



A Brief Review about the Effect of Honey on Diabetic Foot Ulcer; from In Vitro Studies to Clinical Trials

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Abstract

Diabetes mellitus has many complications; one of the most important ones is diabetic foot ulcer (DFU). Due to the increasing prevalence of diabetes in the world and evidences of the role of honey in treatment of DFU, we decided to review the effect of honey on DFU. We searched the keywords of “honey”, “diabetic foot ulcer”, “treatment”, “diabetes mellitus”, “wound dressing” and “wound healing” in indexing systems of PubMed, Scopus and ISI Web of Science between 2007 to 1 Jun 2017, in English and Persian languages. Out of 120 articles published, 20 articles met the inclusion criteria, including one in vivo study, four in vitro studies and 15 human studies. The results showed the efficacy of honey as a wound healing agent in some types of wounds. Mechanisms of healing methods included hyper osmosis, stimulating cytokine production, producing transforming growth factor- β 1 and etc. In some articles, honey was used in combination with other medications like *Commiphora molmol*, *Nigella sativa* and povidone iodine. Honey showed minor side effects, in some studies, like mild burning or minor sensation. Despite these complications, the treatment was not stopped and in some cases the disorder was resolved by changing the combination ingredients. Although, the reviewed studies showed healing effect for honey in DFU, more studies are needed to confirm the efficacy.

Keywords: biological product; complementary therapies; diabetic foot; honey; wound healing

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Introduction

Diabetes mellitus is a global public health problem that has involved all countries. Its complications, especially diabetic foot ulcer (DFU), are having many economic and social problems and affect the quality of patients' life [1]. Generally, the prevalence of diabetes is increasing in the world and it is estimated to grow up to 366 million, by 2030 [2]. The disease is also common in Iran with prevalence of 7.7% in the age range of 25 to 64 years [3]. According to WHO reports, it is expected that there will be 5.2 million Iranians with diabetes mellitus in 2025 [4].

Diabetes is a systemic metabolic disorder and involves almost all parts of the body [2]. It has several complications such as peripheral neuropathy, peripheral vascular disease and foot trauma which cause these patients to be prone to DFU [5]. One of the causes of increased mortality in the patients with DFU is long-term hospitalization resulting in reduction of the immunity level; so the patients are more susceptible to hospital infections and inevitably it causes amputation [6].

Existing treatments include de sloughing and debridement, pressure relief, antibiotic therapy,

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wound dressing, cultured human dermis, granulocyte colony stimulating factor therapy, platelet-derived growth factor therapy, hyperbaric oxygen therapy, ketanserin, bone-marrow-derived stem cells, negative pressure dressings and bioengineered skin equivalents [7-8]. Often these treatments are not complete and do not result in 100% wound healing; for example, in the antibiotic therapy, infection is treated, not the ulcer [9]. Hyperbaric oxygen therapy can reduce the risk of major amputation, but it does not seem to be helpful in minor amputation and wound healing [8]. Although Infectious Disease Society of America guidelines are suitable for many diabetic patients, they are not recommended for chronic and hard-to-heal ulcers [9].

Due to the high prevalence, high medical cost and a lack of definite treatment for DFU, it is needed to find new therapeutic methods. Considering natural products and traditional remedies could be an approach to find new methods with increasing worldwide notice which are approved by World Health Organization (WHO) [10]. Honey is one of such traditional and natural products that is believed to possess wound healing effect in DFU [10].

Honey has been used for therapeutic purposes from ancient times and in complementary and alternative medicine [11]. The product was used to treat local ulcer and other skin disorder in the form of ointment [12-13]. In various traditional systems of medicine like Ayurveda, Chinese and Persian medicine, honey was used historically for treatment, in particular for ulcers [14]. Alongside the treatment purposes, it was an important source of carbohydrates and sweeteners before 18th century, because there was no industrial prepared sugar [13]. Furthermore, as a common treatment, honey had been used in the treatment of foot ulcer in leprosy patients, from 1951 to 1967 [15].

Today, natural remedies are welcome worldwide, in particular in Iran because of its root in the history and culture of people. Among the natural remedies, honey is widely welcome due to its availability [16,17]. Based on this historical background and safety of honey, there are many investigations to evaluate wound healing effect of honey, in particular for DFU in conventional medicine [18]. Therefore, in this study, we aimed to evaluate the effectiveness of honey for healing DFU through reviewing the previous *in vitro*, *in vivo* and clinical studies.

Methods

The key words of “honey”, “diabetic foot ulcer”, “treatment”, “diabetes mellitus”, “wound dressing” and “wound healing” were searched in the databases and indexing systems of PubMed, Scopus and ISI Web of Science to find papers published between 2007 to 1 Jun 2017, in English and Persian languages. Then, among the searched papers, *in vitro* and *in vivo* surveys and any type of clinical studies (case reports, case series, clinical trials, etc.) were included in the study and others were excluded. Finally, the selected papers were considered and analyzed.

Results and Discussion

Among 128 searched papers, there were 20 articles which met the inclusion criteria and were included in the study (figure 1). The papers covered four *in vitro* studies (on *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli* Extended-Spectrum Beta-Lactamase (*E coli* ESB), *Proteus mirabilis*, *Streptococcus pyogenes*, *Morganella morganii*, Methicillin-resistant *Staphylococcus aureus* (MRSA) and Community associated MRSA (CAMRSA)); one *in vivo* study on mice and 15 human studies articles including two case reports, one case series and 12 clinical trials. The papers showed both the effect of honey solely or in combination with other components like *Commiphora molmol*, *Nigella sativa* and povidone iodine. One of the products was a commercialized honey based formulation namely EDYPHAR ointment containing 5% natural royal jelly and 1% panthenol (table 1).

The articles showed that honey was effective in wound healing, but it was not effective in some wounds due to their large size and thus the organ was amputated [27,29,30]. Although the main mechanism for effect of honey was reported to be its antibacterial activity, in some articles unknown mechanisms were suggested [20,21,29,36]. In others the mechanisms including stimulation of cytokine production by monocyte [19], induction of the growth of granulation tissue and epithelialization [19,22,30,32,33,35,37], were reported. Diluted honey contains an enzyme that produces hydrogen peroxide [23,26]. Also, it can affect induction of wound regeneration similar to regeneration of epithelial cell [23]. Other mechanisms are acting by hyperosmolarity [24,26,28,35,38], making alkaline environment

[27], and minimizing water availability to bacteria [24,26,28]. Also, 10-hydroxydecanoic acid in royal jelly induces the fibroblast cell line to produce transforming growth factor- β 1 that is important for collagen production and inhibits matrix metallo proteinases (MMPs) [25,31]. Royal jelly proteins activate keratinocytes by increasing the mRNA level of selected cytokines and MMP9 [31], increasing lymph flow [35,37] and stimulating the rate of MMP9 concentration [38].

In most articles there were no reported side effects. While, in two articles honey had shown some unwanted effects in the patients. It was reported that patients experienced mild burning sensation [27] and some patients (n=4) reported minor sensation by application of an ointment which contained zinc oxide, *Aleo vera*, sunflower oil, *Calendula officinalis*, vitamins C and E and cod liver oil (retinol, vitamin E), therefore it was not clear that the complication occurred due to other compounds or honey [32]. But, previous studies have shown that some of these

ingredients like zinc oxide [39] and *Aloe vera* [40] could cause dermatologic reactions and side effects. Furthermore, in one paper fungi as well as two different genera of bacteria (*Paenibacillus* and *Bacillus*) were isolated from food grade honey and was suggested as a concern for healthcare practitioners [20].

Honey is a supersaturated sugar solution (having fructose, glucose, other disaccharides, etc.) and also contains amino acids, acids, vitamins (including riboflavin, pantothenic acid, niacin, thiamin, pyridoxine and ascorbic acid) and minerals (like potassium, sulfur, chlorine, calcium, phosphorus, magnesium, sodium and iron) [41]. These components are responsible for honey effects. Based on the results and the efficacy of honey on wound healing solely or in combination with other ingredients, honey can be a good candidate as the base for wound healing formulation. It could be a safe base with therapeutic effects.

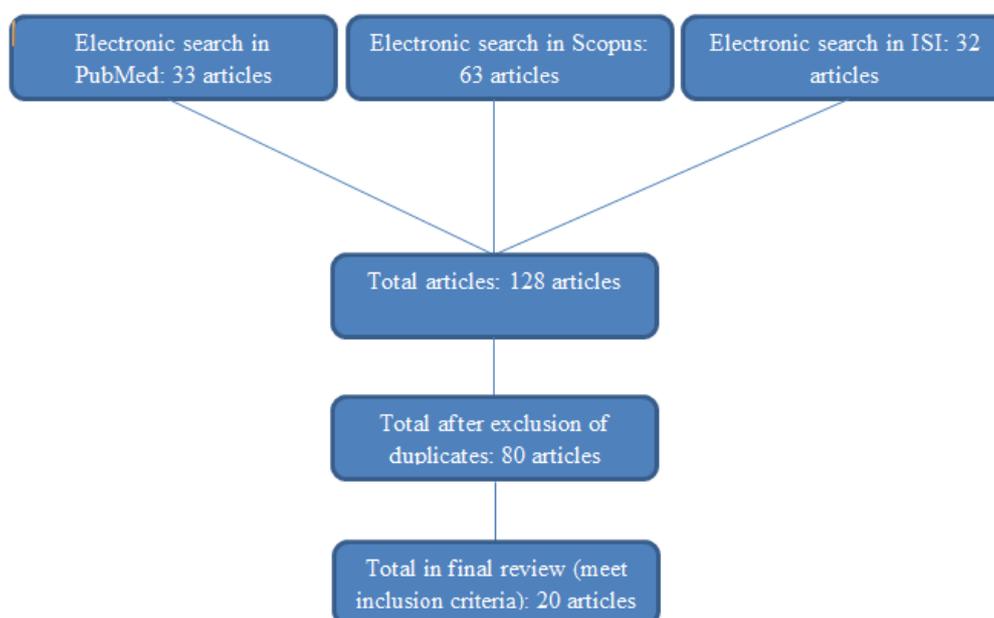


Figure 1. Flowchart of searching strategy

Conclusion

The results support the efficacy of honey on DFU, but there is a limitation because of the few number of published papers, in particular clinical studies. Although the results showed that honey

could be used as a complementary, effective and safe treatment for DFU, it needs more works to confirm the effects and also consider any probable unwanted effects.

Table 1. Details of included papers in the review

Objectives	Type of study	Target and sample size	Dosage form/Dose/Duration	Main outcomes	Reference
Effect of honey on <i>Pseudomonas aeruginosa</i>	In vitro	152 stains of <i>Pseudomonas aeruginosa</i> ,	Mixed honey and sterile Mueller Hinton agar by different concentrations 1% and 25%/ 37C for 24 hours	Types of honey tested with MIC 10% to 20% were responded to isolate of <i>Pseudomonas aeruginosa</i> from them.	[19]
Effect of honey on CA-MRSA	In vitro	CA-MRSA ST35, 5134, 4388, 4266, 4526 and 5090, Columbia blood agar	106 colony-forming units of each types of CA-MRSA were inoculated into each types of honey,37C for 24 hours	All CA-MRSA decreased by all types of honey.	[20]
Honey, commiphora molmol and nigella sativa	In vitro	Blood agar plate, <i>S.aureus</i> , <i>E.coli ESBL</i> , <i>Proteus mirabilis</i> , <i>Strep.pyogenes</i> , <i>Morg morganii</i> , <i>MRSA</i>	Honey, commiphora molmol and nigella sativa/ForNP6: Honey. MBC was read after 24 hours incubation as the least concentration showing no growth	All of NPs with 50% concentration could be enough to kill them after one day. NP4 and NP5 had most antibacterial effective	[21]
Efficacy of honey hydrogel <i>E. coli</i> and <i>S. aureus</i>	In vitro	<i>E. coli</i> and <i>S. aureus</i> , tryptic soy agar	Carboxymethyl cellulose (CMC) powder (20 wt%) and honeys (0, 5, 15 and 20 wt%) were Soluble in pure water, 37C for 3hr	Propolis-honey based hydrogel had inhibitory effect on two strains of bacteria.	[23]
Efficacy of honey hydrogel wounds	In vivo	Female mice, 2 wounds, weight between 18 and 24g, aged 5 weeks	Carboxymethyl cellulose (CMC) powder (20 wt%) and honeys (0, 5, 15 and 20 wt%) were Soluble in pure water, applied for 2 weeks	Honey/CMC hydrogel was faster in healing wound	[23]
honey-curcumin hydrogel composite	In vivo	Wistar rats (n=6) for each control and drug groups	Curcumin/honey hydrogel sponges, 2cm ² of drug on the skin of rats, applied for 7 days	All treated rats had significantly well formed granulation tissue in compression with controlled group by day 7	[22]
Efficacy of Royal jelly on wounds	Case series	8 patients (3 females-5 males), average aged 62±6 years old	Sterile natural Royal Jelly5%, applied up to healing wounds	Most (7) of them were healed completely within about 6 weeks	[25]
Efficacy of MPH (myrrh, bee propolis and honey)	Case report	a 65-year-old male with DFU (3cm) in the right foot	A paste consisting of myrrh (50g), bee propolis (800mg) and honey (MPH)..	The patient was healed after 4 weeks	[24]
Efficacy of honey in recalcitrant DFU	Case report	A 65 years old female, with diabetes of 25 years, BMI = 23 kg/m ² , ex-smoker length of 10*5 cm ²	Natural honey, sterile spatula, non-adhering foam	The patient was healed after 7 weeks.	[26]
Efficacy of EDYPHAR ointment	Clinical trial	60 patients , limb-threatening diabetic foot infection, aged range 18 to 70 years old	1–3g PEDYPHAR ointment, applied up to healing wounds	All of the ulcers in group1,3 and 92% of group 2 improved completely in 2 months	[27]
Compare effect of honey and povidone-soaked gauze	Clinical trial	30 patients, Wagner grade-II ulcers and non-insulin dependent DM, aged range 35 to 65 years old	Drug group: commercial honey /control group: povidone iodine solution 10% soaked gauze. The end point of the study was healing the wounds	Honey had an significant wound healing effect comparable with povidone-soaked gauze	[28]
Efficacy of natural honey	Clinical trial	The14 foot wounds (Wegener's Grade I to IV) of 12 patients (8 males and 4 females), aged range 35 to 65 years old	Natural honey, applied up to healing wounds	All except one of them were healed well	[29]

Table 1. Continued

Objectives	Type of study	Target and sample size	Dosage form/Dose/Duration	Main outcomes	Reference
Efficacy of pure raw untreated commercial honey	Clinical trial	30 patients, all ages, both sexes	Medium-pored non-sterile gauze/Pure raw untreated commercial honey, applied to wound for 3months till healing.	Most had been decreasing of ulcer size, improvement in stage of them and completely closed	[30]
Therapeutic effect of honey-based products	Clinical trial	22 patients with lower extremity wounds (6 males and 16 females), average aged 64 years old, 3 types patients: healthy, venous insufficiency and diabetes	Two types of honey ointment (L Mesitran Ointment) and soft gel (L-Mesitran soft gel) including 48% and 40% medical grade honey, respectively. Products were applied daily. The primary outcome was full healing of the wounds.	The average time of healing for all of the participants (healthy, diabetic, etc.) in the study was 65 days.	[32]
Comparison of therapeutic effect between honey dressing and pyodine dressing	Clinical trial	100 patients with Wegener's Grade I to IV unilateral (63 males and 37 females), aged range 38 to 70 years old, 2 groups	"Honey dressing" group: Honey/"Conventional Pyodine dressing" group. Recovery times were 2-4, 5-7 and 8-10 weeks and final outcome were when the organ were healed or amputated.	Honey dressing group was also able to more improvement and lesser amputation	[33]
Effect of Manuka honey, taken Swab culture, Shapiro Wilk test	Clinical trial	63 type II diabetic patients with Wegener's Grade I and II lower limb neuropathic ulcers, male and female, average aged 56 ± 14 years for group 1 and 57 ± 15 years for group 2	Manuka honey-impregnated dressing (Medihoney Tulle Dressing), conventional dressing (CD, saline-soaked gauze dressing), applied for 4 months	Manuka honey dressings had declined significantly in period of NDFU recovery.	[34]
Efficacy of honey, Swab culture	Clinical trial	172 patients (102 males and 70 females), above 17 years old	Honey was applied in the DFU patients up to healing the wounds	Honey dressing could decrease number of amputation and increased process of wound healing significantly. Wounds became healthy within 7 to 35 days.	[35]
Assessing the efficacy of RJ	Clinical trial	25 patients with 64 DFUs (19 males and 6 females), average aged 60 years old	Treatment group: sterile Royal Jelly vs. Placebo group, applied up to healing wounds	90.6% of placebo group and 93.8% of RJ group were healed completely.	[31]
Effect of Aleo vera and Honey Gel	Clinical trial	39 patients with nonischemic, noninfected DFUs (19 males and 20 females), average aged 56.3 ± 10.2 years old	Treatment group: 50% Aleo vera gel and 25% honey/Placebo group: lacking Aleo vera gel and honey, applied for 8 weeks	95.5% of patients in drug group and 78.6% of patients in placebo group were healed	[36]
Comparing the efficacy of the honey dressing and normal saline dressing	Clinical trial	375 patients (Wagner's grade 1 or 2), above 17 years old, two groups	Treatment group: Beri honey/Control group: normal saline, applied up to healing wounds	Completely healing in honey group was more than normal saline group.	[37]
Analyzing of efficacy of nAg, MH and conventional dressing	Clinical trial	31 diabetic patients, wound size equal to or larger than 1cm, 39 above years old, 3 groups	Acticoat absorbent and Medihoney gel sheet vs. Paraffin tulle, for 3 months	The nAg group from the point of healing completely and size reduction rate was better than other.	[38]

Author contributions

Fahimeh Khosravi contributed to data gathering and drafting the manuscript; Arman Zargarani contributed to the study design and analysis of the data. Both authors approved the final draft of the manuscript.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

DFU: Diabetic foot ulcer; WHO: World health organization