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-β1 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

Citation: Khosravi F, Zargaran A. A brief review on the effect of Honey on diabetic foot ulcer; from in vitro studies to clinical trials. Res J Pharmacogn. 2019; 6(3): 85-91.

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,
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 ESBL), Proteus mirabilis, Streptococcus pyogenes, Morganella morgani, Methicillin-resistant Staphylococcus aureus (MRSA) and Community associated MRSA (CA-MRSA)); 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...
A brief review on the effect of Honey on diabetic foot ulcer

[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-β1 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, Aloe 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, pantothentic 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](image)

**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.
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<th>Objectives</th>
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<tr>
<td>Effect of honey on <em>Pseudomonas aeruginosa</em></td>
<td>In vitro</td>
<td>152 stains of <em>Pseudomonas aeruginosa</em>, CA-MRSA ST35, 5134, 4388, 4266, 4526 and 5090, Columbia blood agar</td>
<td>Mixed honey and sterile Mueller Hinton agar by different concentrations 1% and 25%/ 37°C for 24 hours</td>
<td>Types of honey tested with MIC 10% to 20% were responded to isolate of <em>Pseudomonas aeruginosa</em> from them.</td>
<td>[19]</td>
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<td>Effect of honey on CA-MRSA</td>
<td>In vitro</td>
<td>Blood agar plate, *S.aureus, E.coli ESBL, Proteus mirabilis, Strep.pyogenes, Morg morganii, MRSA</td>
<td>Honey, commiphora molmol and nigella sativa/ForNP6: Honey, Carboxymethyl cellulose (CMC) powder (20 wt%) and honeys (0, 5, 15 and 20 wt%) were Soluble in pure water, 37°C for 3hr</td>
<td>All CA-MRSA decreased by all types of honey.</td>
<td>[20]</td>
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<td>Honey, commiphora molmol and nigella sativa</td>
<td>In vitro</td>
<td>Wistar rats (n=6) for each control and drug groups</td>
<td>Curcumin/honey hydrogel sponges, 2cm² of drug on the skin of rats, applied for 7 days</td>
<td>Propolis-honey based hydrogel had inhibitory effect on two strains of bacteria.</td>
<td>[23]</td>
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<td>Efficacy of honey hydrogel <em>E. coli</em> and <em>S. aureus</em></td>
<td>In vitro</td>
<td>Female mice, 2 wounds, weight between 18 and 24g, aged 5 weeks</td>
<td>Honey/cMC hydrogel was faster in healing wound</td>
<td>Efficacy of honey hydrogel wounds</td>
<td>[23]</td>
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<td>Efficacy of honey hydrogel wounds</td>
<td>In vivo</td>
<td>Wistar rats (n=6) for each control and drug groups</td>
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<td>Efficacy of honey hydrogel wounds</td>
<td>[22]</td>
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<td>honey-curcumin hydrogel composite</td>
<td>In vivo</td>
<td>Mixed honey, applied up to healing wounds</td>
<td>Sterile natural Royal Jelly®, applied up to healing wounds</td>
<td>All of them were healed completely within about 6 weeks.</td>
<td>[25]</td>
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<td>Efficacy of Royal jelly wounds</td>
<td>Case series</td>
<td>8 patients (3 females-5 males), average aged 62±6 years old</td>
<td>Sterile natural Royal Jelly®, applied up to healing wounds</td>
<td>Most (7) of them were healed completely within about 6 weeks.</td>
<td>[24]</td>
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<td>Efficacy of MPH (myrrh, bee propolis and honey)</td>
<td>Case report</td>
<td>A 65 years old male with DFU (3cm) in the right foot</td>
<td>A paste consisting of myrrh (50g), bee propolis (800mg) and honey (MPH)</td>
<td>The patient was healed after 4 weeks.</td>
<td>[19]</td>
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<tr>
<td>Efficacy of honey in recalcitrant DFU</td>
<td>Case report</td>
<td>A 65 years old female, with diabetes of 25 years, BMI = 23 kg/m², ex-smoker length of 10*5 cm²</td>
<td>Natural honey, sterile spatula, non-adhering foam</td>
<td>The patient was healed after 7 weeks.</td>
<td>[26]</td>
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<td>Efficacy of EDPYPHAR ointment</td>
<td>Clinical trial</td>
<td>60 patients, limb-threatening diabetic foot infection, aged range 18 to 70 years old</td>
<td>1-3g EDPYPHAR ointment, applied up to healing wounds</td>
<td>Efficacy of EDPYPHAR ointment</td>
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<td>Compare effect of honey and povidone-soaked gauze</td>
<td>Clinical trial</td>
<td>30 patients, Wagner grade-II ulcers and non-insulin dependent DM, aged range 35 to 65 years old</td>
<td>Drug group: commercial honey /control group: povidone iodine solution 10% soaked gauze. The end point of the study was healing the wounds</td>
<td>Compare effect of honey and povidone-soaked gauze</td>
<td>[28]</td>
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<td>Efficacy of natural honey</td>
<td>Clinical trial</td>
<td>The 14 foot wounds (Wegener's Grade I to IV) of 12 patients (8 males and 4 females), aged range 35 to 65 years old</td>
<td>Natural honey, applied up to healing wounds</td>
<td>Efficacy of natural honey</td>
<td>[29]</td>
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Table 1. Continued

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


**Abbreviations**

DFU: Diabetic foot ulcer; WHO: World health organization