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Review Article

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Honey and propolis for management of diabetic foot ulcers

Abstract

Diabetes mellitus (DM) hyperglycemia may lead to hyperplasia and micro vascular dysfunction and delays wound healing process by increasing reactive oxygen species (ROS) accompanied by low levels of inflammatory cytokines and an increase in matrix metalloproteinases (MMPs). Consequently, prolonged healing process with the worst complication diabetic foot ulcers (DFUs) as when it fails to heal fating limb amputation. Apitherapeutic (honey and propolis) wound dressing achieved successful accelerated healing with infection control by the action of their antimicrobial, anti-inflammatory and antioxidant properties. The present review dealt with their activity with DFUs as study of: *in vitro* antimicrobial activity against DFUs isolated pathogens, *in vitro* their activity towards immune cellular wound healing elements and *in vivo* their application for induced DFUs animal models as well as their topical application for DFUs patients either natural or nanoformulated scaffold dressings. Available literatures proved the synergistic wound healing activity of different mixed apitherapeutic products together and recommended to be used in mixed formula either naturally or nanoformulation.

Keywords: apiterapy, honey, propolis, diabetic wound ulcers, nano apitherapeutic wound healing.

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Introduction

Healing of wounds is a complicated process targeting tissue restore begins just after the damage with hemostasis followed by three stages named; inflammation, proliferation and remodeling,[1–3] where the proliferative stage occurs after the injury by 2 or 3 days.[4] DM is a progressive and chronic endocrine disorder results in hyperglycemia[5] and inflammatory state which impairs wound healing through multifactorial mechanisms,[6,7] excessive inflammation and reduced angiogenesis.[8] Among the worst complications of diabetes, the development of DFUs is one of the major public health challenges usually precedes diabetic foot amputations.[9]

Diabetic foot ulcers (DFUs) development

DFUs are devastating micro-vascular complications of diabetes[10] characterized by delayed wound healing because of decreased collagen concentration of and granulation tissue formation,[5] increases reactive oxygen species (ROS) production[11] enhancing hypoxia damage[12] with decreased myofibroblast formation and increase in matrix MMPs[13,14] resulting in weakened wound contraction and delayed healing.[15] Fast healing of diabetic wounds remains a major clinical challenge[16] as patients whose ulcers failed to heal had higher tumor necrosis factor-a, monocyte chemo attractant protein-1, matrix metallopeptidase 9 (MMP-9), and fibroblast growth factor 2 serum levels – which are the main factors associated with failure to heal DFUs - when compared with those who healed.[17] The prolonged inflammation status caused by hyperglycemia in the microcirculation might lead to endothelial hyperplasia and microvascular dysfunction[18] and capillary basement membrane thickening,[19] neuropathy[20,21] and other of deadly complications.[11,22] Moreover, DM impairs immuno cellular (neutrophils and macrophages) function,[23] including cell adherence, chemotaxis, phagocytosis, and cytokine production and secretion.[24] In diabetic wounds, macrophages produce excessive pro-inflammatory cytokines, neutrophils cytotoxic enzymes, free radical spices,[4] then further oxidative stress leading to further tissue damage and delayed pathological healing.[8]

DFUs neuroischemic pathology of the foot

DM is characterized by neuro degenerative disorders of the peripheral nervous system targets sensory, autonomic, and to lesser extension motor neurons[19] with neuroischemic pathology of the patient's foot.[25] The main consequence of this neuropathy is the risk of DFUs as any peripheral skin cuts, unaware injuriy, pessure ulcer[26] or callus might remain unnoticed[6,27] results with unperceived lesion[28] with ischemia, hypoxia, decreased angiogenesis predisposing bacterial infection.[10] These lesions begin as superficial ulcer, progressing to deep tissue infection with osteomyelitis[18] fating limb amputation.[20,29] DFUs are still considered a public health challenge promoting microbial biofilm formation by the presence of multidrug-resistant microorganisms (MDR) and microbial biofilm[19,30–32] which maximizes resistance,[33] leading to foot ulceration and delayed wound healing[9] threating high rates of lower-limb amputations.[29] Despite recent advances in antimicrobial therapy, DFUs remain serious problem since most of them ultimately turn into diabetic gangrene if left untreated.[34] Thus, there is a need for a continued search for affordable agents with speed and no side effects for treating ailments[29] especially in developing countries.[35]

Wound healing bioactivity of honey and propolis

Honey is rediscovered as a potent highly effective medicament in wound dressing with short duration[2] and known as an "all in one" remedy for diabetic wound healing[34] and affordable secure treatment.[29] It is rich in bioactive compounds such as methylglyoxal, hydrogen peroxide, phenolics, and bee defensin-1 peptide[31] with low moisture content, high osmolarity, acidity[29] and polyphenols that have been found to possess antibacterial properties[36] and other different phytochemical and phytopharmaceutical compounds (mainly flavonoids and polyphenols).[37–40] These micro compounds reduce the number of mast cells and neutrophils, accelerating the revival process and wound healing.[40] As these micro compounds are widely documented exhibited potent antimicrobial activity[2,33,38,41–43] especially those biofilm producers,[2,30–32,36] anti-inflammatory

potency,[44,45] antioxidant potential[46] and free radical scavenging ability formed by polymorph nuclear neutrophils.[34] As well as having immunomodulation action at the wound site,[29,45] so they are recommended for management of DFUs. Honey[47] and propolis[48] can reduce the activity of cyclooxygenases I and IIthat inhibits the synthesis of prostaglandins involved in the inflammatory responses by the lipoxygenase pathway[49] aiding in wound healing. Apiproducts with their bioactive micro components have other biological functions as enhancement of the proliferation and migration of skin cells, promotion of vascularization at the site of wound and inflammatory regulation[16] by the action of α— actin[50] and chrysin,[14] where the dysregulation of wound healing phases (Matrix MMPs and their inhibitors[13]) is an important variance between diabetics and non-diabetic patients.[29]

In vitro antimicrobial testing of honey and propolis against pathogens isolated from DFUs

The *in vitro* studies of honey against DFUs isolates - which are mostly MDR bacteria[19] revealed potent antimicrobial activity; *St aureus,*[51–55] MRSA, *Pseudomonas aeruginosa,*[53–56] *E. coli*[54,56] *Proteus mirabilis,*[30,54] and *Clostredium sp.*[54] Also, propolis antimicrobial action was obtained *in vitro* against DFUs isolates; *St aureus,*[57–59] *Candida albicans,*[58] *Pseudomonas, E. coli.*[57]

In vitro testing of honey and propolis against DFUs cellular elements

Several studies *in vitro* honey or propolis healing activity, when diabetic healing human keratinocytes[12,60–62] and fibroblasts[63] were activated, where the activated fibroblast replaces the fibrin-based provisional matrix with collagen-rich granulation tissue[5,27] with collagen deposition[50,61,64] which aids in remodling phase in wound healing concluded higher wound closure rates.[50,64,65] Activated keratinocytes[60] play a role in inflammatory cytokines production during the inflammation phase of wound healing[66] as promoted the expression of tumor necrosis factor alpha (TNF-a), interleukin 1β, transforming growth factor beta (TGF-β),[14,67] as well as MMP-9 messenger ribonucleic acid (mRNA) in primary keratinocytes.[66] The prolonged wound healing mainly is due to down-regulation of KGF, IL- 10, PDGF, IGF-1, EGF, as well as HIF cytokines, but up-regulation is due to TNF-a, IL-6, and TGF-b2[10] which the laters might be suppressed by the action of honey and propolis micro components.[68] To investigate the effect of honey with propolis extraction on human dermal fibroblast cells, an *in vitro* study[62] concluded significant impact on wound healing with a higher wound closure percentage and higher cell migration rate. The immunomodulatory action of honey[3,23,45] and propolis[23] and its constituents at noncytotoxic concentrations, specifically an anti-inflammatory activity in LPS-treated cells by inhibiting cytokine production.[69] Honey peroxide and non-peroxide mechanisms are responsible for promoting wound healing[19] since in an *in vitro* study,[70] H_2O_2 produced by diluted honey by the wound exudate can induce the entry of extracellular calcium[34] that plays an important role in wound repair and closure.[61]

Flavonoids and polyphenols (bioactive components present in honey and propolis) have been shown to promote wound healing[37,40] by many factors; 1- Lowering inflammatory cell influx in situ. 2- Boosting angiogenesis by stimulating the vascular endothelial growth factor.[29] 3- Fibroblastic proliferation promotion or speeding up re-epithelization[50,62] as they antimicrobial and angiogenesis promoter effects.[71] 4- Decreasing wound size by collagen deposition and angiogenetic markers (HIF-1a, VEGF).[50]

In vivo studies of honey and propolis in induced DFUs of animal models

In vivo, to study wound healing action of honey solo dressing on DFUs, standard back or nape wounds were adopted in induced diabetic animal models; mice[50,72,73] and rat[5,29,68] while topical propolis application was carried for diabetic mice[14,22,27] and rat[74] accelerated wound contraction with speed healing rate in all above mentioned studies and increased fibroblasts expression in diabetic rats.[75] Moreover, similar obtained results were achieved in diabetic male rats with honey combined with royal jelly, olive oil and propolis extract[76] due to its antioxidant, anti-inflammatory, and antibacterial properties. Honey application in either male[14,72,76] or female[24] induced diabetic rats obtained the smallest wound surfaces, higher wound contraction and accelerated wound closure.[5,19,68,76] Some studies[77,84] obtained that topical application of propolis solely for induced diabetic rats[77] or mice[78] increased the healing of full-thickness wounds, but epithelial closure failed and increased the expression of fibroblasts within the traumatic ulcer healing process in diabetic[75] rats with direct signaling FGF- 2 that can enhance the proliferation of fibroblasts and accelerate the healing of ulcers.

Wound dressing with ethanolic extract of propolis in induced diabetic mice[14] resulted in wound closure, tensile strength and expression of different molecules such as α—actin,[50] which is cytoskeletal and its regulation of is tightly controlled and regulated by the stimulated keratinocytes, fibroblasts, epithelial and endothelial cells.[75] Topical application of propolis nano particles for induced diabetic,[79] non-diabetic mice[80] or non-diabetic rats[81–83] accelerated wound healing even single topical propolis cream application.[84] Topical application of honey and propolis dressing for DFUs animal models - in the above mentioned studies - resulted in great wound contraction, increased re- epithelialization, high proliferation markers, collagen deposition and angiogenetic markers (HIF-1a, VEGF)[50] leading to faster wound healing and wound closure[50,78] comparing with classical treatment in the same studies and gave promising apitherapeutic topical management for human clinical diabetic foot ulcer since it is relatively highly effective, free of adverse effects and very cost-effective.[35,85]

Apitherapeutic mechanisms to manage DFUs

Honey when be diluted by wound exudates – in topical dressing - produces hydrogen peroxide that induces fibroblast infiltration, promotes angiogenesis and stimulates the vascular endothelial growth factor.[86] Its acidity and osmotic effects stimulates the activity of phagocytes and lymphocytes at the wound site.[87] It has broad spectrum bactericidal activities, helps manage wound infections, promotes the growth of epithelium, and reduces swelling and absorbs edema around wounds[88,89] just after four hours post application.[19] So, for diabetic patients with either DFUs[17,26,90–92] or bed sores,[88] honey dressing can reduce the time needed for wound debridement, wound healing, bacterial clearance, speed up wound healing and bacterial clearance rates.[34] Honey stimulates monocytes, macrophages,[87] neutrophils, keratinocytes, and fibroblasts activities.[60] Wide range studies[22,27,56,78,82] proved that propolis promotes and accelerates wound healing mainly by the action of chrysin[81] and other flavonoids[39] through stimulation of both fibroblasts and epithelial cells[65] to be increased in numbers resulting in collagen formation[38,61,64,80] and granulation tissues.[93] Propolis chrysin regulates the expression of MMPs and their tissue inhibitors[14] which is the main cause to reduce wound size[49] up to wound closure.[50,78]

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Clinical topical apitherapeutic application for DFUs patients

Honey is ideal dressing in cases of diabetic foot wounds particularly in the developing countries[35] as itis an environmentally based cost and clinically effective dressing. More importantly, honey is very safe for DFUs patients as it does not result in any complication (local or systemic).[19] For DFUs patients, various apitherapeutic (honey or propolis) dressing were applied as topical application of honey either solely,[1,21,56,93–99] with olive oil,[100,101] with propolis extract[25] or with bee venom.[102] All these studies, the apitherapeutic wound dressings accelerated DFU healing judged by infection control rates,[61,95,96] promotion boosting immune cellular elements,[23,45,69,87] reduced the time needed for wound debridement,[89] tissue maturation and wound re-epithelization. With all previous studies, honey wound dressing reduced patient hospitalization and amputation rates.[19] Honey dressing is safer for treatment of FDUs[21,52,95] since topical honey dressing is more effective than conventional pyodine, povidone-iodine[85] or betadine[103] dressing in terms of recovery time[21,90] leadind to complete wound closure.[92] Manuka honey topically is widely tried cocluded that it is very effective for wound healing in DFUs patients[21,88,97,104–106] and more effective than iodine, paraffintulle, olive iol, nanocrystalline and silver dressings.[107]

Topical propolis extract dressing,[47,48,57] its extract spray[108] or its lotion form[109] application for DFUs patients indicated the effectiveness of the intervention in reducing wound size. Topical application of honey with propolis proved synergistic action of healing quality and acceleration in male standard wounded in induced diabetic[63,77,95,96] or non-diabetic rats.[49] The topical application of honey with propolis for non-diabetic patient's wounds[110] or those with DFUs[111,112] proved the decreased wound areas significantly up to complete closure enhancing re-epithelization.[2] So it is recommended to use both api-products together for management chronic wounds especially those DFU wounds[49,77,104] or when be contaminated with antibiotic resistance pathogens[55,56] specially those biofilm producers.[19 30–32,36] Either *in vitro* or *in vivo* experimental studies rather than clinical apply for diabetic patients,[34,111,112,94] honey or propolis accelerated wound healing, it is proved that honey enriched together with propolis extract is an excellent source of antimicrobial[33,49,97] and antioxidant[113] with synergistic activity[2] maximizing the solo action of each.

Nano of single apitherapeutic product for diabetic wound dressing application

Nanomaterials may undergo novel chemical and physical changes in their structure as a result of their smaller size, indicating increased reactivity, solubility[114,115] improvement of the drug delivery, absorption and bioavailability having biocompatibility, non-toxicity, and biodegradability properties.[116] Wide range studies about apitherapeutic nanoformula scaffold have emerged as a promising therapeutic option in diabetic wound management application[117]) which was applied using single apiproducts ; honey,[34,88,89,92,101,106–121] propolis,[3,59,79,119,122–126] bee venom,[127,128] bee wax.[129] In vitro study of poly diallyldimethyl ammonium chloride / honey nanofiber[34] exhibited an excellent antibacterial activity (99.9%) against MRSA,[130] *S. aureus & E. coli*, while in topical application for DFUs achieved the best wound-healing properties with formation of high amounts of fibroblast cells, collagen fibers, and connective fibrils in the treated wounds.[34] Another in an *in vitro* study, nanofiber chitosan loaded honey olive oil cream increased antioxidant wound healin mediators.[101] Several propolis nanoformulations have been found and proven to have biological effects.[116] These nano particles stimulates fibroblast proliferation *in vitro* and it be preferable since resulting high rate of wound closure *in vivo* when be applied for DFUs patients.[79] More advanced nano propolis-loaded poly lacticco-glycolic acid[124] or polyvinyl-alcohol gelatin nanofibers[59] increases human fibroblast cells proliferation, activates antioxidant activity[131] and antibacterial agent against *E.coli, S. aureus* and *Candida albicans.*[124] When prolpolis extract nano particles is loaded (Pro-ZnO NPs) may give inhibitory activity against α-amylase and α-glucosidase with promting antioxidant effects.[132] Propolis nano formulation gave positive results comparing with propolis extract cream.[3] Topical application of a chitosan-blend film containing bee venom accelerated wound healing in diabetic mice through improvement of cellular elements and antioxidant cytokines.[127] Different forms of nano propolis wound dressings, such as foam, polyurethane,[82] nano-propolis fibers,[133] hydrogels[134,135] or chitosan bee venom hydrogel[136] were applied.

Wide scale of different honey nano fabrication[34,81,131,133] scaffolds were applied for DFUs with the mechanism of different multifunctional bioactive microcomponents[120] as honey nanoparticles (smart wound dressings). Honey hydrogels scaffold dressing,[137,138] topical ointments,[11] honey loaded nanocrystalline silver,[91,139] modified-honeycomb-structure scaffold,[140] honey polyvinyl alcohol nanofiber membrane, honey microneedles[130] or poly diallyl dimethylammonium chloride / honey nanofiber[34] to manufacture wound dressing for human DFUs resulted in complete healing[118] exploring its effectiveness in promoting wound healing, tissue regeneration, and antimicrobial activity with complete wound closure (5-12) days.[34] Honey nanofibrous bandages, films, hydrogels, hydrocolloids, tulle, foams, or gauzes stimulates cell proliferation and angiogenesis,[10,141] while chitosan topical gel and film were effective in promoting tissue granulation and DFU closure.[142] Honeynano chitosan hydroge[135] and with mixture of different types of propolis,[137] higher acceleration of wound re-epithelialization and closure[65] was obtained. It is suggested that these safe green nanomaterials fulfill their undoubtedly large therapeutic potentials.[108]

Nano of mixed apitherapeutic products for diabetic wound dressing application

Some studies proved the synergistic effect of nano application of honey with propolis ointment[49] orlotion,[109] propolis with bee venom[51] or honey with mixture of nano propolis / venom.[133] Wound dressing hydrogel loaded with honey bee propolis extract proved to be an antimicrobial wound healing agent,[110,134] while pectin, propolis and honey could be combined towards the fabrication of wound- healing patches are advantageous compared to traditional techniques,[143] mostly it is suggested that apitherapeutic wound dressing especially honey effectively promotes healing in DFU.[144] Honey pomegranate bee venom nanofiber wound dressing[102] has potent *in vitro* antimicrobial action against *E.coli and S. aureus* rather than *in vivo* study, it increased wound closure percentages.

Conclusion

The study concluded that for DFUs, apitherapeutic wound dressing is a promising alternative chemotherapeutic antimicrobial, wound healing accelerating and promoting agent without any risk of developing resistance or disease complication. The study ascertains the recommendation of using mixture of safe green apiproducts either naturally or nanoformulation to obtain synergistic actions of many apitherapeutic activities.

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Conflicts of interest

Author declare there are no conflicts of interest.

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