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Effectiveness of honey dressing in the treatment of diabetic foot ulcers: A systematic review and meta-analysis

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ABSTRACT

Objective: Honey dressing has been applied in the treatment of diabetic foot ulcers (DFUs). However, there is a lack of research showing ample evidence that honey dressing is more effective in the treatment of DFUs than other dressings. This study aimed to examine the effects of honey dressing on wound-healing process for DFUs.
Method: We searched for evidence regarding honey dressing used in the treatment of DFUs in various databases. We selected randomized controlled trials (RCTs) and quasi-experimental studies for meta-analysis.
Results: The meta-analysis showed that honey dressing effectively shortened the wound debridement time, wound healing time, and bacterial clearance time; it increased the wound healing rate and bacterial clearance rate during the first one to two weeks of use.
Conclusion: Our findings suggest that honey dressing effectively promotes healing in DFUs. Further research is needed to elucidate these findings so that this form of treatment can be widely applied.

1. Introduction

Diabetic foot ulcers (DFUs), which are caused by changes in peripheral blood vessels and nerves, can lead to severe and chronic complications in diabetes [1]. These complications include infection and lower extremity amputation, which have become one of the major causes of disability and death among diabetes patients [2]. With a prevalence rate of 4–10% [3], DFUs not only constitute an enormous economic burden on patients, but they can also negatively affect their quality of life [4]. A wide range of measures have been applied in the management of DFUs, including debridement, blood glucose control, and infection prevention; however, the clinical effectiveness of these methods is still poor. At present, wound dressing plays an integral part in managing DFUs. Different types of wound dressings can be applied to DFUs, including conventional dressing (such as iodine dressing), functional dressing (such as hydrocolloid dressing), and honey dressing [5]. Clinicians have increasingly recognized the value of choosing suitable dressings to manage DFUs, which can help accelerate wound healing processes, inhibit the propagation of microbes, and improve the wound-healing rate.

Some studies have reported that honey dressing is effective in treating DFUs. Honey dressing, is clinically defined as honey placed on common surgical gauze, which is then applied to promote wound healing, additionally, this honey has been processed to meet physiochemical testing standards for medical use [6]. Research has shown that honey has broad-spectrum bactericidal properties, aids in the management of wound infection, enhances the proliferation of epithelium, and absorbs edema around the wound [7,8]. A prospective observational study randomly investigated 30 diabetes patients treated with honey dressings, and found that after three months of treatment, complete healing was significantly achieved in 43.3% of foot ulcers [9]; additionally, there was an observed reduction in ulcer size with formation of healthy granulation tissue in another 43.3% of patients [9].

Other research has showed similar findings, however, the number of studies and the quality of data are limited. Jull et al. conducted a systematic review regarding the application of honey dressing for all wounds, but this study did not provide subgroup analysis and special report on DFUs [10]. Furthermore, a previous systematic review, related to the effects of honey dressing on DFUs, lacked quantitative synthesis [11]. Other meta-analysis specific to honey dressing applied to DFUs had a considerably low number of subjects [5,12]. This can be attributed to the fact that the application of honey dressing on DFUs has not been used extensively. To date, there is a lack of research that provides sufficient evidence that honey dressing is more effective in the treatment of DFUs than other dressings. We conducted this systematic review and meta-analysis to evaluate the role of honey dressing as an effective intervention for the treatment of DFUs and to provide a reliable basis for the future clinical work based on our analysis.

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2. Materials and methods

2.1. Literature search strategy

We conducted the search process in several medical databases, which included: PubMed, the Cochrane Library, Web of Science, EMBASE, China National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM), Database for Chinese Technical Periodicals (VIP), and Wanfang Digital Journal Full-text Database. We used the following search strategy for the PubMed database: ((honey dressing) or (honey) or (honey-impregnated dressing) or (honey-coated dressing) or (honey bandage)) AND ((diabetic foot [MeSH Terms]) or (foot, diabetic) or (diabetic feet) or (feet, diabetic) or (foot ulcer, diabetic) or (foot ulcer [MeSH Terms])). We used similar keywords to search the other selected databases and the Google search engine. The process of literature retrieval consisted of four steps: (1) retrieve associated systematic reviews and meta-analyses from the Cochrane Library; (2) retrieve relevant original studies from the databases, followed by the analysis of the title, abstract, and keywords of each publication for the purpose of choosing suitable search keywords; (3) retrieve all relevant information from the databases using the keywords; and if the abstract was in accordance with the inclusion criteria, the study underwent further investigation; (4) use the associated study and obtained references to search further. We focused on studies published in the English and Chinese language. Electronic searches were performed in databases from their inception to October 2017. Each study was carefully examined, including the names of all authors, to avoid duplication of data.

2.2. Eligibility criteria

2.2.1. Types of studies

We selected an assortment of randomized controlled trial (RCT), quasi-experimental, cohort, cross-sectional, and observational studies. We selected RCTs and quasi-experimental studies for meta-analysis. We only conducted a descriptive analysis for observational studies.

2.2.2. Types of participants

We included studies involving patients (aged ≥18 years) with DFUs. The diagnosis of diabetes was not limited to any type. The Wagner classification of DFUs was also not limited.

2.2.3. Types of interventions

Studies were eligible if they focused on honey in the treatment of DFUs. We excluded studies that assessed multifaceted interventions, as this made it difficult to isolate and attribute the effect of honey dressing on DFUs.

2.2.4. Types of outcomes

Eligible studies included at least one of the following outcomes: wound healing rate, bacterial clearance rate, wound debridement time, wound healing time, and bacterial clearance time. Complete ulcer healing was defined as complete epithelialization of the wound, which would not need cleaning or dressing in any part. Wound debridement time was defined as the period from the beginning of treatment to the time in which necrotic tissues were cleared. Bacterial clearance time was measured as the duration from initial treatment to the time in which wound swab cultures were negative.

2.3. Data extraction

Two researchers independently extracted the data from selected studies and entered it in a standardized data extraction table; a third party was consulted for resolution of any disagreement. The data extracted, included (1) baseline characteristics of the included studies, such as title, author, year, and country (2) characteristics of patients, including age, Wagner classification, duration of diabetes, and sample size (3) intervention measures, such as follow-up time, (4) reported outcomes of interest, (5) the quality of included studies, and (6) grading of the literature.

2.4. Quality evaluation of studies

Two researchers independently evaluated the quality of the included studies, and a third party was consulted for resolution of any disagreement. For RCTs and quasi-experimental studies, we used criteria from the Cochrane Handbook for Systematic Reviews of Interventions [13]; We evaluated the risk of bias of RCTs and quasi-experimental studies based on the following criteria: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. We categorized each item as having low, unclear, or high risk of bias. For the studies eligible for meta-analysis, if the study fully met the above criteria, the quality of the study was classified as grade A. If the study partially met the above criteria, the quality of the study was classified as grade B. If the study did not satisfy the above criteria at all, the quality of the study was classified as grade C. Our meta-analysis excluded studies with grade C, owing to its poor quality.

2.5. Statistical analysis

Meta-analysis was conducted using the Review Manager (RevMan) 5.3 software. The summary measures were reported as odds ratios (*ORs*) or as a standard mean difference (*SMD*) with 95% confidence intervals (*CI*). The presence of heterogeneity among trials was assessed using Chi-square test, and the extent of the inconsistency was measured by I^2 statistics. A fixed-effects model was used for a two-sided P value > 0.1 and $I^2 < 50\%$. A random-effects model was calculated for a two-sided P value < 0.1 and $I^2 \geq 50\%$. A two-tailed P-value < 0.05 was deemed statistically significant.

3. Results and discussion

3.1. Results of the database search

Our search strategy identified 244 potential studies. After excluding irrelevant studies (n = 71) and duplicates (n = 120), 53 full-text studies were assessed for eligibility. Among them, 41 studies did not meet the inclusion criteria. Ultimately, 11 studies were included in the systematic review. Among them, only one study [14] was published in Chinese, and the rest were published in English [9,15–23]. The flow diagram of study identification process is illustrated in Fig. 1.

3.2. General characteristics and quality of the selected studies

The characteristics of studies concerning RCTs and quasi-experimental studies are described in Table 1. The studies included were published from 2013 to 2017, and included 756 patients from five countries, including locations in China, Pakistan, Greece, Iran, and Saudi Arabia. Sample sizes ranged from 20 to 348 subjects. The mean age ranged from 54 to 65.6 years. The duration of diabetes ranged from 12.76 to 17 years. The follow-up time ranged from 4 to 17 weeks. Among them, two studies [14,19] with three subgroups were subdivided in two different RCTs each. Hence, six studies were included in the current meta-analysis [14–19], which comprised seven RCTs and one quasi-experimental study.

The assessment of risk bias of studies concerning RCTs and quasi-experimental studies are listed in Table 3. The quality of all included studies [14–19] was grade B. All studies [14–19] described withdrawals and dropout numbers and reasons clearly. Three studies [14,17,19] carried out a concrete sequence randomization process, two studies

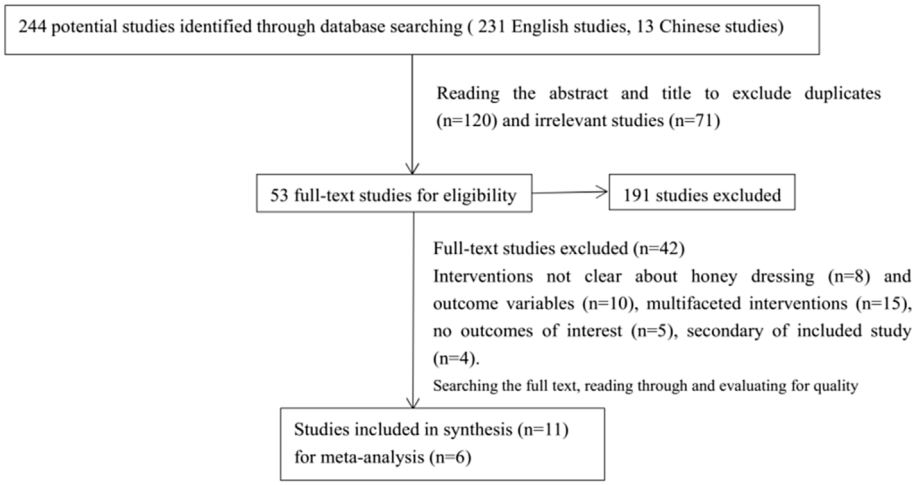

Fig. 1. Flow diagram of study identification.

[15,16] performed a double-blinded process, and two studies [15,19] conducted an allocation concealment. Four [14,17–19] were at high risk for the blinding of participants and personnel criteria as well as outcome assessment criteria. Four studies [14,16–18] did not performed the allocation concealment process, which may have resulted in possible selection bias. Therefore, we suggest that future studies should specify recruitment methods and recruit participants in a more systematic manner to improve the representativeness of the sample.

The characteristics of observational studies are described in Table 2. The studies were published from 2008 to 2011, and comprised 274 patients from four countries, including locations in Egypt, Pakistan, Iran, and Saudi Arabia. Sample sizes ranged from 4 to 172 subjects. The mean age ranged from 52.3 to 62 years. The follow-up time ranged from 3 to 6 months. No observational studies reported the duration of diabetes. Among observational studies included, there were three prospective observational studies [9,21,23], one case series [20], and one experimental study [22]. There was no case control study conducted.

3.3. Results of meta-analysis

3.3.1. The effectiveness of honey dressing on wound healing rate

We included five studies in this analysis, which comprised 616 patients [15–19]. Among them, one was quasi-experimental study [18] and the rest were RCTs [15–17,19]; additionally, among them, two studies with three subgroups [14,19] were subdivided in two different RCTs each. The heterogeneity test showed $I^2 = 22\%$ ($P = 0.27$), and a fixed-effect model was used. The results with an $OR = 1.85$ (*95% CI:* 1.28 to 2.68, $P < 0.01$) indicated that honey dressing correlated with a higher wound healing rate when compared to other dressing types (Fig. 2).

3.3.2. The effectiveness of honey dressing on bacterial clearance rate after one week of treatment

We included two RCT studies in this subgroup analysis, which comprised 203 patients [14,16]. Among them, one study with three subgroups [14] was subdivided in two different RCTs. The heterogeneity test showed $I^2 = 0\%$ ($P = 0.43$), and a fixed-effect model was considered. The results with an $OR = 4.55$ (*95% CI:* 2.22 to 9.35, $P < 0.01$) suggested that honey dressing was associated with a higher bacterial clearance rate after one week of treatment when compared to other dressings (Fig. 3a).

3.3.3. The effectiveness of honey dressing on bacterial clearance rate after two weeks of treatment

We included two RCT studies in this subgroup analysis, which comprised 203 patients [14,16]. Among them, one study contained three subgroups [14] which was subdivided in two different RCTs. The heterogeneity test showed $I^2 = 0\%$ ($P = 0.61$), and a fixed-effect model was used. The results with an $OR = 4.15$ (*95% CI:* 2.17 to 7.93, $P < 0.01$) revealed that honey dressing was associated with a higher bacterial clearance rate after the first two weeks of treatment as compared with other dressings (Fig. 3b). Furthermore, Kamaratos et al. [16] investigated the efficacy of honey dressing in one RCT, in which 100% of patients in the honey dressing group presented with sterile ulcers until four weeks, whereas, only 87.1% of patients in the saline soaked dressing group presented with sterile ulcers during that same time period. Guo et al. [14] studied an RCT specific to DFUs, which indicated that patients with DFUs applied with honey dressing had a significantly superior bacterial clearance rate during the first three weeks when compared with patients who were treated with functional and conventional dressings (100%, 71.43%, 54.29%, respectively; $P < 0.001$).

3.3.4. The effectiveness of honey dressing on bacterial clearance time

We included one study in this analysis, which comprised 140 patients [14]. This study with three subgroups was subdivided in two different RCTs [14]. The heterogeneity test showed $I^2 = 23\%$ ($P = 0.25$), and a fixed-effect model was used. The results with a $SMD = -0.91$ (*95% CI:* −1.26 to −0.56, $P < 0.01$) suggested that honey dressing was associated with an earlier bacterial clearance time as compared with other dressings (Fig. 4).

3.3.5. The effectiveness of honey dressing on wound debridement time

We included one study in this analysis, which comprised 140 patients [14]. This study with three subgroups was subdivided in two different RCTs [14]. The heterogeneity test showed $I^2 = 22\%$ ($P = 0.26$), and a fixed-effect model was considered. The results with a $SMD = -1.62$ (*95% CI:* −2.00 to −1.23, $P < 0.01$) suggested that honey dressing was associated with a shorter wound debridement time than other dressings (Fig. 5).

3.3.6. The effectiveness of honey dressing on wound healing time

We included three RCT studies in this analysis, which comprised 267 patients [14–16]. Among them, one study with three subgroups was subdivided in two different RCTs [14]. The heterogeneity test showed $I^2 = 94\%$ ($P < 0.01$), and a random-effect model was considered. The results with a $SMD = -1.30$ (*95% CI:* −2.45 to −0.15, $P < 0.01$) revealed that honey dressing was associated with a shorter wound healing time than other dressings (Fig. 6). Additionally, one RCT which investigated 30 diabetes patients, found that the mean healing time of the foot ulcers in the standard dressing group was 15.4 days

Table 1
Characteristics of RCT and quasi-experimental studies.

Author	Sample size Honey/ Control	Country	Age (years) Honey/Control	Wagner classification	Duration of diabetes (years) Honey/Control	Intervention		Follow-up time	Study design	Outcome measures	Results
						Experimental	Control				
Guo et al. a [14],2013	35/35	China	55.72 ± 29.14	II-III	12.76 ± 7.53	Honey dressing	Functional dressing	4 weeks	RCT	① Bacteria clearance time and bacteria clearance rate ② Area of healing rate ③ Wound healing time and wound healing rate ④ Wound debridement time	① In the honey group, the bacterial clearance, and area of healing rate were significantly higher than control groups. ② In the honey group, the average clearance time, bacterial clearance, wound debridement time and treatment time were shorter.
Guo et al. b [14],2013	35/35	China	55.72 ± 29.14	II-III	12.76 ± 7.53	Honey dressing	Conventional iodine dressing	4 weeks	RCT	① Bacteria clearance time and bacteria clearance rate ② Area of healing rate ③ Wound healing time and wound healing rate ④ Wound debridement time	① In the honey group, the bacterial clearance and area of healing rate were significantly higher than control groups. ② In the honey group, the average clearance time, bacterial clearance, wound debridement time, and treatment time were shorter.
Siavash et al. [15],2015	32/32	Iran	60 ± 7/60.6 ± 7	0-III	17/16	Royal jelly	Placebo	3 months	RCT	① Wound healing rate ②Wound healing time ③Depth, length and width reduction rate	① Depth, length and width reduction rate, duration of complete healing, and incidence of complete healing did not show any significant difference.
Kamaratos et al. [16],2014	32/31	Greece	56 ± 14/57 ± 15	I-II	NR	Manuka honey-impregnated dressing	Saline soaked dressing	6 weeks	RCT	① Wound healing time ② Wound healing rate Wound healing rate ③ Bacteria clearance time	① Mean healing time: Honey group: 31 ± 4 days, Control group: 43 ± 3 days ② Percentage of sterile wound: Honey group: 78.13%, 15.62%, 38.7%, 6.25% for I, II, III, IV week, respectively. Control group: 35.5%, 12.9%, 0%, 12.9% for I, II, IV, VI week, respectively. ③The percent of ulcers healed did not differ significantly between groups.
Imran et al. [17],2015	179/169	Saudi Arabia	54(47–64)/54(47–63)	I-II	NR	Honey dressing	Normal saline dressing	120 days	RCT	① Wound healing rate ② Wound	① Wound healing rate: Honey group: 75.97%, Control group: 57.39%

(*continued on next page*)

Table 1 (*continued*)

Author	Sample size Honey/ Control	Country	Age (years) Honey/Control	Wagner classification	Duration of diabetes (years) Honey/Control	Intervention		Follow-up time	Study design	Outcome measures	Results
						Experimental	Control				
										healing time ③ Wide effects of dressing methods ④ Patients' satisfaction to treatment ⑤ Deterioration of wounds	② Wound healing time Honey group: 18 days (range 6–120 days) Control group: 29 days (range 7–120 days)
Jan et al. [18],2016	50/50	Pakistan	56 ± 8	I-IV	NR	Honey dressing	Pyodine dressing	10 weeks	quasi-experimental study	① Wound healing rate ② Amputation rate ③ Wound healing time	① Percentage of ulcer recovered:Honey group: 60%, 34%, 6% for 2–4 weeks, 5–7 weeks, and 8–10 weeks, respectively.Control group: 30%, 26%, 44% for 2–4 weeks, 5–7 weeks, and 8–10 weeks, respectively. ② p: 28% Control group: 34% ③ Recovery rate Honey group: 72% Control group: 66%
Tsang et al. a [19],2017	11/11	China	65.6 ± 11.42/63.36 ± 11.31	NR	13.3 ± 9.63/14.82 ± 10.44	Manuka honey dressing	Nanocrystalline silver dressing	12 weeks	RCT	① Wound healing rate ② Ulcer size reduction rate ③ Bacteriology, and clinical signs of wound infection ④ Change in TNF- α, IL-1α, and MMP-9 levels	① Wound healing rate: Honey group: 50% Control group: 81.8% ② Ulcer size reduction rate: Honey group: 86.12% Control group: 97.45% ③ Nanocrystalline silver dressing showed a greater rate of microorganism reduction although it was not significant.
Tsang et al. b [19],2017	11/10	China	65.6 ± 11.42/66.1 ± 12.31	NR	13.3 ± 9.63/15.20 ± 9.88	Manuka honey dressing	Conventional dressing	12 weeks	RCT	① Wound healing rate ② Ulcer size reduction rate ③ Bacteriology, and clinical signs of wound infection ④ Change in TNF- α, IL-1α, and MMP-9 levels	① Wound healing rate: Honey group: 50% Control group: 40% ② Ulcer size reduction rate Honey group: 86.21% Control group: 75.17%

NR: not reported.
Guo a [14] and Guo b [14] came from one study, Tsang a [19] and Tsang b [19] came from one study.

Table 2
Characteristics of observational studies.

Author	Sample size	Country	Intervention	Age (year)	Wagner classification	Follow-up Time	Study design	Results
Moghazy et al. [9], 2010	30	Egypt	Topical honey	Mean: 52.3	NR	3 months	Prospective observational study	①Complete healing was significantly achieved in 43.3% of ulcers, and failure of treatment was observed in 6.7% of ulcers. ②Decrease in ulcer size and increased healthy granulation tissue was significantly observed in another 43.3% of patients. ③Bacterial load of all ulcers was significantly reduced after the first week of honey dressing.
Siavash et al. [20], 2011	8	Iran	Topical honey	62 ± 6	NR	3 months	Case series	①Seven of the eight ulcers healed. ②Mean duration of complete healing was 41 days. ③One ulcer did not completely heal but improved to 40% smaller in length, 32% in width, and 28% in depth. ④The mean length, width, and depth reduction rates were 0.35 mm/day, 0.28 mm/day, and 0.11 mm/day, respectively.
Surahio et al. [21], 2009	172	Saudi Arabia	Topical honey	≥18 (total)	NR	NR	Prospective observational study	①Wounds became healthy within 7–35 days. ②Three patients underwent big toe amputation, two patients underwent below knee amputations.
Tasleem et al. [22], 2009	4	Pakistan	Honey ointment containing 20% active antimicrobial honey	53.8 ± 5.1	NR	NR	Experimental study	① 95% of diabetic foot ulcers healed with a mean healing time of 20 days (range 8–40 days).
Abdelatif et al. [23], 2008	60	Egypt	Topical royal jelly	54.6 ± 8.8	I-V	6 months	Prospective pilot study	①96% of patients of grade I, grade II, and grade III presented with complete healing.

NR: not reported.

Table 3
Assessment of risk of bias in RCT and quasi-experimental studies.

Study	Random sequence generation	Blinding process		Allocation concealment	Incomplete outcome data	Selective reporting	Other bias	Quality grade
		Blinding of participants and personnel	Blinding of outcome assessment					
Guo et al. a [14],2013 Guo et al. b [14],2013	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk	B
Siavash et al. [15],2015	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	B
Kamaratos et al. [16],2014	Unclear risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	B
Imran et al. [17],2015	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk	B
Jan et al. [18],2016	Unclear risk	High risk	High risk	High risk	Low risk	Low risk	Low risk	B
Tsang et al. a [19],2017 Tsang et al. b [19],2017	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	B

Guo a [14] and Guo b [14] came from one study, Tsang a [19] and Tsang b [19] came from one study.

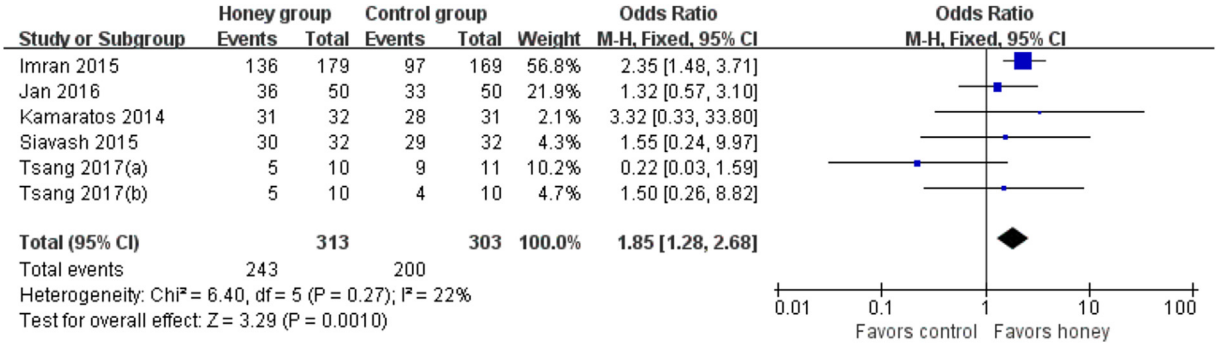

Fig. 2. The effectiveness of honey dressings on wound healing rate.

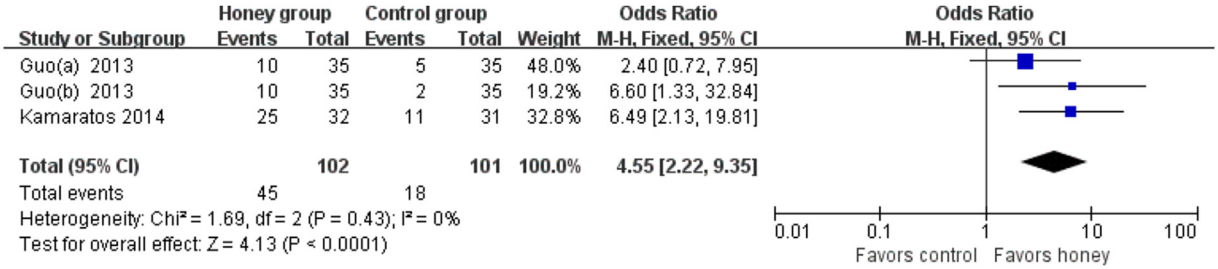

Fig. 3a. The effectiveness of honey dressings on bacterial clearance rate during the first week.

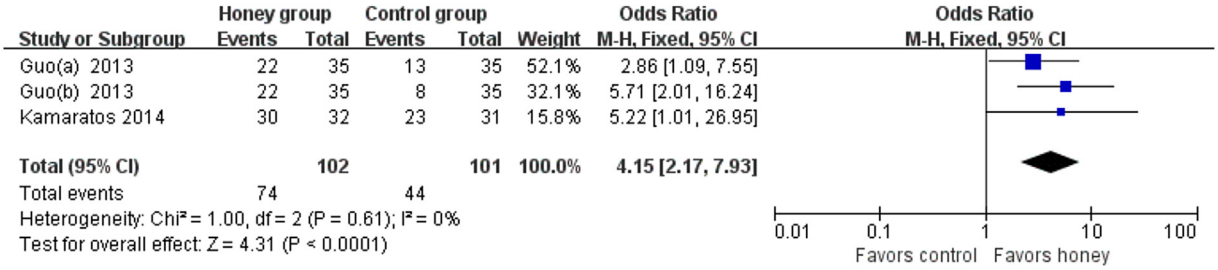

Fig. 3b. The effectiveness of honey dressings on bacterial clearance rate during the first two weeks.

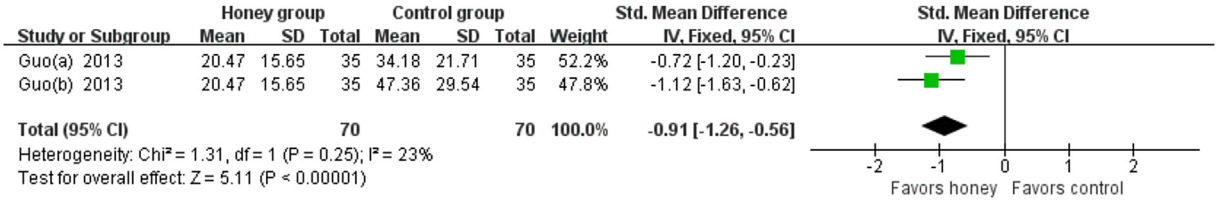

Fig. 4. The effectiveness of honey dressings on bacterial clearance time.

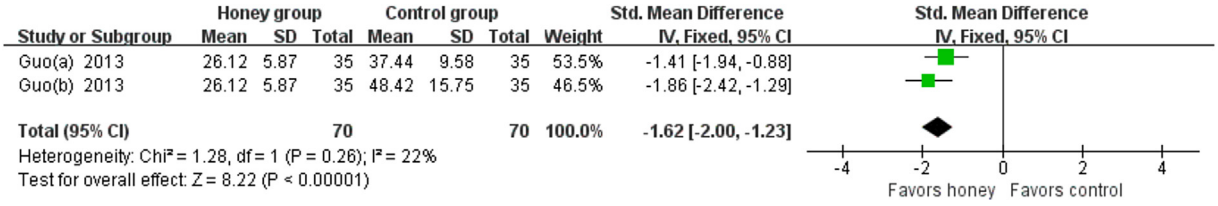

Fig. 5. The effectiveness of honey dressings on wound debridement time.

(range 9–36 days) compared to 14.4 days (range 7–26 days) in the honey dressing group ($P < 0.05$) [24]. Previous study reported that the mean healing time of foot ulcers was longer in the control group than in the honey dressing group ($P < 0.05$) [17].

3.4. Results of observational studies

There were five observational studies in this review. All the observational studies have shown that honey could increase wound healing rate and shorten wound healing time. Furthermore, honey was associated with a decreased risk of amputation.

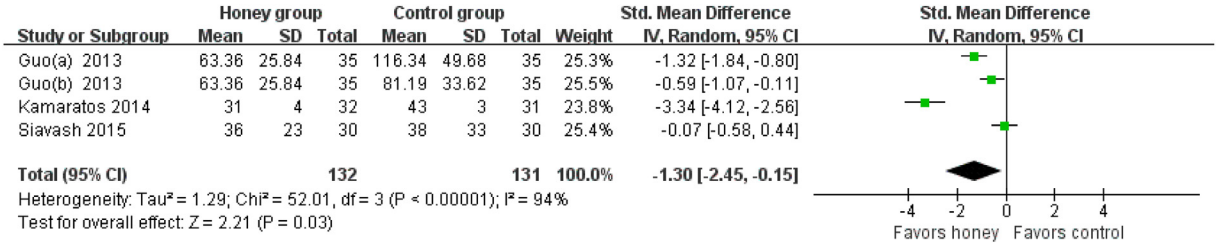

Fig. 6. The effectiveness of honey dressings on wound healing time.

3.5. Honey wound-care capabilities

Overall, this study highlighted major findings on the effectiveness of honey dressing in the treatment of DFUs. Although honey has been used in wound dressing for thousands of years, its value has been proved in recent years [8]. Honey is acidic with a pH of around 3.2–4.5, and it has been reported that low pH could inhibit the activity of protease, hence reducing the destruction of the matrix needed for tissue repair [8,25]. Additionally, an acidic environment could increase the release of oxygen from hemoglobin, thus positively affecting the wound healing process [26]. Other studies have indicated that an alkaline environment was beneficial to the growth of microbes, so the acidity of honey may inhibit the reproduction of microbes. Additionally, 3–6 atm of pressure were favorable for the proliferation of bacteria [26]. Meanwhile, honey is also a kind of hypertonic solution with an osmotic pressure about 105 atm of pressure. Thus, the high osmolarity of honey could effectively inhibit growth of bacteria, and its high viscosity could help to provide a protective barrier to prevent infection; furthermore, the osmotic effect could absorb pus and eliminate odor [6].

Research has found that honey contains hydrogen peroxide, which is essential to protect against infection and clean wounds, even in low concentrations, thus effectively expediting the wound healing process [27]. Moreover, hydrogen peroxide was produced upon dilution of honey by the enzymatic activity of oxidases added in the nectar by bees, and it has been suggested to be a major antibacterial factor in certain types of honey [16]. Collectively, the antibacterial properties of honey are mainly attributed to its osmolarity (high sugar content), acidic pH, and the presence of hydrogen peroxide. Previous studies also revealed that honey had methyl syringate and methylglyoxal, which could contribute to its antibacterial property [28, 29]. Thus, the variation in the intensity of antibacterial action of honey may be owing to non-peroxide components like methylglyoxal, bee defensin-1, polyphenols, and phenolic acids [11].

Additional studies have shown that honey can activate macrophages. Thus, an unhealed wound could change from a chronic inflammatory status to state of hyperplasia and reconstruction under the activation of macrophages [30]. Furthermore, honey could also improve mitosis of B-lymphocytes and T lymphocyte, and promote phagocytosis of neutrophils, therefore enhancing antibacterial activity and improving wound repair [6]. Other research has shown that honey has a wide spectrum of action; it is active against gram negative, gram positive, aerobic, and anaerobic bacteria, including all resistant strains of bacteria such as MRSA and VRE [31]. Moreover, honey could offer other essential trace elements, which could aid in the healing process [32]. A previous systematic review evaluating the effects of dressing on DFUs indicated that total treatment time, mean purge time of ulcers, healed area of ulcers, and ratio of purging germ in the honey dressing group were better than that of control group, respectively, and with statistically significant differences [12]. Kateel et al. [11] has demonstrated that honey dressing is a safe and important tool for wound care. Our study concluded that honey dressing could expedite both the wound healing rate and bacterial clearance rate, and shorten wound debridement time, wound healing time, and bacterial clearance time.

3.6. Limitations

Our findings should be interpreted in the context of the following study limitations. Of all the studies included in the meta-analysis, four studies did not conduct a concrete allocation concealment process [14,16–18], four studies did not conduct double blinding [14,17–19], which may increase the potential risk of biased results.

Furthermore, owing to the few studies included in meta-analysis, we did not make funnel plots to assess possible publication bias. Additionally, we only included six studies for meta-analysis [14–19], in which certain studies had limited participants, and where two studies with three subgroups were subdivided into two different RCTs each [14,19]. Given the limited number of studies in this field and the various methodological flaws of included studies, more RCTs with rigorous study designs are needed.

Moreover, there was no uniform type of honey evaluated in these studies. Among the studies included in meta-analysis, three studies did not describe the specific type of honey used [14,17,18], two studies focused on manuka honey [16,19], and only one study focused on royal jelly [15]. Hence, we could not conduct a subgroup analysis of the type of honey used in the dressing. More specifically, we could not perform a subgroup analysis because the type of honey was unclear in three studies [14,17,18]. Hence, we could not support a comparison between other types of honey and manuka honey. Additionally, we could not conduct a subgroup analysis to provide a pooled result about the effectiveness of royal jelly because only one study focused on this [15]. Therefore, we could not support a comparison between manuka honey and royal jelly. Furthermore, the sample size related to manuka honey was considerably small [16,19], which limited our ability to conduct subgroup analysis to provide sufficient evidence. Consequently, large-scale and well-designed studies could further elucidate whether the different types of honey could affect outcomes. Further research need to focus on the effectiveness of honey dressing in treating DFUs to provide new evidence.

It is important to note that the meta-analysis only focused on studies published in Chinese and English; we did not perform a retrieval study in other languages, which may have influenced the results. Future studies need to collect comprehensive information to prove the effect of honey dressings on the treatment of DFUs. Clearly, large-scale, multicenter, and prospective studies would be warranted to account for these potential biasing factors. Despite these limitations, our findings may help clinicians in choosing suitable dressings to improve the healing process of DFUs when effective interventions are lacking.

4. Conclusions

Despite the limitations of this study, the evidence indicates that honey dressing can increase the wound healing rate and the bacterial clearance rate. In addition, it can shorten wound debridement time, wound healing time, and bacterial clearance time. Therefore, the application of honey dressings in the management of DFUs may be able to shorten the length of hospital stays, save health resources, enhance confidence of patients, and promote patients' satisfaction to treatment. Additionally, honey has advantages in economical cost, which is worth

investigating for wide use. Prospective, well-designed and large-scale studies are needed to elucidate the efficacy of honey dressings on the wound-healing process for DFUs so that this method can be applied clinically.

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Conflicts of interest

None declared.

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