for its medicinal properties in many traditional practices. The ancient Egyptians, and also the Greeks and Romans, as well as the Chinese civilizations, used honey and other beehive products not only food but also as medicine and ointment. Honey was used both for personal care and for wounds, burns, and also for gut diseases [3].

Honey is a complex mixture of several compounds which relies on factors such as the floral source, geographical location, and processing methods [4]. However, the basic honey composition typically includes sugars, water, organic acids, amino acids, enzymes, minerals, and vitamins, as well as polyphenols and volatile compounds [5].

Honey is a supersaturated solution or semi-solid natural product manufactured by honeybees from flower nectar [6]. Bees convert nectar and flower secretions by merging them with specific substances of their own. This product is dehydrated and kept in the honeycomb for ripening and maturing [7]. Honey's color can vary from pale yellow to darkish red to black depending upon the plant source. Dark-colored honeys have been shown to contain more phenolic acids but fewer flavonoids than light-colored ones [8].

The chemistry of honey varies depending upon the geography of the sample. There is no standard scale globally. Depending on the source(s) of nectar, honey can have a variable composition.

The main component of honey is sugars (80–85%), primarily fructose and glucose. The carbohydrate components of honey contain various types of mono- and disaccharides. The average concentrations of fructose, glucose, sucrose, and reducing sugars are 38.38%, 30.31%, 1.31%, and 76.65%, respectively. Irrespective of the origin or variety of honey, the fructose/glucose ratio remains the same (i.e., 1.23) [9].

Honey also contains water, in an amount typically ranging from 14% to 20% depending on its moisture content [10] (see Figure 1). Honey contains a variety of organic acids, such as gluconic acid, acetic acid, formic acid, and citric acid [11]. Moreover, bees add enzymes to honey. The most important enzymes are invertase, amylase, and glucose oxidase [12]. It is also possible to find trace amounts of vitamins and minerals, including vitamin B complex, vitamin C, iron, calcium, etc. [13]. The polyphenol content of honey depends on the floral source [8]. Meanwhile, volatile compounds (aldehydes, esters, ketones, etc.) are responsible for honey's flavor and aroma [14].

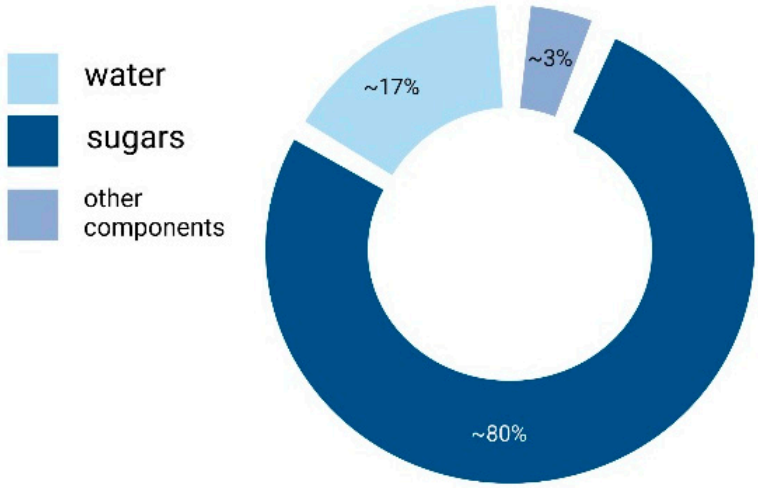

Figure 1. Main components of honey. See text for more details on honey composition. Created with BioRender.com.

The exact composition and quality rely on numerous environmental factors during manufacture such as weather, humidity inside the hive, condition and quality of nectar, and the honey's treatment during extraction and storage.

The average composition of 490 honey samples from around the United States was determined, showing a wide range of some components due to the equally wide range of nectar sources. Single-source honeys show a lower range of values because of the greater consistency in the composition of the nectar [9].

For example, honey's phenolic acid content is influenced by the nectar's botanical source and by the geographic location [15]. In addition, the total phenolic content is also considerably influenced by the season [16].

The most notable property of honey is its antibacterial activity. Honey has also been shown to prevent microorganism growth. This kind of effect is also of interest for several applications, such as for skin maintenance and repair, as testified by the development and marketing of γ-irradiated manuka medical grade honey. For this honey, there is also a specific parameter, called the Unique Manuka Factor (UMF), that represents equivalents of a phenol solution yielding a certain inhibition in a radial diffusion assay on *Staphylococcus aureus* [17,18].

Manuka honey, which is produced by *Leptospermum scoparium* flowers, a New Zealand plant, merits special consideration for its biological properties, in particular for its antimi-

crobial and antioxidant capacities, combining against bacteria hydrogen peroxide content with non-peroxide activities [19,20].

Manuka honey exhibited efficacy against many pathogenic microorganisms, including *S. aureus*, *Salmonella typhimurium*, and *Escherichia coli* [21,22]. Other studies have demonstrated that honey was also effective against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci and hemolytic streptococci [21]. Biofilm growth and its persistence within wounds can represent a factor to impaired healing and some authors have revealed important anti-biofilm effects of several honey samples, including manuka honey, against *Enterobacter cloacae* and *Proteus mirabilis* [15].

There is also in vivo evidence of the antibacterial effects of honey in wounds, in particular for diabetic foot ulcers [15,16].

However, newly recognized local honey types may be as good as or even better than manuka honey based on their impressive antimicrobial activity [23].

Indeed, the low moisture content and high sugar content of honey make the wound environment able to inhibit bacterial growth [24].

Many parameters contribute to honey's antibacterial potential, such as high viscosity and low water content. Furthermore, the low pH of honey (normally ranging from 3.2 to 4.5, depending on the floral source) inhibits the survival of many microorganisms [24,25].

Moreover, the salivary glands of bees release an enzyme, called glucose oxidase, converting glucose to gluconic acid and hydrogen peroxide. This hydrogen peroxide contributes to impeding the growth of bacteria [26].

Besides hydrogen peroxide, honey possesses other bioactive molecules contributing to its antibacterial effects [15]. These molecules are flavonoids, phenolic compounds, defensin-1, and methylglyoxal (MGO). The content of these bioactive molecules varies depending on honey type, floral source, processing method and storing conditions [16].

Other interesting compounds with previously described antimicrobial, anti-inflammatory and wound-promoting properties obtained from bees include propolis and royal jelly.

2. Honey and Skin Regeneration

Honey played an important role in traditional medicine for centuries [17]. However, it has a limited application in modern medicine due to a lack of scientific support [18]. Since a few decades ago, thanks to the renewed interest in ethno-pharmacology and the use of principles of natural origin, several laboratories have begun to study the properties of honey not only in terms of antibacterial effects [27].

Honey has been evaluated for its effects on both keratinocytes and fibroblasts in the context of wound healing [28,29].

In particular, Ranzato and co-workers [29] have previously demonstrated that different honey types are not cytotoxic for human keratinocytes. Moreover, honey is also able to promote cellular migration and proliferation. The authors observed that honey was also able to induce on keratinocytes some traits of epithelial-to-mesenchymal transition (EMT).

EMT is a biological process in which epithelial cells, which are typically organized in sheets and have a more stationary nature, undergo a transformation into mesenchymal cells, showing a more migratory phenotype and have a spindle-like shape [30].

Honey-driven wound closure is induced by keratinocyte re-epithelialization activation, but the EMT induction ability differs noticeably among honeys, according to their botanical origin [29].

Ca^{2+} signaling plays a crucial role in wound healing, including keratinocyte biology [31]. It regulates various cellular processes, such as migration, proliferation, differentiation, and cell–cell adhesion, all of which are critical for the successful closure and restoration of the wounded skin [32]. The understanding the complex interplay between keratinocyte and Ca^{2+} signaling [31] during wound healing is of crucial importance, providing insights into potential therapeutic targets for enhancing the healing process.

Martinotti et al. [33] demonstrated how honey triggers intracellular Ca^{2+} changes in keratinocytes. Micromolar levels of H_2O_2 released extracellularly by honey cross the

plasma membrane by aquaporin-3 (AQP3) [34]. This H_2O_2 activates Ca^{2+} channels [35], such as Orai1 and TRPM2 [36], inducing Ca^{2+} entry from the outside and triggering wound closure (Figure 2).

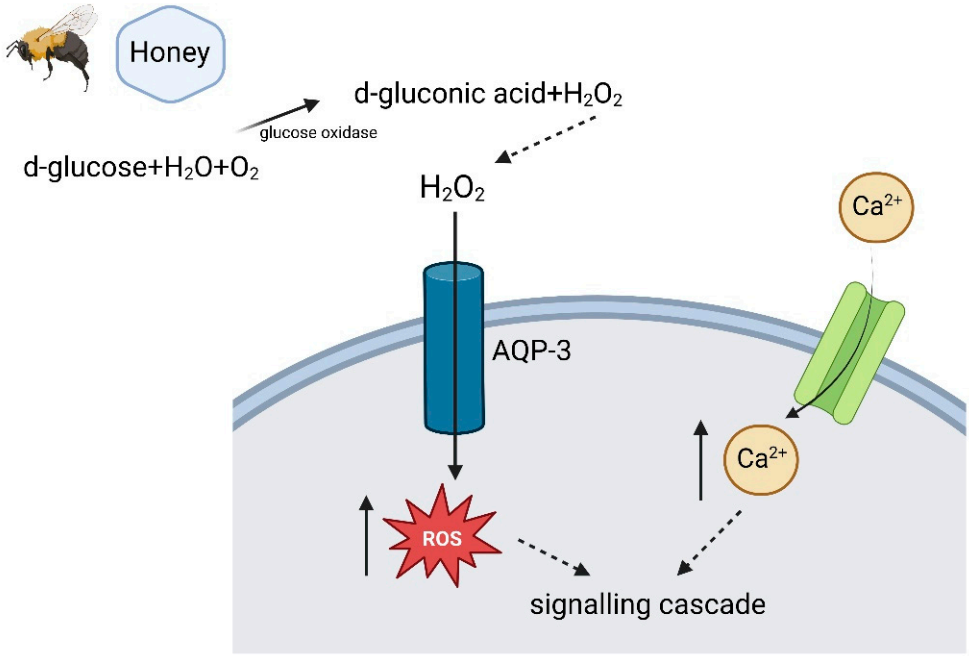

Figure 2. Molecular mechanism of honey's action on keratinocytes as characterized in Martinotti et al. [33]. Honey is able to induce the production of micromolar level of H_2O_2 in the extracellular space through glucose oxidase. This H_2O_2 cross the plasma membrane through aquaporin-3 (AQP-3), triggering intracellular responses. Created with BioRender.com.

This is the first observation demonstrating how honey exposure affects $[Ca^{2+}]_i$ regulation in keratinocytes due to hydrogen peroxide production and redox regulation of ion channels.

Honey has been shown to interact with the immune system, controlling cytokine production [7]. Honey is a natural ready-to-eat product rich in flavonoids. Some authors have proposed that honey flavonoids can mitigate inflammatory processes, and thus currently support studies of the anti-inflammatory potential of honeys [37].

Honey has been also reported to exhibit anti-inflammatory effects by modulating the production and release, in the monocytic cell line, MonoMac-6 (MM6), of pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumor necrosis factor-alpha (TNF-α), and consequently dampening inflammation in wound healing [38,39]. Likewise, honey seems to either reduce or activate the ROS production from neutrophils, also depending on the wound microenvironment [40]. Moreover, macrophages can be affected by a variety of factors to change their phenotype and thus affect their function. However, very few data are available on honey's ability to induce polarization of macrophages on M1-M2 during the inflammation process. It has been shown that there is not a specific modulation on the expression of gene markers of macrophage polarization with the honey treatment [41].

Ranzato et al. [28] also demonstrated that honey is able to promote the proliferation and migration of fibroblasts. Studies have demonstrated that honey can stimulate the growth of fibroblasts. Honey can also enhance the migration of fibroblasts into the wound bed, facilitating the healing process. In particular, the authors compared the results with those obtained from platelet lysate [42,43], showing a stronger outcome of honey on wound closure as a chemoattractant. These results could be of a therapeutic importance, favoring, during the proliferative phase, fibroblast invasion of the wounded site [44].

Moreover, they demonstrated that different honeys (e.g., acacia, buckwheat, and manuka honey) are able (at concentration of 0.1% v/v) to improve fibroblast wound repair capabilities via in vitro scratch wound assay [45].

Synthesis and deposition of collagen represents an important step of the extracellular matrix remodeling for wound repair [43]. Metalloproteinases (MMPs) and their inhibitors (TIMPs, tissue inhibitors of metalloproteinases) are essential in wound and tissue repair [46]. Majtan et al. [47] and Ranzato et al. [29] have reliably confirmed that honey exposure induces MMP-9 expression in a human keratinocyte cell line.

In fibroblasts, TIMP or MMPs upregulation by honey was limited to MMP-3 induction with manuka, and TIMP-1 with buckwheat and manuka honey. The TIMP-1 increase upon buckwheat treatment has been correlated to the anti-inflammatory properties of this protein, considering that it has been boosted in fibroblasts by cytokine exposure [48].

3. Honey and Endothelial Repair

In the framework of wound healing, endothelial repair is a crucial process that occurs to restore the integrity and functionality of blood vessels within the wound area [49]. In fact, optimal wound healing requires a coordinated response involving various cell types, including endothelial cells [50].

Endothelial cells play a central role in angiogenesis by proliferating, migrating, and organizing into functional blood vessels. Angiogenesis supplies oxygen and nutrients to the wound site, facilitating tissue repair [51].

Endothelial cells are activated in response to wound signals, such as growth factors and cytokines released by various cell types [52]. This activation triggers endothelial cell proliferation, migration, and the expression of adhesion molecules that facilitate their recruitment to the wound area.

Disruption or dysfunction of endothelial repair can lead to impaired wound healing, such as delayed angiogenesis or impaired vascular integrity [53].

A new strategy for endothelial injury treatment is to resort to using honey, due to its several virtues and pharmacological properties [26,54].

Ranzato et al. [55] demonstrated low cytotoxicity of buckwheat honey on bEND5 cells, an immortalized mouse cell line from brain capillary endothelial cells. Moreover, the scratched endothelial cells showed a 2.5–3 fold increase in wound closure upon honey exposure. Again, a main factor in the endothelial wound healing process is intracellular calcium signaling [56], and the authors demonstrated a Ca^{2+} activation of cells after exposure to honey.

Exposure to honey produces an increase in extracellular H_2O_2, and this peroxide could pass in the cells through a specific aquaporin, i.e., aquaporin-3 (AQP-3). Such an aquaporin is also present in endothelial cells [57] and allows the entry of H_2O_2 that could start the signaling cascade. The increase in hydrogen peroxide, in the cytoplasm, induces the activation of Ca^{2+}-channel TRPM2 [58], provoking an entry of Ca^{2+} from outside, the PLC-IP_3 activation [59] and then the release of Ca^{2+} from the endoplasmic reticulum [60].

Taken together, these data suggest the pivotal role of honey-produced H_2O_2 as a mediator of endothelial cell physiology in response to buckwheat honey exposure, suggesting the central role played by Ca^{2+} signaling.

Moreover, honey has been shown to increase the production of nitric oxide (NO) in endothelial cells [61]. NO is a signaling molecule produced by endothelial cells that regulates vascular tone, blood flow, and other important functions [62]. Increased NO production can improve endothelial function and overall vascular health.

NO shows many cardio-protective effects, which include inhibition of platelet aggregation, vascular tone, regulation of blood pressure, prevention of smooth muscle cell proliferation and leukocyte adhesion [62]. Some honey flavonoids have been shown to reduce cardiovascular risks by diminishing oxidative stress and increasing NO bioavailability [61], deserving additional experimental and clinical investigation for honey application.

4. Honeydew Honey

Honeydew honey (HH), also known as forest honey, is a type of honey produced by bees collecting honeydew secretions from aphids or other sap-sucking insects found in trees [63]. HH is increasingly valued by consumers and the food industry, due to its valuable nutritional and medicinal qualities, which are different from floral honey [64]. Moreover, HH showed equivalent or, in some cases, higher activities compared with medical-grade kanuka and manuka honey [65]. HH shows a darker color and a high polyphenol content, as well as more antioxidants and antibacterial activity compared to blossom honeys [66], highlighting this honey as a potential health-promoting food.

Moreover, the season of HH production is longer in comparison to blossom honey because the former begins in the second half of August and lasts until the end of October. This prolonged production season is essential for the income of beekeepers living in marginal areas, and is thus important for sustainable agriculture.

However, in respect to blossom honey, there are few anecdotal data about the biological effects of HH. Martinotti et al. [64], due to wide ethnopharmacological use of HH, demonstrated that honeydew honey has low cytotoxicity on skin fibroblasts and keratinocytes, thereby allowing HH to be considered safe for external application on skin. Moreover, an in vitro scratch wound assay showed that HH produces an increase in wound-healing abilities in both skin cells. Analysis of cell signaling, through use of specific inhibitors, also demonstrated that HH acts in the same way in both cell types, and Ca^{2+} signaling seems to play a basic role.

More data are already available for HH effects in controlling bacterial growth. Slovak fir honeydew honey demonstrated good antibacterial activity against wound pathogens and multi-drug-resistant clinical isolates of *Stenotrophomonas maltophilia* [67]. In general, HH exhibits greater antibacterial effects with both inhibitory and bactericidal properties, with remarkable outcomes in inhibiting antibiotic resistant bacteria [68].

5. Propolis

Propolis is a resinous substance that bees collect from various sources, such as exudates, buds and plants in the north temperate zone, extending from the Tropic of Cancer to the Arctic Circle [69]. The main sources of propolis are willow, birch, alder, elm, beech, conifer, and horse-chestnut trees [70].

Bees utilized propolis to seal and protect their hives. Propolis has been traditionally used in folk medicine for its therapeutic effects, and scientific research in recent years has also considered its potential benefits for health.

There are substantial data demonstrating that propolis possess antibacterial, antiviral, antifungal, and antiseptic effects, as well as anti-antioxidant and anti-inflammatory properties.

A huge number of bioactive compounds are present in propolis, including phenolic acids, terpenes, and flavonoids, and many other components. These compounds contribute to its antimicrobial and anti-inflammatory properties, which can be beneficial for wound healing. These beneficial activities are more numerous in propolis from tropical regions than in temperate climates, imitating the richer vegetal diversity observed in the former [71].

Moreover, such characteristics can also change depending on the polyphenol content, which varies in turn with area vegetation, geographical origin, seasonal variation, and propolis state (aged or fresh) [72].

Propolis exhibits broad-spectrum antimicrobial properties, helping to fight against various types of microorganisms, including bacteria, fungi, and viruses [73,74]. These effects are mainly due to the synergistic activity of the many compounds present in propolis [73]. It has generally been found that propolis' antibacterial activity is greater against Gram-positive than Gram-negative bacteria [75]. This is explicated by the specific organization of the Gram-negative bacteria outer membrane and by the hydrolytic enzyme present in propolis [76]. In particular, artepillin C (3,5-diprenyl-p-coumaric acid) is one of the numerous phenolic compounds present in propolis [77]. Moreover, artepillin C also shows

anti-inflammatory properties facilitated by prostaglandin E and nitric oxide inhibition and modulation NF-kappaB [78].

Propolis also displays anti-inflammatory effects, principally due to its high content of polyphenols, thus inhibiting inflammatory mediator production, such as cytokines and prostaglandins, and supporting the healing process [79,80].

Martinotti et al. [81] explored the effects of propolis on wound closure. Propolis showed extremely low cytotoxicity and an important chemoattractant effect for keratinocytes. The authors also assessed the interactions between extracellularly produced H_2O_2 and aquaporin-3 (AQP-3).

Propolis is generally considered an anti-oxidant; however, in some circumstances, it may also act as a pro-oxidant oxidative promoting environment [82]. For this pro-oxidant action, there is the need for transition metal ions and some phenolic compounds. These phenols are present in propolis (such as chrysin, pinocembrin, and galangin) and they act as temporary electron carriers in redox reactions, in which electrons from ferrous ions are relayed to oxygen molecules producing superoxide, after which H_2O_2 is made [81]. Furthermore, the H_2O_2 content, due to propolis induction, is very low, having a positive effect on cell signaling [83].

ROS produced by propolis treatment could diffuse across the plasma membrane through AQP3, modifying intracellular reactions.

Taken together, these data support further studies to characterize propolis as an adjuvant in wound healing management.

6. Royal Jelly

Royal jelly (RJ) is an acid colloid (3.6–4.2 pH) composed mainly of sugar, proteins, lipids, water, vitamins, and some mineral salts [84,85], produced by worker bees and used to nourish and develop queen bees [86].

RJ, a traditional cure for various skin injuries [87], has not been extensively utilized in clinical practice or studied for wound management, principally due to the lack of knowledge on the RJ bioactive molecules and on the precise mechanisms boosting the wound repairing ability [88].

Therefore, there is limited scientific exploration focused on RJ's effects on wound repair. However, some research has proposed that RJ expresses positive effects in promoting wound repair due to bioactive components.

The topical application of RJ on diabetic foot ulcers suggests that RJ can positively boost wound repair [89,90], and RJ is able to promote tissue healing in animal models [91].

However, few studies have characterized the influence of RJ on skin cell phenotype (e.g., fibroblasts and keratinocyte). In fact, there are some data concerning the increase in fibroblasts, upon RJ exposure, of transforming growth factor β (TGF-β) and type I pro-collagen [92].

Bucekova and co-workers identified an RJ component able to induce the increase in matrix metalloproteinase-9 (MMP-9) [16]. They identified defensin-1 as the main factor responsible for inducing MMP-9 secretion and in vitro keratinocyte migration. Defensin-1 also improves wound closure and re-epithelialization in rats, promoting wound healing in vivo [16].

Moreover, several studies have also elucidated an antiaging/anti-senescence property of royal jelly components. These effects have been estimated in multiple cellular models, such as human peripheral blood monocytes (PBMCs) isolated from aged and young human donors, human embryonic lung fibroblasts (HFL-I), or dermal microvascular endothelial cells [93–95]. The lipid and protein content of RJ can downregulate mTOR pathway and insulin-like growth signaling, upregulating epidermal growth factor signaling (EGF) and dietary restriction signaling [96].

7. Honey and "Green Chemistry"

Green chemistry focuses on designing and developing chemical procedures, processes, and products to make them environmentally friendly and more sustainable, minimizing their impact on human health and the planet. Green chemistry is devoted to decreasing or eliminating dangerous substance use, waste generation reduction, and endorsing energy proficiency.

In this contest, honey utilization is a very promising way to realize this new "green" approach [97].

Honey is a renewable resource and it can be harvested without negatively impacting the environment. Moreover, honey is a non-toxic compound posing minimal risks to human health and to the environment.

Honey has been successfully proposed as an agent in the green synthesis of silver nanoparticles (AgNPs) [97–99], widely used as standard antibacterial therapy for wounds [98,100,101]. Poly-sugars of honey can perform both reduction and stabilization of metallic ions required for AgNPs synthesis [102]. Moreover, Obot and collaborators [103] used honey and sunlight irradiation for silver nanoparticle production.

Malaysian honey has also been used to realized silver nanoparticles in an easy, reproducible and cost-effective green approach [104]. Honey was utilized as a reducing and stabilizing agent in the place of dangerous chemicals, such as sodium borohydride and formamide.

Taken together, information about honey usage for the synthesis of AgNPs shows that nanoparticles manufactured using honey with more antimicrobial efficacy showed better additive or synergistic properties than nanoparticles alone [105]. Some problems are still present, and the main limitation is the use of correct honey type or the use of standardized honey [106].

Himalayan honey has also been utilized for the preparation of iron oxide nanoparticles (IO-NPs) [107], which are interesting for their antioxidant and antibacterial effects. Himalayan honey plays an interesting role in IO-NP synthesis due to the presence of antioxidant compounds such as flavonoids and phenolic molecules [1,26]. These results are also very appealing for biomedical applications because the IO-NPs loaded with honey presented a synergistic result in inhibiting bacterial growth.

Nur Afini Ismail and co-workers [108] realized copper nanoparticles (Cu-NPs) utilizing Australian honey as stabilizing and reducing agents with ascorbate as a supporting reducing molecule.

Moreover, Wu et al. [109] obtained carbon nanoparticles from commercial honey.

These data confirm the suitability of honey for nanoparticle synthesis. In particular, the great variability of compounds present in honey can help the rate of metal ion reduction, nanoparticle formation, and stabilization.

Furthermore, scaffolds represent an important help for wound and tissue repair [110], and honey can be very useful for scaffold synthesis [111]. Scaffolds created with manuka honey and gellan gum are able to promote cartilage healing, stimulating the growth and differentiation of chondroblasts [112,113].

8. Conclusions

Honey is included in the International Nomenclature of Cosmetic Ingredients (INCI) under the names of "Honey" or "Mel" (CAS no. 8028-66-8) and is classified as a humectant/emollient/moisturizing product. A huge amount of skin care formulations enclosing honey or other beehive products are available in the literature [114].

Honey is antibacterial, fungicidal, and a hygroscopic agent, and it can nurture the skin, contributing to normalizing the mildly acidic pH of the higher protective skin layer [114].

The application of honey alone to skin, as exists in popular uses, is not usually employed in cosmetic approaches, due to thinning, stickiness, and liquefaction; therefore, honey is, in most products, utilized in proportions ranging from 1 to 10% [115], and it is used depending on the kind of cosmetics [113–115].

Honey is assessed as appropriate for skin care, and its systematic usage is assumed to keep the skin juvenile, delaying the formation of wrinkles [114,116,117]. Moreover, the inhibition of microbial species by honey in vivo has the potential to clear infections, remove malodors, and prevent cross-infection [118].

Honey has been shown to be much more than a simple food product, but rather a valuable medical product with multiple mechanisms and beneficial virtues, in particular as a wound-healing booster (in Figure 3, we summarized the effects of honey on the classical phases of wound healing).

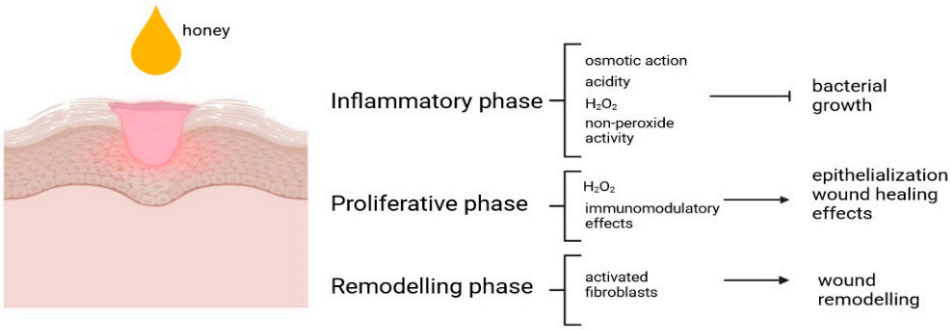

Figure 3. Modulatory effects of honey on classical phases of wound healing. Created with BioRender.com.

Some skin disorders, such as atopic dermatitis, contact dermatitis, and psoriasis, are considered to be immune-mediated skin disorders, although their etiology is not fully understood. However, it is difficult to conclude what effects honey can have in the treatment of immune-mediated skin disorders, and more research is necessary for a better understanding of honey's role [114].

Rosacea is an inflammatory skin disorder, characterized by facial papules, pustules redness, and telangiectasia. Some recent data suggest a therapeutic value of kanuka honey for anti-inflammatory and antibacterial properties in rosacea treatment [119].

Other studies have investigated the role of honey for treatment of acne as well as for dermatitis prophylactic treatment [120] and for treatment of cutaneous leishmaniasis [121]. Results are not definitive, but some limitations have been identified based on the type of honey used, the method of application, and the duration of application. These studies examining the effectiveness of honey in the treatment of skin disorders are relatively few, but they are interesting in supporting the idea that honey may be therapeutic. However, larger studies, with a more standardized approach, are urgently needed.

Skin, like other human tissues, experiences injurious modifications as a consequence of the passage of time. Skin aging is a complex process triggered by numerous factors, such as random cell damage during metabolic processes, and by environmental stimuli (temperature, air pollution, smoking, UV, etc.) [122].

AQP3 plays a significant role in skin, and also in its aging process. Increasing evidence has shown that AQP3 facilitates cell migration, proliferation, and re-epithelialization during wound healing, and skin recovery after injury is enhanced when AQP3 is stimulated. However, if AQP3 expression level decreases, many of aging's hallmarks, like dryness, thick skin, wrinkle formation, pigmentation, and decreased elasticity, appear [123].

Decreased AQP3 levels in the aged skin reduce skin elasticity and cause dry skin and barrier function failure, so any factor that increases AQP3 protein expression and/or activation maintains the level of cell hydration, helps wound healing, and supports fibroblast activity [124,125].

Some data [26,33,81] have shown that honey and propolis are able to increase the expression level of AQP3, leading to acceleration of the healing process through an AQP3-dependent mechanism.

Such properties, in addition to antibacterial effects, could make the honeybee products very stimulating for a possible synergistic effects with other medical wound dressings, such as platelet products, and with other natural products, such as jojoba liquid wax [126], in order to improve tissue restoration.

Moreover, the main problem is the way to administer honey and other honeybee products for wound healing purposes. Further researches are strongly needed to develop honeybee products in bio-compatible formulations with adjustable density and viscosity to be easily used for skin care purposes.

Recent advances reported in the literature [127] suggest that biocompatible molecules such as chitosan and/or alginate can be exploited as supporting matrices to incorporate honey (and/or other molecules with pharmaceutical interest), thus favoring honey delivery to tissues.

Further research can greatly exploit the bioactive properties of honey and other honeybee compounds, leading in the future to the production of a medicinal product with high value in cosmetics and dermatology.

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