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Original Article

Effects of honey dressing for the treatment of DFUs: A systematic review

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ABSTRACT

Background: Honey dressing has been applied to clinical practice for many types of disease for centuries. Many researchers have studied the effects of honey dressing for the treatment of DFUs (diabetic foot ulcers), and no systematic review has considered effects of honey dressing on DFUs. A systematic review performed to objectively evaluate the effectiveness of honey dressing in the treatment of DFUs.

Methods: We include all original studies found for the key words honey and diabetic foot ulcers. Mean effect sizes and confidence intervals are pooled from study effect sizes according to standard methods, and these are considered for various common types of honey dressing interventions separately.

Results: A total of 4 RCTs involving 258 participants were included, and 3 trails involving 228 participants met the quantitative analysis and 1 study involving 30 participants met qualitative analysis. Results of meta and descriptive analyses showed that total treatment time, Mean purge time of ulcers, ratio of purging germ, healed area of ulcers in honey dressing group are better than that of control group, respectively, and with statistically significant differences.

Conclusions: Honey dressing was superior of traditional dressing for treatment of DFUs. Due to limitations in the quantity of published studies, this conclusion has yet to be carried out in large, multicenter study to validate.

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1. Introduction

DFUs and infections are a major cause of morbidity in patients with diabetes mellitus (DM) [1], and DFUs necessitate more hospital admissions than any other complication of DM [2,3], and are the main risk factor for no-traumatic lower-extremity amputations [4], DFUs have induced deeply impact on life quality of patients with DFUs [5]. The curative ratio of DFUs is rarely, and the extreme result is result from complex mechanisms and all kinds of infections. The research of treatment methods on DFUs is focus on surgical debridement intervention and bio-debridement therapy. A super effective intervention has been unrevealed for the limitation of the number and quality of study [6], so the nursing on DFUs becomes a key intervention to help patients with DFUs to keep relative health status. Selected an appropriate dressing is a major point to effective disinfected and removal of the necrotic tissue of ulcers, modify the micro-condition of wounds, and accelerate wounds healing.

Honey dressing has been applied to clinical practice for many types of disease for centuries [7]. As a wound dressing, honey dressing can provide a moist micro-environment with antimicrobial properties, has anti-inflammatory effects, reduces edema and exudates, promotes angiogenesis and granulation tissue formation, induces wound contraction, stimulates collagen synthesis, facilities debridement and accelerates wound epithelialisation [8–12]. In terms of advantages, many researchers have studied the effects of honey dressing for the treatment of DFUs, and these conclusions are uncertainty. So we are tried to objectively evaluate the effectiveness of honey dressing in the treatment of DFUs according to the systematic review of evidence-based medicine based on published literature, and provide an objective suggestion to select an appropriate intervention to patients with DFUs.

2. Materials and methods

2.1. *Included and excluded criteria*

2.1.1. *Study style of article*

Randomized controlled trials (RCTs) and the articles of Chinese and English language are eligible our study.

2.1.2. *Object of study*

Specific diagnostic criteria have been revealed to identify these patients with DFUs. Wagner grade of DFUs is not a limitation of our study. But patients accompanied by other diseases, such as last-stage of cancer and steroid treatment carried out is not eligible.

2.1.3. *Interventions of study*

Honey dressing is provided into the study group and other interventions were carried out in the control group.

2.1.4. *Outcome measure*

The outcome measure of interest was total treatment time of wounds, wounds healed the ratio, germ purge ratio in different treatment period and mean time of cleaning out.

2.1.5. *Excluded criteria of article*

Literature of non-RCTs, animal study, case, review, the idea of specialist, non-honey dressing or combine honey dressing with other medical interventions applied, in-sufficient data, lack of data met our study and do not translate effective sort were ineligible the study.

2.2. *Search strategy*

We searched 6 electronic databases including PubMed, the Cochrane Library, ISI Web of Science, CNKI (China national knowledge infrastructure), VIP (Chinese periodical full-text databases) and Chinese Wanfang Data using combinations of the terms honey, diabetic foot, diabetic feet, "foot, diabetic", "feet, diabetic", "foot ulcer, diabetic" and randomized controlled trials, controlled clinical trials, random* (the symbol is a truncation operator to achieve expended electric searched). The references of included articles were manually searched.

2.3. *Data extraction and quality assessment*

Searches were carried out and data extracted by two independent searchers (Tian Xu and Li-Juan YI). Each trial identified in the search was evaluated for design, patient eligibility criteria, and outcome measures. Any dis-agreement between searchers concerning the eligibility of a trial was resolved via consulting a third searcher (Guo-Min Song or Li Ma or Yan Wang). Duplicate studies and records were excluded based on screening of titles and abstracts. All remaining articles were screened in full text.

Quality assessment of these trials included in the study was performed by each searcher according to Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.

2.4. *Statistical analyses*

The total treatment time of wounds, wounds healed the ratio, germ purge ratio in different treatment period and mean time of cleaning out were calculated and were compared among participants who were treated with honey dressing and control group. We evaluate homogeneity trials included in I^2. If I^2 was $\geq$50%, the trials were considered to be indicated heterogeneous, a random effects model was conducted, If I^2 was $<$50%, the studies were considered to be homogeneous, a fixed effects model was performed. Pooled summary statistics of the differences in the ratio or mean for the individual study are shown. Pooled differences in ratio or means were calculated and a two-sided p value <0.05 was considered to indicate statistical significance. Moreover, sensitivity analysis was conducted based on the leave-one-out approach. All analyses were performed using Stata meta-analysis software, version 12.0.

3. Results

3.1. *Selection of trials*

A total of 41 trials were included in the initial literature search and add 1 trail to the searched result, and 3 trials [13–15] that

included 228 participants were remained according to inclusion and exclusion criteria met quantitative analysis and 1 trail [16] that included 30 patients met qualitative analysis. The grouping criteria of Siavash A et al. [15] is the number of wounds and included 25 patients and 64 wounds. The flow diagram of literature retrieval and trial selection was revealed (Fig. 1).

3.2. Trial characteristics

A total of 258 participants were included. Characteristics of 4 trials are presented (Table 1). The methodological quality assessment of included trials was revealed (Fig. 2).

3.3. Meta analysis on total treatment time of wounds between honey dressing and control groups

The main characteristics and outcomes from each individual trial are recorded (Table 1). All of the trials reported the total treatment time of wounds in treatment of patients with DFUs from the honey dressing group and control group, respectively. All four trials were enrolled in the meta-analysis examining the effect of honey dressing on foot ulceration in patients with diabetes. There was heterogeneity in the overall treatment time among the four studies [$p = 0.00$, $I^2 = 94.9\%$]. A trimming and filled method was performed to explore sensitive analysis, and the results revealed consistence. Therefore, there are without clinical and methodological heterogeneity among all trials, and a random-effects model of analysis was conducted. Pooled differences in overall treatment time after intervention revealed a difference between the honey dressing group and control groups [SMD = −1.28, 95%CI (−2.46, −0.07), $p = 0.04$] (Fig. 3). Moreover, the study conclusion of comparison on honey dressing and povidone iodine dressing showed that the overall treatment time in the honey dressing group (14.4 days) is better than that of povidone iodine dressing group (15.4 days), with statistically significant difference ($p < 0.005$).

3.4. Meta analysis on mean purge time of wounds between honey dressing group and control groups

A total of two trials reported the mean purge time of wounds of honey dressing and control group, including 75 patients. There was homogeneous in mean purge time of wounds among the two studies [$p = 0.25$, $I^2 = 25.2\%$]; therefore, a fixed-effects model of analysis was used. Pooled differences in mean purge time of wounds after intervention revealed

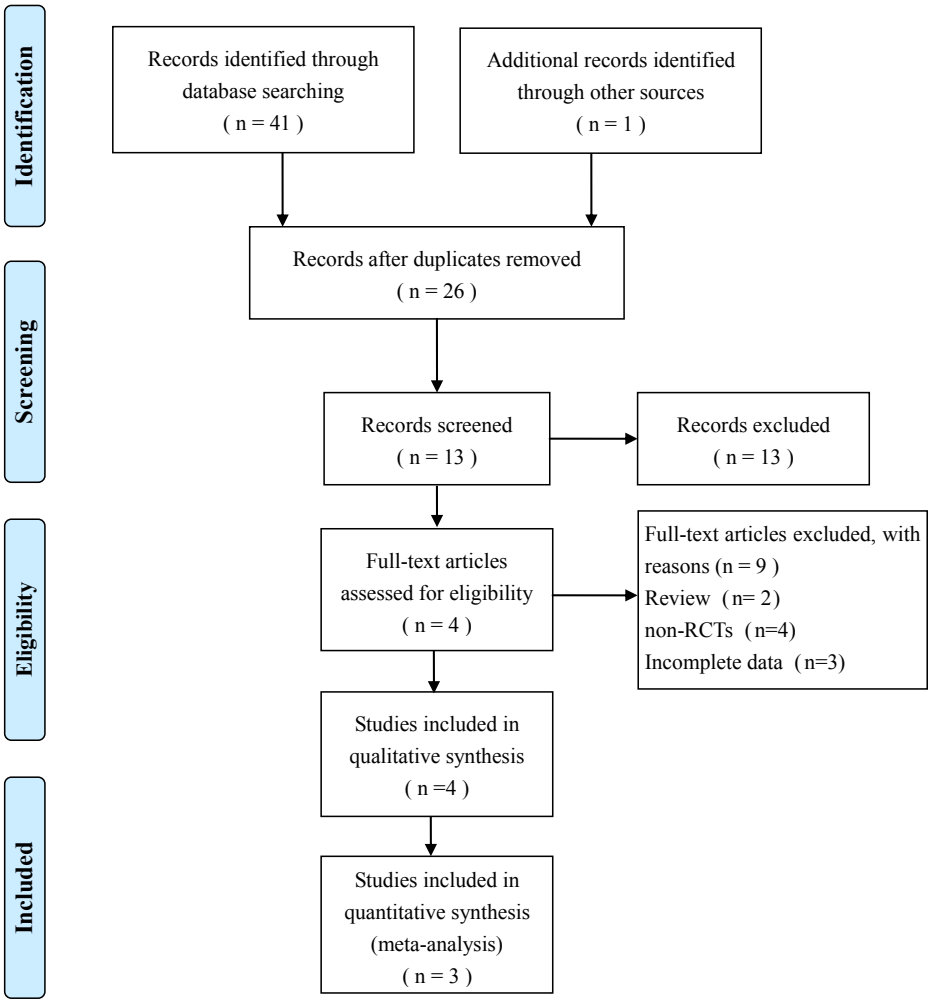

Fig. 1 – Flow chart of literature retrieval and trial selection.

Table 1 – Characteristics of 4 trials identified in the literature search.

Study included	Country	Age (T/C)	NO. of participant (T/C)	Interventions		Methods	Baseline	Outcomes
				Study (T)	Control (C)			
Guo 2013 (1) [13]	China	55.72 ± 29.14	35/35	Honey dressing	Functional dressing	Random sequence	No difference	The bacterial clear rate; mean time of the bacterial clear rate; healed rate of wounds in different period; debridement time; overall treatment time
Guo 2013 (2) [13]	China	55.72 ± 29.14	35/35	Honey dressing	Povidone iodine dressing	Random sequence	No difference	The bacterial clear rate; mean time of the bacterial clear rate; healed rate of wounds in different period; debridement time; overall treatment time
Alexandros 2012 [14]	Greece	(56 ± 14)/(57 ± 15)	32/31	Honey dressing	Traditional dressing	Unclear	No difference	The bacterial clear rat; curative rate; overall treatment time
Siavash 2013 [15]	Iran	(60.6 ± 7.0)/(60.0 ± 7.0)	25	Honey dressing	Placebo dressing	Unclear	No difference	Curative rate; overall treatment time

significations difference between the honey dressing and control groups [SMD = −0.92, 95%CI (−1.27, −0.57), $P = 0.00$] (Fig. 4).

3.5. *Meta analysis on the germ purge ratio in different treatment period between honey dressing and control groups*

A total of three trials reported the germ purge ratio in different treatment period of honey dressing and control group, including 133 patients. There was heterogeneity in the germ purge ratio in second and third weekend treatment period among the three studies [$p = 0.02$, $I^2 = 74.4\%$; $p = 0.14$, $I^2 = 54.2\%$]; therefore, a subgroup and random-effects model of analysis was used. Pooled differences in the germ purge ratio in different treatment period after intervention revealed significations difference between the honey dressing and control groups [RR = 2.32, 95%CI (1.51, 3.57), $P = 0.00$; RR = 1.70, 95%CI (1.02, 2.83), $P = 0.04$; RR = 1.56, 95%CI (1.19, 2.04), $P = 0.00$] (Fig. 5). Pooled differences in the germ purge ratio in forth treatment period after intervention revealed no significations difference between the honey dressing and control groups [RR = 1.08, 95%CI (0.92, 1.27), $p = 0.37$]. Pooled differences in the germ purge ratio in different treatment period after intervention revealed significations differences between the honey dressing and control groups [RR = 1.63, 95%CI (1.26, 2.12), $p = 0.00$] (Fig. 5).

3.6. *Meta analysis on curative rate of wounds between honey dressing and control groups*

A total of two trials reported the curative rate of wounds of honey dressing and control group, including 88 patients. There was homogeneous in mean purge time of wounds among the two studies [$p = 0.71$, $I^2 = 0$]; therefore, a fixed-effects model of analysis was used. Pooled differences in the curative rate of wounds after intervention revealed no significations difference between the honey dressing and control groups [RR = 1.05, 95%CI (0.96, 1.16), $p = 0.29$] (Fig. 6).

3.7. *Meta analysis on curative area of wounds in different treatment period between honey dressing and control group*

A total of two trials reported the curative area of wounds in different treatment period of honey dressing and control group, including 70 patients. There was heterogeneity in the curative area of wounds in different treatment period among the two studies [$p < 0.01$, $I^2 = 91\%$; $p < 0.01$, $I^2 = 87\%$]; therefore, a random-effects model of analysis was used. Pooled differences in the curative rate of wounds after intervention revealed significations difference between the honey dressing and control groups [SMD = 1.45, 95%CI (0.59, 2.31), $p = 0.00$] (Fig. 7).

3.8. *Funnel plot of publication bias*

All included studies were performed analysis of Begg's and Egger's plot to determine publication bias from all the literature. The P value from the Begg and Egger is 0.31 and 0.09,

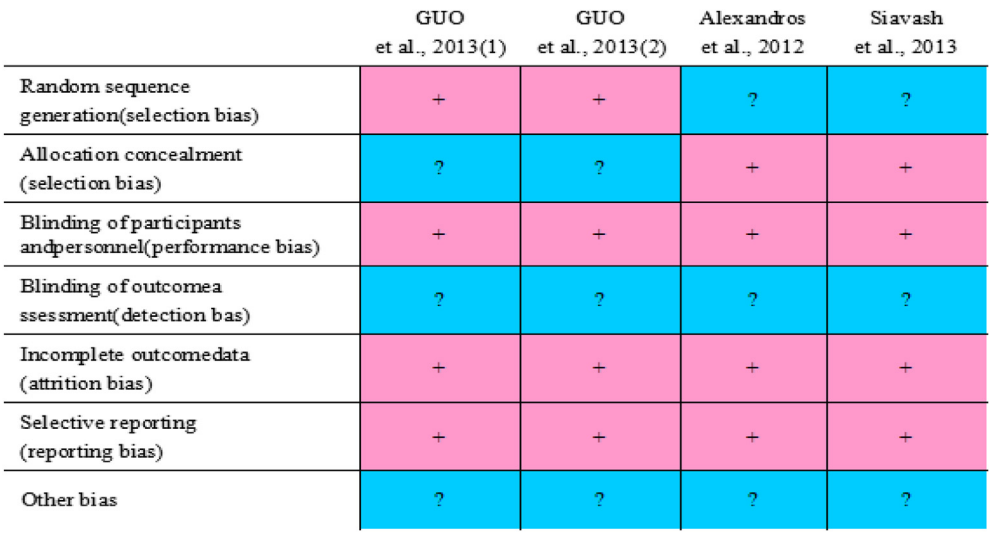

Fig. 2 – Risk of bias summary: authors' judgments about each risk of bias item for each included study.

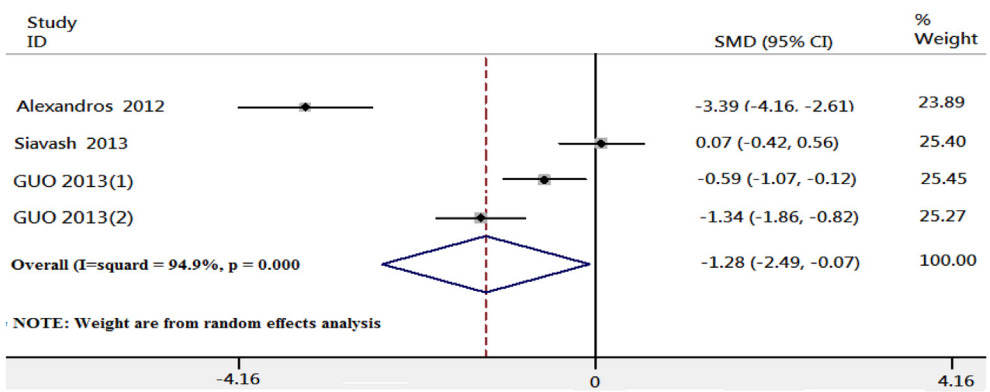

Fig. 3 – Meta analysis on total treatment time of wounds between study and control groups.

respectively, and the Egger's plot is summarized (Fig. 8), which indicated no publication bias exists in included trials.

4. Discussion

DFUs are full-thickness penetration of the dermis of the foot in a person with DM. DFUs and infections are the major sources of morbidity in individuals with DM Approximately 15% of individuals with DM develop a foot ulcer and a significant subset will ultimately undergo amputation (i.e.14–24% risk with that ulcer or subsequent ulceration) [17–19]. It has been estimated worldwide that every 30 s a lower limb is lost because of DM, and its incidence will increase because of the expected rise in type 2 DM in future, and DFUs also have a significant negative impact on health-related quality of life. Today, many interventions were used to treat DFUs included traditional surgery and bio-therapy [20]. Selected appropriate medical dressing is key to effective monitor and control deterioration of wounds under the limitation of effective and specific therapy. More and more medical dressing including general dressing (i.e. povidone

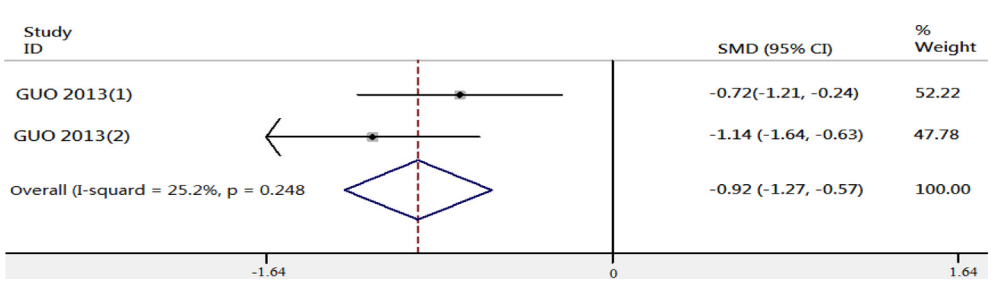

Fig. 4 – Meta analysis on mean purge time of wounds between study and control groups.

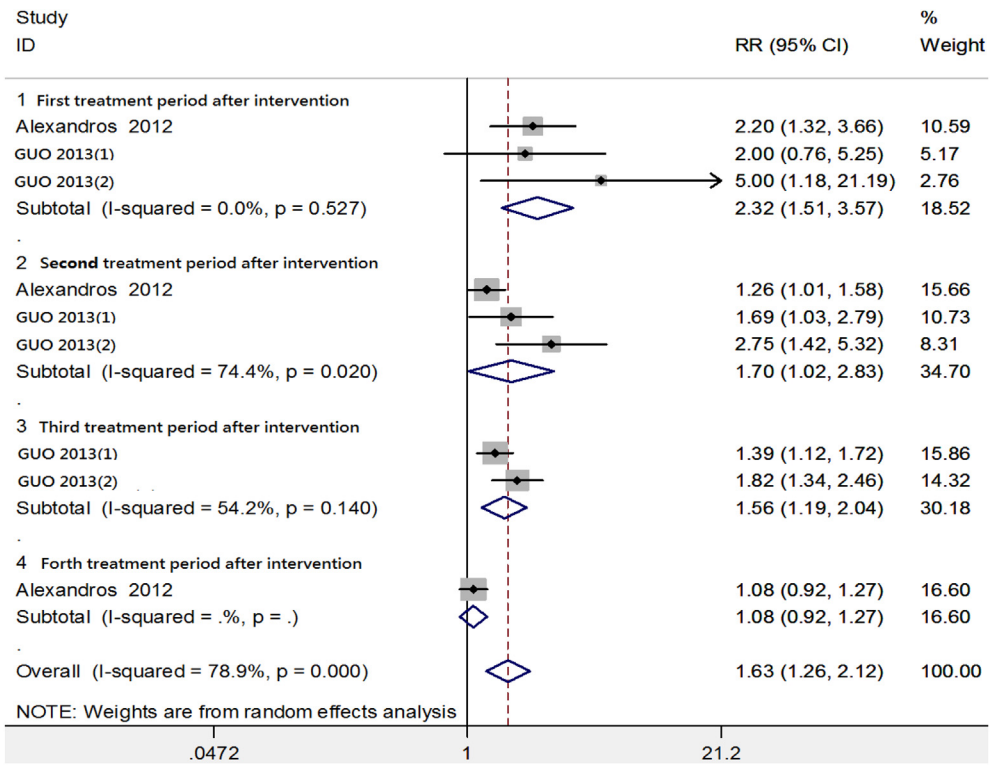

Fig. 5 – Meta analysis on germ purge ratio of ulcers in different treatment period between study and control groups.

iodine dressing), functional dressing (i.e. ionic silver dressing and hydrocolloid dressing), and honey dressing was used for treatment on DFU. The healing properties of honey have also been known from long and recently there has been a resurgence of interest about the ability of this natural product to assist wound healing with numerous reports in the international bibliography, but scanty scientific studies did not provide enough evidences to justify it benefits in the treatment of diabetic foot DFUs. This aim of our study aim to investigate the effectiveness of honey dressing in the treatment of patients with DFUs.

The findings of meta-analysis suggest that honey dressing may be more effective than control interventions for the overall treatment time to healing honey dressing, but the conclusion should be carefully used for clinical treatment of DFUs due to rare trails met our study, and some studies with multi-center, double blind, and randomized controlled trials should been carried out. A total of 2 trails from an identical study reported mean purge time of wounds and lack of evidences from more research, so the conclusion should be carefully used for clinical treatment of patients with DFUs through the pooled results revealed a statistically significant difference. A total of 3 trials reported the bacterial clearance rate in different treatment period, and the pooled result showed that the efficacy in honey dressing group is better than that of control group. As a wound dressing, honey provides a moist environment with antimicrobial properties, has anti-inflammatory effects, reduces edema and exudates, promotes angiogenesis and granulation tissue formation, induces wound contraction, stimulates collagen synthesis, facilitates debridement and accelerates wound epithelialisation [21]. Hydrogen peroxide (H_2O_2) is produced upon dilution of honey by the enzymatic activity of oxidases added in the nectar by bees, and it has been suggested to be the major antibacterial factor in at least some kind of honey. Apart from being an antiseptic H_2O_2 stimulates macrophage chemotaxis,

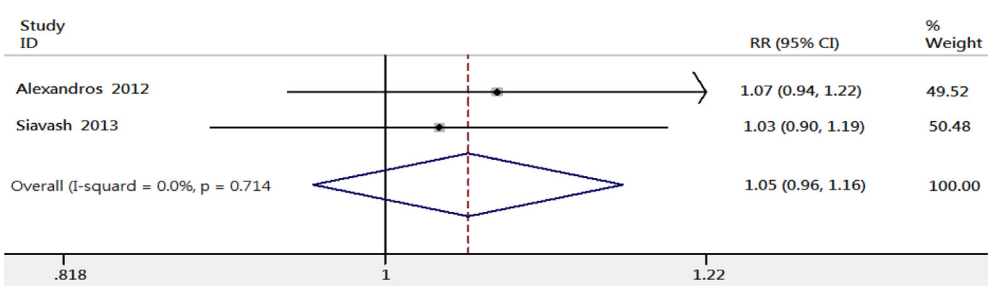

Fig. 6 – Meta analysis on curative rate of wounds between study and control groups.

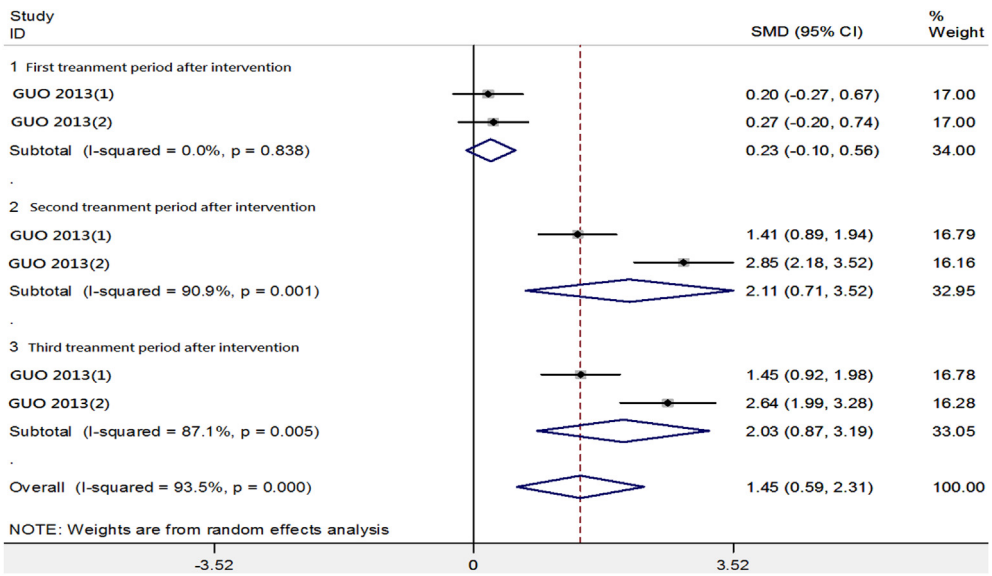

Fig. 7 – Meta analysis on curative area of wounds between study and control groups.

induces vascular endothelial growth factor (VEGF) expression at the transcriptional level and consequently promotes angiogenesis and stimulates fibroblast proliferation while also possessing antioxidant action, protecting the local wound milieu from oxidative stress (OS) [22–26]. A total of 2 trails reported healing rate in different treatment period, and the pooled results have no statistical difference. A total of 2 trails reported healing area of wounds and the result revealed that the efficacy in honey dressing is better than that of control group. The acidification of the alkaline environment of chronic non-healing ulcers by honey has also been proposed as another mechanism by which honey induces healing, and acidification inhibits protease activity, induces fibroblast proliferation and establishes an aerobic environment, all of which aid in the healing process [12]. Nitric oxide (NO) is an important mediator in inflammation, cell proliferation and immune response and is actively implicated in wound healing [27,28]. NO metabolites contained in honey [29] and an induction of NO production by honey in different body fluids constitute another mechanism by which honey induces wound healing, given the antimicrobial and immunoregulatory actions of NO [30]. Moreover, the result of Shukrimi A, et al. [16] showed that the curative efficacy in honey dressing is better than that of in povidone iodine dressing group, and the side effect and cost are lower in honey dressing than that of in the control group.

There are a number of limitations of this systematic review. That needs to be acknowledged. Firstly, and perhaps most notably, only a small number of trials met the inclusion criteria, thus reducing the power of the analyses. Only English and Chinese language literature was considered for publication, so it is possible that other relevant trials may have been identified, if the search had been extended to literature in other languages. The differences in wound etiology and the methodological heterogeneity could have led to some bias in the meta-analysis.

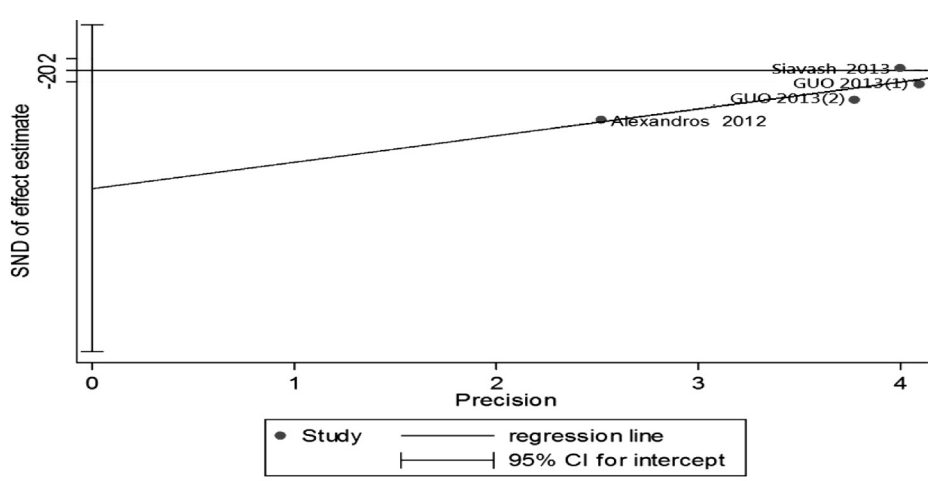

Fig. 8 – Egger's funnel plot of publication bias.

5. Conclusion

There is insufficient high-quality evidence available in the current literature regarding the effectiveness of honey dressing for the treatment of DFUs. Hence, the findings from this systematic review are by no means definitive. Nevertheless, the findings suggest that honey dressing may be more effective in decreasing overall treatment time and mean clearance time of wounds, and increasing the bacterial clearance rate and the healed area of wounds in different treatment period compared with control dressing. There is a need for high-quality RCTs to clarify the effectiveness of honey dressing for the treatment of DFUs.

Contributions

Study design: TX, WY; data collection: TX, YLJ; data analysis: TX, WY; manuscript preparation: TX, ML, WY and SGM.

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Conflict of interest statement

The authors declare that they have no competing interests.

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