MedCrave
Step into the World of Research
International Journal of Complementary & Alternative Medicine

Editorial

Open Access
CrossMark

Honey and propolis for wound healing

Abstract

Background: Wound healing has global healthcare concept where fighting infection, rapid cure, correct epithelization with minimal scar formation and feasible potent wound dressing management is targeted through recent researches with natural products. There is a renaissance in apitherapy wound dressing especially those related to honey and propolis. The review acted with the activity of these api-products on wound healing as antimicrobial, immunomodulator, antioxidant and anti-inflammatory agents referring to some mechanism of action. Recent api-products nanofabrication wound dressings have advantages of easy applicable potent with different api-products activities and short treatment regimen especially those polymeric networks. Moreover, maintaining wound moisture suitable for fast re-epithelialization. Rather than, small diameter, high porosity, narrow diameter distribution, gas permeation.

Volume 16 Issue 1 - 2023

Abdul-Hafeez MM, Hamouda SM
Animal Health Research Institute, Egypt

Correspondence: Abdul-Hafeez M, Animal Health Research Institute, Assiut lab, ARC, Egypt,
Email mohhafeez555@gmail.com

Received: November 08, 2022 | **Published:** January 10, 2023

Introduction

Wound healing is a recovering process of damaged tissues by replacing dysfunctional injured cellular structures.[1] occurred through three main phases; inflammation, proliferative, and tissue remodeling[2] to form a complex and continuous process but dynamic and orderly process, characterized by a series of overlapping of these interact phases. Honey is one of the oldest known medicines which have been "rediscovered" in later times by the medical profession, especially for dressing wounds management since its effectiveness.[3] Both stingless bees (*Trigona spp.*)[4] and sting bees (*Apis spp.*)[1] produce honey with excellent nutritional and medicinal value with potent antimicrobial action[5,6] and enhance wound healing by reducing the level of inflammation, edema, and pain through suppression the activities of cyclooxygenases 1 and 2 (COX1 and COX2).[7] Correct treatment of chronic wounds and ulcers is a complex process, which requires de-trauma, drainage and anti-inflammatory therapies,[8] so honey is a favorable as it promotes tissue repair[9] re-epithelization,[10] collagen deposition,[2] debridement action,[11] plays a role in tissue regeneration since honey-induced extracellular Ca2+ entry results in wound healing, which is consistent with the role played by Ca2+ signaling in tissue regeneration.[12] Rather than it has durable adhesive characteristics for skin graft fixation.[13] Propolis is collected directly by honey bee-workers from trees, shrubs and plants, then it is prepared resinous substance with very wide list of biological activities[14] {e.g., antibacterial[5,15] immunomodulatory.[16]

Apitherapeutic use of honey was used in wound dressing topically as it is.[9,17,18] or with modified formulations as honey chitosan-based[19] or alginate-based hydrogel.[20] While propolis topical dressing[21] or its extract was used in either ointment formulation.[22] The topical application of propolis extract gel increases the expression of FGF-2 and fibroblasts within the traumatic ulcer healing process,[23] absolute ethanolic extract propylene glycol preparation dressing[24] or even wound spray[15,24] since these api products contain compounds with anti-bacterial, anti-oxidant, anti-inflammation, immunomodulation activity as well as collagen matrix production.[1] Additionally, to their wide spectrum antimicrobial activity[5,6,15] the wound-healing potential of honey and propolis is referred mainly to micro components contents of flavonoids, phenolic acids, and several other phytochemicals with their antioxidant and anti-inflammatory properties.[25]

Antibacterial activity: Direct exposure of honey against microorganisms has multifactorial actions as, physically (free acidity[26] and hyper osmolarity since microorganisms can't survive and grow in the hypertonic sugar solution or in low pH medium).[27] Biochemically, enzymatic system (catalase, glucose oxidase and peroxidase[28] that produces continuous hydrogen per oxide[12] by glucose oxidase, an enzyme derived from the honeybee[29] and other enzymes; β□glucosidase, α/β□amylase, maltase, esterase, etc..[30] As well as various biochemical nonenzymatic substances potent biological micro components mainly flavonoids and phenolic compounds.[31] Different flavonoids (kaempferol, quercetin, pinobanksin, chrysin, galangin, pinocembrin[32] with different antimicrobial mechanisms such as inhibition of nucleic acid synthesis[33] inhibition of cytoplasmic membrane function, inhibition of energy metabolism, inhibition of the attachment and biofilm formation,[34] inhibition of the porin on the cell membrane, alteration of the membrane permeability, and attenuation of the pathogenicity.[31] The hydroxyl and superoxide free radicals contribute to the antibacterial activity of honey due to powerful damaging effect on the bacterial cells and DNA.[30] Flavonoids and phenolic acids (derived from plant origin) are highly bioactive particles and present great molecular diversity, but phenolics (phenolic acids, flavonoids) are the most abundant and have the highest antiradical activity.[35] Honey[36] and propolis[37] stimulated ROS generation, TLR-2 and TLR-4 expression and the production of proinflammatory cytokines by murine macrophage and enhanced its bactericidal activity.[38] Propolis, also has abundant different polyflavonoid and phenolic compounds which proved to have antimicrobial activities[39] depending on the type of floral nectar, geographical location of production, climatic conditions, seasonal factors, soil composition, as well as the production process.[40] Different potent phenolic compounds (syringic acid, ferulic acid, cinnamic acid, benzoic acid, and caffeic acids).[32] Methylglyoxal (MGO) is recognized as being the bioactive component responsible for the antibacterial activity of manuka honey[41] and Italian cherry or almond honey, which showed higher concentrations of MGO compared to honeys from other botanical species.[42] It is documented[43] that MGO correlates with the antimicrobial activity.

Against wound pathogens *in vitro*, honey[5,6] or propolis[5,15] while *in vivo,* honey[6,9] or propolis[15] resulted in promising therapeutic actions recommending its usage as wound dressing management[25] as wound pathogen cleansing promotes subsequent tissue.[44]

Antioxidant action: Reactive oxygen species (ROS) play a crucial role in the preparation of the normal wound healing response, so antioxidant wound dressings must regulate the balance between low and high levels of ROS,[45] since the imbalance between oxidative stress and antioxidant scavengers leads to damage of important

Submit Manuscript | http://medcraveonline.com

©2023 Abdul-Hafeez et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

biomolecules in the cells.[46] Moreover protecting host cells against damage by free radicals must be targeted.[40] The antioxidant action of either stingless bee honey,[4] or sting bee honey[47,48] is proved, since it has antioxidant properties which are either enzymatic (catalase, glucose oxidase and peroxidase) or non-enzymatic substances (ascorbic acid, α-tocopherol, carotenoids, amino acids, proteins.[28] More than 150 phenolic compounds in honey have been investigated which correlate with antioxidant activity, including phenolic acids, and flavonoids.[35] Polyphenols in honey or propolis, especially flavonoids and phenolic acids, have been reported to be solely responsible for the antioxidant and other medicinal effects of honey.[49] Myricetin (flavonoid) is present in many fruits and has many biochemical properties such as antioxidant, anti-allergic, anti-inflammation, and immunomodulatory function.[8] increases expression of serum proinflammatory cytokines e.g.; interleukin IL-1β and tumor necrosis factor (TNF- β).[1] Egyptian fennel honey increases the activity of certain antioxidant markers (glutathione peroxidase, superoxide dismutase),[46,48] while manuka honey, in comparison to other honeys is characterized by a high content of polyphenols and relatively high antioxidant capacity[50] with a new glycoside, MSYR (methyl syringate), recently detected and named leptosin where its concentration correlates with the antimicrobial activity and may represent a specific marker of manuka honey.[51] These micro components may enhance membrane permeability and repress bacterial motility as it influences ion permeability of the internal bacterial membrane and cause the dissemination of the membrane potential[52] as its *in vitro* activity[25] moreover, *in vivo* it may stimulate the immune system activating the mechanisms involved in the microorganisms killing.[53]

Anti-inflammatory activity: Just wound developed, inflammation resulted through four steps; hemostasis, inflammation, proliferation, and remodeling by the interactions among cytokines, growth factors, blood and cellular elements, and the extracellular matrix.[1] Cellular elements include neutrophils which release mediators e.g. Tumor necrosis factor (TNF), and interleukins (IL-1 & IL-6)[54] to amplify the inflammatory response, stimulating interleukin (IL-8 to) respond to repair during wound healing[55] while monocytes infiltrate the wound site and become activated macrophages that release growth factors that stimulate new capillary growth, collagen synthesis, and fibrosis[56] initiating the formation of granulation tissue. Monocytes and macrophages play a critical role in tissue development, homeostasis, and injury repair[57] as, in wound healing macrophages, express high levels of arginase -1 in response to interleukin (IL-4), which allows them to generate precursors for collagen and fibroblast stimulating factor, thus supporting their role in extracellular matrix deposition and wound closure,[21] where the activated macrophage supports the ongoing process by phagocytosis of the debris and secretion of growth factors, chemokines, and cytokines.[58] Macrophages promote and address inflammation, eliminate apoptotic, and support cell proliferation and tissue recovery after injury.[59] Honey[60] and propolis[54,60] stimulate monocytes and macrophage and increase the release of cytokines, chemokines, and matrix-degrading enzymes resulting in expression of markers of pro-inflammatory pathways such as IL-1, IL-10, IL-6, cyclooxygenases (COX-2), TNF-□, NF-□B, I□B□,.[61] transforming growth factor beta (TGF-□) which is the master regulator of fibrosis[62] lipoxygenase (LOXs), NO, nitric oxide synthase (iNOS), and prostaglandins[63] due to their phenolic or tocopherol compounds.[61] Moreover, all bee products, including honey, propolis, royal jelly, bee venom, and bee pollen, or their bioactive chemical constituents solely like polyphenols, demonstrate interesting therapeutic potential in the regulation of inflammatory mediator production as per the increase of TNF-α, IL-1β, IL-6, Il-2, and Il-7, and the decrease of ROS production.[37]

Immunomodulatory effects: It is known that dysregulated immune response initiates or exacerbates by existing comorbidities, multiple tissue injury or wound contamination[64] resulting in wound long stand healing and chronicity[65] characterized by unresolved inflammation, nonmigratory epidermis, impaired fibroblast function and extracellular matrix deposition, decreased angiogenesis, increased levels of proteases, and bacterial colonization and/or infection.[66] The multifunctional immunomodulatory properties of honey have attracted much attention.[67,68] especially in wound healing[64] even stingless bee honey.[69] Just wound develops, platelets and neutrophils infiltrate the injury site initiates mediator cytokines mediators[54] and create contact with exposed collagen and extracellular matrix (ECM) components to form a fibrin clot.[64] Immunomodulatory action of honey[20,37,64] and propolis[37,67] is widely discussed since successful api-treatment of a broad range of wound types particularly those chronic infected forms[49] for wounds with impaired healing, including delayed acute injuries and chronic injuries[70] which often stems from a dysregulated immune response initiated or exacerbated by existing comorbidities, multiple tissue injury or wound contamination[64] especially diabetic foot.[24 70–73] where diabetic patients, it have shown that honey can reduce serum TNF-α, IL-6, IL-1ß and TGF-ß by inhibiting NF-Kß.[61] Polyphenols to down regulate the activation of TNF the master key of the genetic regulation of immunity and inflammation.[1] The activation of these immune cells and factors initiates the inflammatory process, facilitate wound cleansing and promote subsequent tissue healing.[44]. The biological activities of propolis involved in wound healing and tissue regeneration correlates with its antimicrobial, anti-inflammatory and immunomodulatory properties.[74]

The antimicrobial synergistic action of both honey and propolis is recommended *in vitro*[5,75] and *in vivo*[10] since their combination stimulates the monocytes/macrophages to release cytokines important for wound healing, and promote neutrophils[54] rather than B-lymphocytes (antibody production)[67] protecting the healing tissue from pathogenic infection.[54] A study[76] concluded that honey supplemented with propolis extract can be an excellent source of antioxidant compounds as significant increase in the content of polyphenolic compounds, including flavonoids and phenolic acids, of which chrysin, pinocembrin, p-coumaric acid, and ferulic acid were present in the highest amounts.

Collagen formation: With topical honey dressing, the low pH could help to create and maintain optimal conditions for fibroblasts activities, such as migration and the organization of collagen where, honey[77] and propolis[2,10] increases migration and proliferation of fibroblasts to the wound enhancing collagen types I and III expression and degradation in wounds matrix.[64] As flavonoids can promote the synthesis of collagen,[2] the fibroblasts that are responsible for the replacement of fibrin clot with scar tissue, slowing the angiogenesis and changing the collagen composition[78] resulting in favorable biochemical environment leading to re-epithelization. In addition to their role in extracellular matrix production and scar tissue formation, fibroblasts release cytokines to provide regulatory control over immune cell function.[77] Moreover, flavonoids increase vascularization and protect the vascular endothelium.[23] It was found that propolis can decrease scar formation, shorten healing time, boost wound contraction, accelerate tissue repair, and ultimately improve patients' quality of life in skin wound healing.[2] Otherwise, the release of honey-propolis-engineered collagen peptides in the wound site increases the absorption and re-epithelization of keratinocytes.[10]

Reducing bacterial biofilm production: Biofilm production is a passive virulence factor facilitating many infectious diseases[79] where certain bacterial genes produce extracellular polysaccharides

to protect these pathogens from antimicrobial agents and cellular immune elements[80] resulting in long standing chronic wounds.[65] So, fighting biofilm production through down-regulation of the biofilm genes may prevent colonization of host tissues including damaged tissues in wounds[81] is of great concern. Multidrug-resistant organisms and their biofilms mediate about 75%[75] 80%[65] up to over 90%[82] of chronic wound group of bacterial cells imbedded in a matrix increasing tolerance to antimicrobials and the host defense system which prevent chronic wound healing.[80,83] Honey reduces biofilm produced by wound *Pseudomonas aeruginosa*[34,84] *Streptococcus pyogenes,*[34] MRSA[81] *Listeria monocytogenes*[85] While, propolis reduces biofilm produced by wound *Coryne. Pseud..*[86] *Proteus mirabilis*[75] *Candida spp*[87] biofilm.

Nanofabrication: Complications of nonhealing wounds have led to the emergence of nanotechnology-based.[66], where nanomaterials with various characteristics improve the therapeutic efficiency of bee products especially for wound healing and skin tissue engineering.[20] Adding nanoparticles to the dressing matrix or using nanoparticles to deliver drugs and cytokines to promote wound healing has proven to be effective.[8] Fabrication of biomaterials with different structures and forms such as films, hydrogel (e.g.; polymeric network forming a three-dimensional matrix) traps liquids as water or wound exudates maintaining wound moisture suitable for fast re-epithelialization.[88] Another advantages of electro-spun nanofibers, sponge, foam that including a small diameter, high porosity, narrow diameter distribution, gas permeation, and high-specific surface to area ratio.[6,89] Various nanoscale strategies were explored for targeting different phases of wound repair[66] where these nanomaterials exhibit intrinsic properties beneficial therapeutic materials for wound treatment (natural as honey, propolis)[10,20,69,90] or employed as delivery vehicles (e.g., silver, gold, zinc)[88] for effective therapeutic agents. Nanoparticle properties increase the probability of biological interaction and injury penetration in films, foams, hydrogels, hydrocolloids, contact layers, and multilayer form dressings.[69,91] Honey and/or propolis was studied in nanofabrication as honey chitosan-based,[19] alginate-based hydrogel,[20] propolis chitosan-based,[92] honey-propolis-engineered collagen peptides,[10] organic-based methanolic pomegranate peel extract,[93] polyvinyl alcohol[94] or propolis nanoparticle.[72] Nanoparticle wound dressing promotes new angiogenesis and tissue regeneration and wound contraction.[95] Also, nano propolis polyvenyl alcohol-based hydrogel.[72] proved efficacy *in vivo* rather than *in vitro*. These pharmaceutical procedures were developed to achieve better performance and improved final outcome.[96] Moreover, topical multiflora honey with silver nanoparticles dressing enhances the efficacy of wound contraction compared to honey alone.[97] These modern delivery techniques to natural bioactive products improves their permeability, bioavailability, and therapeutic efficacy.[90]

Some successful studies concluded that honey hydrogel represents a feasible productive approach and the resultant wound healing effects may be attributed to the synergistic effect of the hydrogel matrix and the incorporated honey.[91] In a study[98] honey and curcumin loaded nanofibrous membrane showed a better wound contraction of 89.05 ± 0.47% in comparison with other methods. Nano propolis mucoadhesive polymeric membrane wound dressing using a casting method employing collagen, chitosan, polyethylene glycol is potent antimicrobial agent against wound pathogens.[99] When honey is used as a primary or adjunct scaffolding component within microneedles, and be combined with other substances for additive effects using new honey-delivery approach enhance wound healing and treatment of bacterial infections on or below the skin barrier.[100] Honey incorporated nanofibrous scaffold activates the prevention of biofilm formation and fast healing of chronic wounds.[94] As honey and propolis have garnered a special interest; combining them with alginate-based nanomaterials has led to promising findings, especially for wound healing and skin tissue engineering.[20] Honey propolis wax collagen hydrolysates exhibit a significant reduction in inflammation and inflammatory markers and helps to obtain a faster wound-healing.[10] Honey-processed *Astragalus* (bioactive peptide amphiphile nanofiber-based hydrogel biomaterial) may stimulate burn wound healing.[48] Propolis nanoparticles have anti-inflammatory and anti-apoptotic effects as decreased expression of TGF-β and increased the expression of Bcl-2 in liver and kidney.[101] Propolis containing nanohydroxyapatite (the main inorganic component in natural bone) was able to hinder the bacterial growth and biofilm formation, as well as be non-cytotoxic to fibroblast cells.[102] For possible cutaneous wound healing applications, there is found synergic effect of chitosan nanoparticles matrix and propolis extract, incorporated in collagen films.[103] A study[72] concluded that propolis polymeric nanofibrous scaffolds for tissue regeneration showed an adequate fiber morphology and did not present any cytotoxicity to fibroblasts *in vitro* resulted *in vivo* as the best wound closure rate (68%) after 7 days in comparison with treated (54%) and untreated controls (20%). Combination of antimicrobial photodynamic therapy or toluidine blue O with propolis nanoparticle leads to synergistic effects and impairing the virulence of *S. mutans*.[104] Ethanolic extract of propolis-loaded poly (lactic-co-glycolic acid) nanoparticles mediates a potent anticandidal of *C. albicans*[105] or antifungal against *Aspergillus flavus*[106] disrupting the morphologic presence and attenuating their virulence. Chitosan-propolis nanoparticles showed synergism with different antibiotics which help decrease antibiotic treatment dose by at least 4-fold in combination therapies.[92]

Conclusion

Honey was used as wound dressing agent in ancient medicine but with modern pharmaceutical formulation, it is rediscovered as a potent highly effective medicament in wound dressing with short duration. Honey has broad-spectrum antimicrobial activity superior than different antibiotics against all studied wound pathogens especially those have multi-antimicrobial resistance. Also, propolis - similar to honey - has these activities since having micro components of flavonoids and polyphenols with antioxidant/anti-inflammatory effect suitable to wound healing process. Both honey and propolis showed significant synergistic antimicrobial effect that they are recommended for wound healing as well as they enhance re-epithelization. Moreover, both of them modulate host immune response, promote collagen synthesis and deposition through fibroblast stimulation and extracellular matrix deposition for wound closure. Bacterial biofilm formation - which maximize antimicrobial resistance and interfere the immune action - can be diminished and reduced by the action of honey or propolis. Subsequently, their use is strongly recommended especially in nanofabrication which conclude its superiority than their traditional use. Many biological nanofabrication of honey or propolis as chitosan-based, alginate-based hydrogel, organic-based methanolic pomegranate peel extract or polyvinyl alcohol are formulated as smart natural apitherapeutic wound dressings. So, the review suggests upcoming nano fabrication of wound dressing research work dealt with both honey and propolis to achieve all above advantages

Acknowledgments

None.

Conflicts of interest

Author declare there are no conflicts of interest.

Funding

None.

References

1. Trinh TX, Nguyen-Van Long, Anh L, et al. A Comprehensive Review of Natural Compounds for Wound Healing: Targeting Bioactivity Perspective. *Int J Mol Sci.* 2022;23(17):9573.
2. Yang J, Anjuan Pi, Yan L, et al. Research Progress on Therapeutic Effect and Mechanism of Propolis on Wound Healing. *Evid Based Complement Alternat Med.* 2022;2022:5798941.
3. Saranraj P, Sivasakthi S. Comprehensive Review on Honey: Biochemical and Medicinal Properties. *Journal of Academia and Industrial Research (JAIR).* 2018;6(10):
4. Ranneh Y, Akim A, Hamid A, et al. Honey and its nutritional and anti-inflammatory value. *BMC Complement Med Ther.* 2021;21(1):30.
5. Hamouda SM, Abd El Rahman MF, Abdul-Hafeez MM, et al. Egyptian fennel honey and/or propolis against MRSA harboring both mecA & icaA genes. *Int J Complement Alt Med*. 2018;1(3):180–185.
6. 6. Liang Y, Zhang H , GuoB. Antibacterial biomaterials for skin wound dressing. *Asian J Pharm Sci*. 2022;17(3):353-384.
7. Yadav A, Verma S, Keshri G, et al. Combination of medicinal honey and 904 nm super pulsed laser-mediated photobiomodulation promotes healing and impedes inflammation, pain in full-thickness burn. *J Photochem Photobiol B*. 2018;186:152-159.
8. Wang F, Zhang W, Li H, et al. How Effective are Nano-Based Dressings in Diabetic Wound Healing? A Comprehensive Review of Literature. *International Journal of Nanomedicine*. 2022:17.
9. Hamouda S, Kuraa H, Abed Zaher M, et al. Apitherapy of Septic Metacarpal and Metatarsal Wounds (An Experimental Study on Donkeys). *Clinical Medicine Research*. 2019;8(4):77-84.
10. Ibrahim H, Muthukumar Thangavelu M, Khalifa A. Honey-Propolis-Engineered Collagen Peptides as Promising Wound-Healing Matrix in Mouse Model. *Molecules*. 2022;27:7090.
11. Al-Ghamdi A, Ansari M. Biological and therapeutic roles of Saudi Arabian honey: A comparative review. *Journal of King Saud University – Science*. 2021;33(2):101329.
12. Martinotti S, Pellavio G, Laforenza U, et al. Propolis Induces AQP3 Expression: A Possible Way of Action in Wound Healing. *Molecules*. 2019;24(8):1544.
13. Maghsoudi H, Moradi S. Honey: A Skin Graft Fixator Convenient for Both Patient and Surgeon. Indian J Surg. (December 2015);77(Suppl 3):S863–S867.
14. Wieczorek P, Hudz N , Yezerska O, et al. Chemical Variability and Pharmacological Potential of Propolis as a Source for the Development of New Pharmaceutical Products. *Molecules*. 2022;27(5):1600.
15. da Rosa C, Bueno I, Quaresma A, et al. Healing Potential of Propolis in Skin Wounds Evidenced by Clinical Studies. *Pharmaceuticals*. 2022;15(9):1143.
16. Touzani S, Embaslat W, Imtara H, et al. In Vitro Evaluation of the Potential Use of Propolis as a Multitarget Therapeutic Product: Physicochemical Properties, Chemical Composition, and Immunomodulatory, Antibacterial, and Anticancer Properties. *Biomed Res Int*. 2019;2019:4836378.
17. Tan M, Adli D, Tumiran M, et al. The Efficacy of Gelam Honey Dressing towards Excisional Wound Healing. *Evidence-Based Complementary and Alternative Medicine*. 2012;805932.
18.)Abdul-Hafeez MM. Testimony for veterinary Apitherapy. *Int J Complement Alt Med.* 2019;2(1):15–22.
19. Abraham SA, Yashavanth G, Deveswaran R, et al. Honey based hydrogel as delivery system for wound healing. *Mater Today Proc*. 2022;49:1709–1718.
20. Al-Hatamleh M, Alshaer W, Hatmal M, et al. Applications of Alginate-Based Nanomaterials in Enhancing the Therapeutic Effects of Bee Products. *Front Mol Biosci*. 2022;9:865833.
21. Hozzein W, Dadr G, Al Ghamdi A, et al. Topical Application of Propolis Enhances Cutaneous Wound Healing by Promoting TGF-eta/Smad-Mediated Collagen Production in a Streptozotocin-Induced Type I Diabetic Mouse Model. *Cell Physiol Biochem*. 2015;37(3):940-954.
22. Oryan A, Alemzadeh E, Moshiri A. Potential role of propolis in wound healing: biological properties and therapeutic activities. *Biomed Pharmacother*. 98;469–483.
23. Puspasari A, Harijanti K, Soebadi B, et al. Effects of topical application of propolis extract on fibroblast growth factor-2 and fibroblast expression in the traumatic ulcers of diabetic Rattus norvegicus. *J Oral Maxillofac Pathol*. 2018;22(1):54-58.
24. Mujica V, Orrego R, Fuentealba R, et al. Propolis as an Adjuvant in the Healing of Human Diabetic Foot Wounds Receiving Care in the Diagnostic and Treatment Centre from the Regional Hospital of Talca. *J Diabetes Res*. 2019;2019:2507578.
25. Afonso A, Gonçalves J, Luís Â, et al. Evaluation of the In Vitro Wound-Healing Activity and Phytochemical Characterization of Propolis and Honey. *Appl Sci*. 2020;10:1845.
26. Pauliuc D, Dranca F, Oroian M. Antioxidant Activity, Total Phenolic Content, Individual Phenolics and Physicochemical Parameters Suitability for Romanian Honey Authentication. *Foods*. 2020;9(3):306.
27. Al-Sayaghi A, Al-Kabsi A, Abduh M, et al. Antibacterial Mechanism of Action of Two Types of Honey against Escherichia coli through Interfering with Bacterial Membrane Permeability, Inhibiting Proteins, and Inducing Bacterial DNA Damage. *Antibiotics (Basel)*. 2022;11(9):1182.
28. Dluya T. Crical Review: Antioxidant Properties And Antibiotic Mechanism Of Honey Against Infectious Diseases. *International Journal of Advances in Life Science and Technology*. 2015;2(2):16-24.
29. Guttentag A, Krishnakumar K, Cokcetin N, et al. Factors affecting the production and measurement of hydrogen peroxide in honey samples. *Access Microbiology.* 2021;3(3):000198.
30. Alaerjani W, Abu-Melha S , Alshareef R, et al. Biochemical Reactions and Their Biological Contributions in Honey. *Molecules*. 2022;27(15):4719.
31. Xie Y, Yang W, Tang F, et al. Antibacterial activities of flavonoids: structure-activity relationship and mechanism. *Curr Med Chem*. 2015;22(1):132-149.
32. Feknous N, Boumendjel M. Natural bioactive compounds of honey and their antimicrobial activity. *Czech Journal of Food Sciences*. 2022(3):163–178.
33. Górniak I, Bartoszewski R, Kro´liczewski J. Comprehensive review of antimicrobial activities of plant flavonoids. *Phytochem Rev*. 2019;18:241–272.
34. Mokhtar J, McBain A, Ledder R, et al. Exposure to a Manuka Honey Wound Gel Is Associated With Changes in Bacterial Virulence and Antimicrobial Susceptibility. *Front Microbiol.* 2020;11:2036.
35. Yayinie M, Atlabachew M, Tesfaye A, et al. Polyphenols, flavonoids, and antioxidant content of honey coupled with chemometric method: geographical origin classification from Amhara region, Ethiopia. *International Journal of Food Properties*. 2022; 25(1):76–92.
36. Talebi M, Talebi M, Farkhondeh T, et al. Molecular mechanism-based therapeutic properties of honey. *Biomed Pharmacother*. 2020;130:110590.

37. El-Seedi H, Eid N, Abd El-Wahed A, et al. Honey Bee Products: Preclinical and Clinical Studies of Their Anti-inflammatory and Immunomodulatory Properties. *Front Nutr*. 2022;8:761267.

38. Raynaud A , Ghezali L, Gloaguen V, et al. Honey-induced macrophage stimulation: AP-1 and NF-**κB** activation and cytokine production are unrelated to LPS content of honey. *Int Immunopharmacol*. 2013;17(3):874-879.

39. Vica ML, Glevitzky I, Glevitzky M, et al. Antibacterial Activity of Propolis Extracts from the Central Region of Romania against Neisseria gonorrhoeae. *Antibiotics (Basel)*. 2021;10(6):689.

40. Martinello M, Mutinelli F. Antioxidant Activity in Bee Products: A Review. *Antioxidants (Basel)*. 2021;10(1):71.

41. Juliano C, Magrini G. Methylglyoxal, the Major Antibacterial Factor in Manuka Honey: An Alternative to Preserve Natural Cosmetics?. *Cosmetics*. 2019;6:1.

42. Terio V, Bozzo G, Ceci E, et al. Methylglyoxal (MGO) in Italian Honey. *Appl Sci*. 2021;11(2):31.

43. Atrott J, Henle T. Methylglyoxal in Manuka Honey – Correlation with Antibacterial Properties. *Czech J Food Sci*. 2009;27.

44. Raziyeva K, Kim Y, Zharkinbekov Z, et al. Immunology of Acute and Chronic Wound Healing. *Biomolecules*. 2021;11(5):700.

45. Comino-Sanz I, López-Franco M, Castro B, et al. The Role of Antioxidants on Wound Healing: A Review of the Current Evidence. *J Clin Med*. 2021;10(16):3558.

46. Abd–El Mooty M, Neveen A EL Nisr, Nahed M Wahba, et al. Influence of intravenous Egyptian fennel honey infusion on the antioxidant activities and some haemo–indices in healthy goats. *Int J Complement Alt Med*. 2018;11(5):281–286.

47. Hegazi A, Al Guthami F, Basiouny M, et al. The effect of Qatada (Acacia hamulosa) honey from Saudi Arabia on the steps of pilonidal sinus healing. *Highlights in BioScience*. 2021;4:2682-4043.

48. Zhou J, Zhang N, Zhao L, et al. Protective Effects of Honey-Processed Astragalus on Liver Injury and Gut Microbiota in Mice Induced by Chronic Alcohol Intake. *Journal of Food Quality*. 2022;5333691.

49. Schilrreff P, Alexiev U. Chronic Inflammation in Non-Healing Skin Wounds and Promising Natural Bioactive Compounds Treatment. *Int J Mol Sci*. 2022;23(9):4928.

50. Gos´lin´ski I, Bartoszewski R, Kro´liczewski J. Comprehensive review of antimicrobial activities of plant flavonoids. *Phytochem Rev*. 2019;18:241–272.

51. Kato Y, Umeda N, Maeda A, et al. Identification of a Novel Glycoside, Leptosin, as a Chemical Marker of Manuka Honey. *J Agric Food Chem*. 2012;60(13):3418-3423.

52. Sforcin J. Biological Properties and Therapeutic Applications of Propolis. *Phytother Res*. 2016;30(6):894-905.

53. Sforcin JM and Bankova V. Propolis: is there a potential for the development of new drugs? *J Ethnopharmacol*. 2011;133(2):253–260.

54. Filipič B, Gradišnik L, Ružić-Sabljić E, et al. Water Soluble Propolis and Royal Jelly Enhance the Antimicrobial Activity of Honeys and Promote the Growth of Human Macrophage Cell Line. *Journal of Agricultural Science and Technology*. 2016;35-47.

55. Eming S, Krieg T, Davidson J. Inflammation in Wound Repair: Molecular and Cellular Mechanisms. *J Invest Dermatol*. 2007;127(3):514-525.

56. Majtan J. Honey: An immunomodulator in wound healing. *Wound Repair Regen*. 2014;22(2):187-192.

57. Ogle M, Segar C, Sridhar S, et al. Monocytes and macrophages in tissue repair: Implications for immunoregenerative biomaterial design. *Exp Biol Med (Maywood)*. 2016;241(10):1084-1097.

58. Tziotzios C, Profyris MB, Sterling J. Cutaneous scarring: Pathophysiology, molecular mechanisms, and scar reduction therapeutics, Part II. Strategies to reduce scar formation after dermatologic procedures. *J Am Acad Dermatol*. 2012;13–23.

59. Koh T, Dipietro L. Inflammation and wound healing: the role of the macrophage. *Expert Rev Mol Med*. 2011;13:e23.

60. Wahba NM, El Nisr NA, Hamouda SM, et al. Intramammary honey infusion: A new trend in the management of subclinical mastitis. *Journal of Animal and Veterinary Advances*. 2011;10(20):2740–2744.

61. Navaei-Alipour N, Mastali M, Ferns G, et al. The effects of honey on pro- and anti-inflammatory cytokines:A narrative review. *Phytother Res*. 2021;35(7):3690–3701.

62. Meng X, Nikolic-Paterson D, Lan H. TGF-β: the master regulator of fibrosis. *Nat Rev Nephrol*. 2016;12(6):325-338.

63. Birkenmaier B, Meadows M, Cherukuri K, et al. Manuka Honey Modulates the Release Profile of a dHL-60 Neutrophil Model under Anti-Inflammatory Stimulation. *J Tissue Viability*. 2020;29(2):91-99.

64. Muire P, Thompson M, Christy R, et al. Advances in Immunomodulation and Immune Engineering Approaches to Improve Healing of Extremity Wounds. *Int J Mol Sci*. 2022;23(8):4074.

65. Mendoza R, Hsieh J, Galiano R. The Impact of Biofilm Formation on Wound Healing. Wound Healing. *Current Perspectives*. 2019;235–247.

66. Hamdan S, Pastar I, Drakulich S, et al. Nanotechnology-Driven Therapeutic Interventions in Wound Healing: Potential Uses and Applications. *ACS Cent Sci*. 2017;3(3):163-175.

67. Sayed SM, Abou El–Ella GA, Wahba NM, et al. Immune defense of rats immunized with fennel honey, propolis, and bee venom against induced Staphylococcal infection. *J Med Food*. 2009;12(3):569–575.

68. McCarthy O, Moser O, Eckstein M, et al. Effect of Oral Honey Consumption on Immune Function Following Ex-Vivo Lipopolysaccharide Stimulation in Healthy Humans. *International Journal of Nutrition*. 2019;3(4).

69. Esa N, Ansari M, Abd Razak S, et al. A Review on Recent Progress of Stingless Bee Honey and Its Hydrogel-Based Compound for Wound Care Management. *Molecules*. 2022;27(10):3080.

70. Bahari N, Hashim N , Akim A, et al. Recent Advances in Honey-Based Nanoparticles for Wound Dressing: A Review. *Nanomaterials (Basel)*. 2022;12(15):2560.

71. Wang C, Guo M, Zhang N, et al. Effectiveness of honey dressing in the treatment of diabetic foot ulcers: A systematic review and meta-analysis. *Complement Ther Clin Pract*. 2019;34:123-131.

72. Alberti T, Coelho D, de Pra´ **M,** et al. Electrospun PVA nanoscaffolds associated with propolis nanoparticles with wound healing activity. *J Mater Sci*. 2020;55:9712–9727.

73. Kitamura H. Effects of Propolis Extract and Propolis-Derived Compounds on Obesity and Diabetes: Knowledge from Cellular and Animal Models. Molecules. 2019;24:4394.

74. Martinotti S.; Ranzato, E (2015): Propolis: A new frontier for wound healing? *Burns Trauma*. 2015;3:9.

75. Kwieci ´ nska-Piróg J, Przekwas J, Majkut M, et al. Biofilm Formation Reducing Properties of Manuka Honey and Propolis in Proteus mirabilis Rods Isolated from Chronic Wounds. *Microorganisms*. 2020;8(11):1823.

76. Habryka C, Socha R, JuszczakL. The Effect of Enriching Honey with Propolis on the Antioxidant Activity, Sensory Characteristics, and Quality Parameters. *Molecules*. 2019;24(23):4394.

77. Russell F, Visagie J, Noll J. Secretion of IL-6 by fibroblasts exposed to Australian honeys involves lipopolysaccharide and is independent of floral source. *Scientific Reports*. 2022;12(1):16628.

Citation: Abdul-Hafeez MM, Hamouda SM. Honey and propolis for wound healing. *Int J Complement Alt Med.* 2023;16(1):12–17.
DOI: 10.15406/ijcam.2023.16.00626

78. Liu E, Gao H, Zhao Y, et al. The potential application of natural products in cutaneous wound healing: A review of preclinical evidence. *Front Pharmacol*. 13:900439.

79. Schulze A, Mitterer F, Pombo J, et al. Biofilms by bacterial human pathogens: Clinical relevance - development, composition and regulation - therapeutical strategies. *Microb Cell*. 2021;8(2):28-56.

80. Thaarup I, Iversen A, Lichtenberg M, et al. Biofilm Survival Strategies in Chronic Wounds. *Microorganisms*. 2022;10:775.

81. Kot B, Sytykiewicz H, Sprawka I, et al. Effect of manuka honey on biofilm-associated genes expression during methicillin-resistant Staphylococcus aureus biofilm formation. *Sci Rep*. 2020;10(1):13552.

82. Theryn G, Glynne-Jones G, Webb J, et al. Ultrasound-mediated therapies for the treatment of biofilms in chronic wounds: a review of present knowledge. *Microb Biotechnol*. 2020;13(3):613-628.

83. Darvishi S, Tavakoli S, Kharaziha M, et al. Advances in the Sensing and Treatment of Wound Biofilms. *Angew Chem Int Ed Engl*. 2022;61(13):e202112218.

84. Pleeging C, Wagenera F, Roosterb H, et al. Revolutionizing non-conventional wound healing using honey by simultaneously targeting multiple molecular mechanisms. *Drug Resist Updat*. 2022;62:100834.

85. Nazzaro F, Fratianni F, d'Acierno A, et al. Anti-Biofilm Properties Exhibited by Different Types of Monofloral Honey. *Proceedings*. 2020;66(1).

86. Santos L, Rodrigues D, Kalil M, V, et al. Activity of Ethanolic and Supercritical Propolis Extracts in Corynebacterium pseudotuberculosis and Its Associated Biofilm. *Front Vet Sci*. 2021;8:700030.

87. Stähli A, Schröter H, Bullitta S, et al. In Vitro Activity of Propolis on Oral Microorganisms and Biofilms. Antibiotics 2021, 10, 1045. https://doi.org/10.3390/antibiotics10091045.

88. Mihai M, Dima MB, Holban A. Nanomaterials for Wound Healing and Infection Control. *Materials*. 2019;12:2176.

89. Alven S, Peter SZ, Aderibigbe B. Polymer-Based Wound Dressing Materials Loaded with Bioactive Agents: Potential Materials for the Treatment of Diabetic Wounds. *Polymers (Basel)*. 2022;14(4):724.

90. Zohdi R, Zakaria A, Yusof N, et al. Gelam (Melaleuca spp.) Honey-Based Hydrogel as Burn Wound Dressing. *Evid Based Complement Alternat Med*. 2012;2012:843025.

91. Ong T, Chitra E, Ramamurthy S, et al. I Cationic chitosan-propolis nanoparticles alter the zeta potential of S. epidermidis, inhibit biofilm formation by modulating gene expression and exhibit synergism with antibiotics. *PLoS One*. 2019;14(2):e0213079.

92. Abou Zekry S, Abdelatif A, Azzazy H. Fabrication of pomegranate / honey nanofibers for use as antibacterial wound dressings. *Wound Medicine*. 2020;28:100181.

93. Kanimozhi S, Kathiresan G, Kathalingam A, et al. Organic nanocomposite Band-Aid for chronic wound healing: a novel honey-based nanofibrous scaffold. Applied Nanoscience. 2020;10:1639–1652.

94. Chaudharya A, Bagb S, Banerjeec P, et al. Wound healing efficacy of Jamun honey in diabetic mice model through re-epithelialization, collagen deposition and angiogenesis. *Journal of Traditional and Complementary Medicine*. 2020;10(6):529–543. Angioi R, Morrin A, White B. The Rediscovery of Honey for Skin Repair: Recent Advances in Mechanisms for Honey-Mediated Wound Healing and Scaffolded. *Appl Sci*. 2021;11:5192.

95. Rani G, Rao B, Shamili M, et al. Combined effect of silver nanoparticles and honey in experimental wound healing process in rats. *Biomedical Research*. 2018;29 (15):3074-3078.

96. Samraj M, Kiruphac S, Elangoa S, et al. Fabrication of nanofibrous membrane using stingless bee honey and curcumin for wound healing applications. *J Drug Deliv Sci. Technol*. 2021.

97. Loureiro K, Barbosa C, Nery M, et al. Antibacterial activity of chitosan/collagen membranes containing red propolis extract. *Pharmazie*. 2020;75(2):75-81.

98. Frydman G, Olaleye D, Annamalai D, et al. Manuka honey microneedles for enhanced wound healing and the prevention and/or treatment of Methicillin-resistant Staphylococcus aureus (MRSA) surgical site infection. Scientific Reports. 2020;10:13229.

99. Izzularab B, Megeed M, Yehia M. Propolis nanoparticles modulate the inflammatory and apoptotic pathways in carbon tetrachloride-induced liver fibrosis and nephropathy in rats. Environmental Toxicology. 2021;36(1):55–66.

100. Grenho L, Barros J, Ferreira C, et al. In vitro antimicrobial activity and biocompatibility of propolis containing nanohydroxyapatite. Biomed Mater. 2015;10(2):025004.

101. Cavalu S, Pasca P, Brocks M. Natural Polymeric Film Encapsulating Propolis Nano-Formulation for Cutaneous Wound Healing. Materiale Plastice. 2019.

102. Afrasiabi S, Pourhajibagher M, Chiniforush N. et al. Propolis nanoparticle enhances the potency of antimicrobial photodynamic therapy against *Streptococcus mutans* in a synergistic manner. Sci Rep. 2020;10(1):15560.

103. Iadnut A, Mamoon K, Thammasit P, et al. In Vitro Antifungal and Antivirulence Activities of Biologically Synthesized Ethanolic Extract of Propolis-Loaded PLGA Nanoparticles against Candida albicans. Evidence-Based Complementary and Alternative Medicine. Volume 2019, Article ID 3715481.

104. Hassanien AA, Shaker EM, El-Sharkawy EE, et al. Antifungal and antitoxin effects of propolis and its nanoemulsion formulation against *Aspergillus flavus* isolated from human sputum and milk powder samples. *Vet World*. 2021;14(9):2306-2312.