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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.

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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

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-α, NF-κB, IκBα,.[61] transforming growth factor beta (TGF-β) 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

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Conflicts of interest

Author declare there are no conflicts of interest.

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