Received: 28 September 2020 | Accepted: 13 December 2020

DOI: 10.1111/iwj.13542

ORIGINAL ARTICLE

IWJ WILEY

Onion extract gel is not better than other topical treatments in scar management: A meta-analysis from randomised controlled trails

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Funding information
Youth Talent Supported Program of Southwest Hospital, Grant/Award Number: SWH2018QNLC-11

Abstract

To evaluate the efficacy and safety of onion extract (OE) gel on scar management, a systematic review was performed by searching Embase, PubMed, Medline, and the Cochrane Library databases, and a meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines. Finally, 13 randomised controlled trails were enrolled for meta-analysis. OE gel increased the total improvement scores assessed by investigators ($P < .00001$) and patients ($P < .00001$) than no treatment, but no differences were detected between OE gel and other commonly used topical treatments assessed by investigators ($P = .56$) and patients ($P = .39$). Moreover, OE in silicone gel increased the total improvement scores assessed by investigators ($P < .00001$) and patients ($P = .0007$) than other treatments. OE gel increased the incidence of total adverse effects compared with no treatment ($P < .0001$) and other treatments ($P = .008$) by a fixed-effects model, and increased the incidence of dropping out caused by intolerance of treatments ($P = .0002$). OE gel not only has no superiority to commonly used topical treatments, but also has the potential to increase the incidence of adverse effects on scar management; OE in silicone gel might be the optimal topical choice for scar treatment; however, more evidences are needed to strength these conclusions.

KEYWORDS

gel, meta-analysis, onion extract, scar

1 | INTRODUCTION

Cutaneous scars are caused by an excessive deposition of collagen during wound healing that result from abnormal response to thermal, postsurgical, and traumatic injuries.[1] Although full maturation of a scar may take up to 2 years, typically, the new scars mature and become lighter and narrower in a few weeks.[2] In some cases, the scars become hypertrophic or result in keloids. The scars can cause pain, itching, discomfort, contracture, and a lessening of self-esteem.[2,3] Thus, promoting wound healing without noticeable scarring and improving scars are important aspects of cosmesis.

Owing to the reported effects of anti-inflammatory, antimicrobial, antiproliferative, and regenerative activities of onion extract (OE),[4] its gel modality has been commercially

available for treating, preventing, and reducing dermatologic scars and keloids in clinic many years.[5] Several clinical trials found this gel was well tolerated and helpful for preventing pathological scarring and improving preexisting scars.[5-9] Thus, it was recommended for clinical scar management by the International Advisory Panel on Scar Management in 2014.[10] However, large-sized randomised controlled trials (RCTs) and the evidence-based data are still lacking. The purpose of this meta-analysis was to evaluate the efficacy and safety of OE gel on scar management and to provide reliable evidence for clinical application.

Key messages

- the efficacy and safety of onion extract (OE) gel on scar management of patients were compared
- a meta-analysis of 13 RCTs was performed evaluating total improvement scores and the incidence of adverse effects
- OE gel has no superiority to commonly used topical treatments
- OE gel has the potential to increase the incidence of adverse effects

2 | METHODS

This meta-analysis was conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement guidelines.[11] All analyses are based on previous articles; therefore, no ethical approvals are required. This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY202080103).

2.1 | Search strategy

Two independent authors searched Embase, PubMed, Medline, and the Cochrane Library from their inception to August 2020 by the following keywords in combination with Boolean operators AND: "*Allium cepa* OR onion OR onions OR onion extract", "scar OR scars OR cicatrix OR cicatrice OR cicatrices OR keloid OR keloids OR cicatricle". No limitations were imposed on language. Search strategy can be found in Appendix A. The bibliographies of retrieved trials and other relevant publications were cross-referenced to identify additional articles. The search results are shown in Figure 1.

2.2 | Inclusion criteria

Two authors independently evaluated the trials according to the PICOS (patients, intervention, comparator, outcome, study design) criteria. (a) Patients: patients with wounds or scars. (b) Intervention: topical gel with OE. (c) Comparator: no topical treatment, placebo gel, or other commonly used topical therapy for scar management. (d) Reported at least one of the following outcomes: quantitative evaluation of the results by one scale, such as the visual analog scale, vancouver scar scale, and Manchester scar scale, the width and/or volume of the scars, patient satisfaction, and adverse events. (e) Study design: RCT. In cases of disagreement, a consensus was reached through discussion with the third author.

2.3 | Data extraction

Two reviewers independently extracted the data by a standard extraction form. These data included author, publication date, country, study design, sample size, age, gender, type and location of scars or wounds, details of intervention and comparator, methods and results of outcome evaluation, adverse events, and the conclusions. The primary outcomes were the total improvement scores by a recognised scale evaluated by investigators and patients. Additional outcomes were the width or volume of the scars, patient satisfaction, and adverse events. We also contacted the corresponding authors of the included studies to obtain the primary data, but no answer was received. In this case, the improvement score was calculated by the baseline score or the highest score of each item minus the endpoint score when it was not reported in the article directly.

2.4 | Assessment of methodological quality

Two authors independently assessed the quality of included RCTs based on the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions*. A "risk of bias" table that included the following contents was created: details on methods of random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other bias. The overall quality of each study was evaluated as "low risk of bias", "high risk of bias", or "unclear risk of bias". Moreover, a modified Jadad 7-point scale was used to quantitative assess the quality of RCTs, and the study with the Jadad score ≥ 4 is considered to be of high quality.[12]

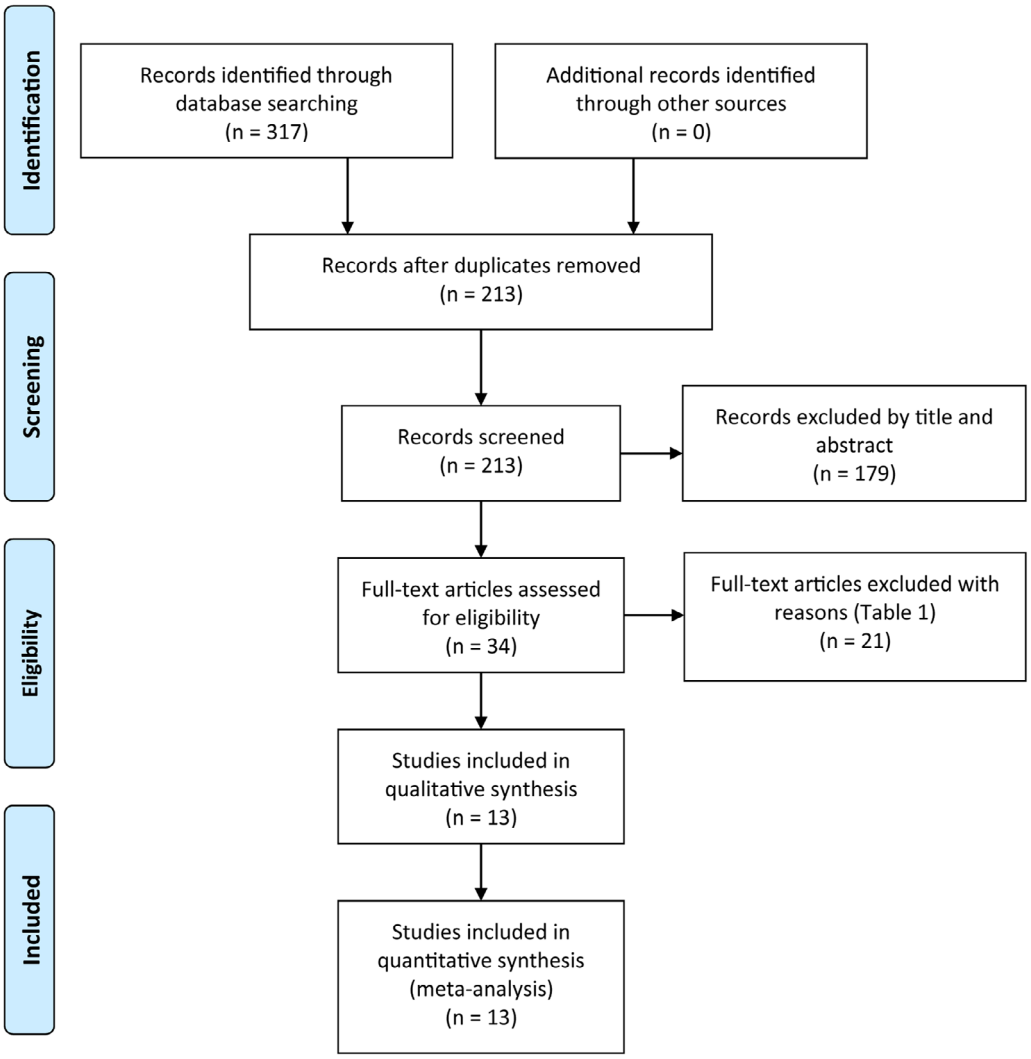

FIGURE 1 The search results and selection procedure

2.5 | Statistical analysis

Meta-analysis was conducted by Review Manager software 5.3. Continuous outcomes were assessed by mean difference (MD) with 95% confidence intervals (CIs), while dichotomous outcomes were evaluated by odds ratio (OR) with 95% CIs. Separate statistics was combined by the inverse variance or Mantel-Haenszel method. P and I^2 values were used to assess heterogeneity among included studies. If $I^2 < 50\%$ and $P > .1$, a fixed-effects model was applied; otherwise, a random-effects model was applied. Sensitivity analysis was conducted by omitting one study in turn. Subgroup analysis of patients with wounds or scars and the control group with or without other topical treatments were performed. $P < .05$ were considered statistically significant.

Reliability and conclusiveness of the available evidence were examined by trial sequential analysis (TSA) software 0.9.5.10 according to the previous meta-analysis,[13,14] which can reduce type I errors caused by multiple testing and sparse data. When the cumulative Z curve crossed the TSA boundary, a sufficient level of evidence for the anticipated intervention effect is reached and no further studies are needed; otherwise, when the Z curve failed to cross the TSA boundary and the required information size (RIS) was not reached, the evidence to reach a conclusion is insufficient. Two-sided tests with a type I error of 5%, a power of 80%, and a low bias or a user-defined MD were used to calculate the RIS.

3 | RESULTS

3.1 | Search results

A total of 213 studies were identified and 179 studies were excluded by reading the title and abstract. After reading the full text of remaining 34 articles, 21 studies

were excluded with reasons in Table 1. Finally, 13 RCTs[1-3,7-9,15-21] were taken into our meta-analysis. The basic characteristics and interventions are summarised in Table 2. Based on the different control groups, we divided the enrolled RCTs into three groups (Table 3): (a) five studies[2,3,7,18,19] compared OE gel versus no treatment concluded that OE gel is superior to no treatment; (b) seven studies[1,3,8,9,15,17,20] compared OE gel vs other commonly used topical treatments (placebo lotion, silicone lotion, silicone gel, and silicone gel sheet) in scar management did not reach consistent conclusions; (c) three studies[9,16,21] compared OE in silicone gel vs other treatments concluded that OE in silicone gel is superior to placebo gel and silicone gel.

3.2 | Quality assessment

Study quality was assessed by the risk of bias (Figures 2 and 3) and Jadad score (Table 2). Seven RCTs[2,3,7,8,16-18] recorded using computer-generated or other appropriate methods for randomisation, but only two[3,17] described allocation concealment. Six studies[1,3,8,15,16,20] were carried out in a double-blind method; 10 studies[2,3,7,8,15-17,19-21] described the implementation of blinding of outcomes; 8 studies[1,3,7-9,16,18,21] presented complete data; and only 1 study[17] showed selective reporting. Two studies[9,19] with a Jadad score < 4 were considered as of low quality. The publication bias was assessed by a funnel plot diagram (Supplemental Figures 1-3). The asymmetrical funnel plot diagrams indicated that there were potential risks of publication bias of the total improvement scores between OE gel and no treatment (Supplemental Figure 1), between OE gel and other treatments (Supplemental Figure 2), and the incidence of adverse effects (Supplemental Figure 3).

TABLE 1 Reasons of full-text article excluded

Number	Reason
8	Full-text was unavailable
5	Conference abstract
4	Non-randomised controlled trail
1	Patients with alopecia areata, neither scars nor wounds
1	Intralesional injection of onion extract, not topical treatment
1	Used topical silicone gel plus herbal extract gel (*Allium cepa*, *Centella asiatica*, *Aloe vera* and paper mulberry)
1	Published in 2008 by Draelos, which was similar with another study published in 2012 by himself

3.3 | Meta-analysis of the primary outcomes

Owing to different scales being used to evaluate the scars in the included studies and none of the scale was able to integrate all of the results (Table 3); thus, we calculated and meta-analysed the total improvement scores evaluated by investigators and patients, respectively. Compared with no treatment, OE gel significantly increased the total improvement scores assessed by investigators [MD = 1.63, 95% CI: (1.04, 2.22), $P < .00001$] and patients [MD = 1.93, 95% CI: (1.20, 2.66), $P < .00001$] (Figure 4), but significant heterogeneities were observed ($I^2 = 89\%$ and $I^2 = 81\%$, Figure 4). Furthermore, significant differences remained when omitting one study in turn for the sensitivity analysis (data not shown); heterogeneities were greatly decreased ($I^2 = 49\%$ and $I^2 = 0\%$, data not shown) when omitting the study of Prager 2018. Moreover, The TSA of OE gel vs no treatment assessed by investigators (Supplemental Figure 4A) and patients (Supplemental Figure 4B) indicated that the Z curve crossed the conventional boundary, TSA boundary, and RIS.

No significant differences were detected between OE gel and other treatments (placebo gel or lotion, petroleum ointment or jelly, silicone lotion, and silicone gel or gel sheet), at the total improvement scores assessed by investigators [MD = −0.16, 95% CI: (−0.70, 0.38), $P = .56$] and patients [MD = 0.37, 95% CI: (−0.47, 1.20), $P = .39$] (Figure 5). When omitting one study in turn for sensitivity analysis, there were still no intergroup differences (data not shown). Furthermore, subgroup analysis of surgical wounds assessed by investigators [MD = 0.09, 95% CI: (−0.43, 0.61), $P = .74$] and patients [MD = 0.74, 95% CI: (−0.78, 2.27), $P = .34$] and scars assessed by patients [MD = −1.05, 95% CI: (−4.33, 2.22), $P = .53$] (Figure 6) found no significant differences between OE gel and other treatments, but scars assessed by investigators found OE gel had a lower total improvement score than other treatments [MD = −1.99, 95% CI: (−3.26, −0.73), $P = .002$] (Figure 6). Moreover, the TSA of OE gel vs other treatments assessed by investigators (Supplemental Figure 5A) and patients (Supplemental Figure 5B) indicated that the Z curve failed to cross the conventional boundary, TSA boundary, and RIS.

Compared with other treatments (placebo gel or silicone gel sheet), OE in silicone gel significantly increased the total improvement scores assessed by investigators [MD = 0.43, 95% CI: (0.29, 0.57), $P < .00001$] and patients [MD = 1.22, 95% CI: (0.51, 1.92), $P = .0007$] (Figure 7). For only two studies were included, sensitivity and subgroup analyses were not applicable.

TABLE 2 The characteristics of included studies

Study (year)	Country	Study design	Wounds or scars	Location	Arm 1/Arm 2/Arm 3		Study arms and the number of wounds or scars received treatment	Follow-up	Jadad score
					Cases (female%)	Age (years)			
Chanprapaph 2012[8]	Thailand	RCT, internally controlled, split-scar study	Caesarean wounds at 1 week after surgery	Abdomen	16 (100)	19–43	**Arm 1**: one-third of the 16 wounds received OE gel (Erase gel, ABCA Pharma Lab) **Arm 2**: one-third of the 16 wounds received vehicle-based gel	12 wk	6
Chung 2006[20]	America	RCT, internally controlled, split-scar study	New surgical wounds after suture removal	Head, trunk, extremities	24 (29)	65 ± 11.25	**Arm 1**: half of the 14 wounds received OE gel; **Arm 2**: half of the 14 wounds received petrolatum ointment	12 wk	6
Draelos 2012[7]	America	RCT, internally controlled	Two bilateral chest wounds after re-epithelialisation completed	Chest	44 (27)	57 ± 6.75	**Arm 1**: 44 wounds received OE gel (Merderma, Merz Pharmaceuticals) **Arm 2**: 44 wounds received no treatment	8 wk	4
Ho 2006[19]	Hong Kong	RCT	Wounds after tattoo removal	Unavailable	60 (38)/60 (44)	37.7 ± 6.8/37.6 ± 6.2	**Arm 1**: 61 wounds received OE gel (Contractubex, Merz Pharma) **Arm 2**: 68 wounds received no treatment	13 to 20 mo	3
Hosnuter 2007[9]	Turkey	RCT	Hypertrophic and keloid scars with duration from 1 mo to 6 mo	Unavailable	24/24/24 (60)	40.3 ± 9.6	**Arm 1**: 21 scars received OE gel (Contractubex, Merz Pharma) **Arm 2**: 19 scars received silicone gel sheet **Arm 3**: 20 scars received combination treatment	6 mo	3
Jenwitheesuk 2012[21]	Thailand	RCT	Median sternotomy wounds at 1 wk after surgery	Chest	28 (39)/26 (50)	51 ± 12.50/48 ± 14.47	**Arm 1**: 28 wounds received OE in silicone derivative gel (Cybele Scagel, Bangkok Botanica) **Arm 2**: 26 wounds received placebo gel	12 wk	5
Jorge 2014[18]	Mexico	RCT	Caesarean wounds after suture removal	Abdomen	31/30 (100)	24.3 ± 6.0/23.7 ± 6.3	**Arm 1**: 31 wounds received OE gel (Contractubex, Merz Pharma)	12 wk	4

TABLE 2 (Continued)

Study (year)	Country	Study design	Wounds or scars	Location	Arm 1/Arm 2/Arm 3		Study arms and the number of wounds or scars received treatment	Follow-up	Jadad score
					Cases (female%)	Age (years)			
							Arm 2: 30 wounds received no treatment		
Karagoz 2009[1]	Turkey	RCT	Postburn scars less than 6 mo	Head, trunk, extremities	32 (63)	24 ± 13	**Arm 1**: 15 scars received OE gel (Contractubex, Merz Pharma) **Arm 2**: 15 scars received silicone gel (Scarfade1, Hanson Medical Inc) **Arm 3**: 15 scars received silicone gel sheet (Epi-DermTM, Biodermis)	6 mo	5
Owji 2018[15]	Iran	RCT, internally controlled	Upper blepharoplasty wounds after suture removal	Upper blephar	36 (100)	51.5 ± 6.5	**Arm 1**: 26 wounds received OE gel (Contractubex, Merz Pharmaceuticals) **Arm 2**: 26 wounds received petroleum jelly	6 mo	5
Perez 2010[17]	America	RCT	Keloids or hypertrophic scars with a diameter of 0.5 to 2.5 cm	Unavailable	10 (40)/10 (25)/10 (40)	42/45/40	**Arm 1**: 5 scars received OE gel (Mederma, Merz Pharma) **Arm 2**: 5 scars received 0.5% hydrocortisone, silicone and vitamin E lotion (Scarguard, Scarguard Labs) **Arm 3**: 5 scars received placebo (Cethaphil moisturising lotion, Galderma Laboratories)	16 wk	5
Prager 2018[2]	Germany	RCT, internally controlled	Two wounds within 3 weeks postsurgery on similar regions	Unavailable	124 (45)	48.6 ± 15.7	**Arm 1**: 113 wounds received OE gel (Contractubex, Merz Pharmaceuticals) **Arm 2**: 113 wounds received no treatment	12–24 wk	4
Song 2018[3]	Republic of Korea	RCT	New surgical wounds after suture removal	Abdomen	30/30/30 (90)	39 ± 6.0/38 ± 6.5/39 ± 6.7	**Arm 1**: 30 wounds received OE gel (Contractubex, Merz Pharma) **Arm 2**: 30 wounds received silicone gel (Kelo-cort, Advanced Bio-Technologies)	12 wk	7

(Continues)

TABLE 2 (Continued)

Study (year)	Country	Study design	Wounds or scars	Location	Arm 1/Arm 2/Arm 3		Study arms and the number of wounds or scars received treatment	Follow-up	Jadad score
					Cases (female%)	Age (years)			
							Arm 3: 30 wounds received no treatment		
Wananukul 2013[16]	Thailand	RCT, internally controlled, split-scar study	Median sternotomy wounds at 1 week after surgery	Chest	30 (43)	4.3 ± 3.63	**Arm 1**: 30 wounds received OE in silicone derivative gel (Cybele Scagel, Bangkok Botanica) **Arm 2**: 30 wounds received placebo gel	6 mo	6

Abbreviations: OE, onion extract; RCT: randomised controlled trial.

3.4 | Meta-analysis of the secondary outcomes

Except the study of Chung 2006,[20] all of the remaining studies recorded the adverse effects and all of them were topical side effects, including itching, burning, stinging, and contact dermatitis. Compared with no treatment [OR = 6.86, 95% CI: (2.86, 16.48), $P < .00001$] or other treatments [OR = 3.72, 95% CI: (1.41, 9.84), $P = .008$] (Figure 8), OE gel significantly increased the incidence of total adverse effects when analysed by a fixed-effects model. However, no significant differences were detected between OE gel with no treatment [OR = 6.16, 95% CI: (0.95, 39.73), $P = .06$] or other treatments [OR = 2.92, 95% CI: (0.64, 13.38), $P = .17$] (Supplemental Figure 6) by a random-effects model, and between OE in silicone gel and other treatments by a fixed-effects model [OR = 5.42, 95% CI: (0.61, 47.71), $P = .13$] (Figure 8) or a random-effects model [OR = 5.14, 95% CI: (0.56, 46.83), $P = .15$] (Supplemental Figure 6). Moreover, we found the incidence of dropping out caused by the intolerance of treatments in OE gel was significantly higher than control group [OR = 12.03, 95% CI: (3.19, 45.38), $P = .0002$] (Figure 9). Other outcomes, such as the volume of the scar and patient satisfaction, due to the limited number of studies, could not be integrated.

4 | DISCUSSION

This meta-analysis aimed to evaluate the efficacy and safety of OE gel in scar management. The data from 13 RCTs found OE gel were better than no treatment, but did not show superiority to other treatments (petroleum ointment or jelly, and silicone lotion, silicone gel, or gel sheet) in the management of scarring. Moreover, this meta-analysis found OE in silicone gel was superior to other treatments (placebo gel or silicone gel sheet) in scar treatment. Finally, OE gel had a potential to increase the incidence of treatment-induced adverse effects, and increased the incidence of dropping out caused by the intolerance of treatments, when compared with no treatment and other commonly used topical treatments.

The total improvement score was the primary outcome in this meta-analysis. Compared with no treatment, OE gel significantly increased the total improvement scores assessed by investigators and patients. These data were further confirmed by sensitivity analysis and TSA. In addition, our data are also consistent with the conclusions in the included studies as well as those studies[5,22,23] excluded for no full-text available or non-RCT, which all concluded that OE gel was superior to no treatment. Taken together, these evidences strongly demonstrate

TABLE 3 Outcomes and conclusions of the included studies

Study	Outcomes	Conclusion
Group 1: studies compared OE gel versus no treatment		
Draelos 2012[7]	The improvement in overall appearance, texture, redness, softness by a 4-point scale (investigator and patients); complications	OE gel is superior to no treatment
Ho 2006[19]	Clinical clearance (investigator) and complications	OE gel is superior to no treatment
Jorge 2014[18]	POSAS (investigator and patients); complications	OE gel is superior to no treatment
Prager 2018[2]	POSAS (investigator and patients); global aesthetic improvement scale (investigator); global comfort assessment scale and satisfaction with scar appearance (patients); complications	OE gel is superior to no treatment
Song 2018[3]	VSS and image panel scale (investigator); body image scale and cosmetic scale (patients); complications	OE gel is superior to no treatment
Group 2: studies compared OE gel versus other treatments		
Chanprapaph 2012[8]	Skin redness index; pliability by a 6-point scale and height by a 4-point scale (investigator); overall cosmetic improvement, pain, itching, discomfort, tightness, hardness by a 4-point scale (patients); complications	OE gel is superior to placebo gel
Chung 2006[20]	Cosmetic appearance, redness, thickness by a 10-point VAS scale (investigator); redness, itchiness, burning, pain by a 10-point VAS scale (patients); overall cosmetic appearance by phone (patients)	OE gel is similar with petrolatum ointment
Owji 2018[15]	Manchester Scar Scale and the overall scar appearance by a 10-point VAS scale (investigator); redness and appearance by phone (patients); complications	OE gel is similar with petroleum jelly
Song 2018[3]	VSS and image panel scale (investigator); body image scale and cosmetic scale (patients); complications	OE gel is similar with silicone gel
Hosnuter 2007[9]	Colour, height, hardness, itching by a 4-point or 3-point scale (patients); complications	OE gel is similar with silicone gel sheet
Karagoz 2009[1]	VSS (investigator); complications	Silicone gel and silicone gel sheet are superior to OE gel
Perez 2010[17]	Scar induction, erythema, pigmentation alteration, pain, itching, tenderness, cosmetic appearance by a 100-point VAS scale (investigator and patients); scar volume; patient satisfaction; complications	OE gel is similar with silicone lotion, both two are superior to placebo lotion
Group 3: studies compared OE in silicone gel versus other treatments		
Jenwitheesuk 2012[21]	VSS (investigator); pruritus and pain scores by a 10-point scale (patients); complications	OE in silicone gel is superior to placebo gel
Wananukul 2013[16]	VSS (investigator); complications	OE in silicone gel is superior to placebo gel
Hosnuter 2007[9]	Colour, height, hardness, itching by a 4-point or 3-point scale (patients); complications	OE in silicone gel is superior to silicone gel sheet

Abbreviations: OE, onion extract; POSAS, patient and observer scar assessment scale; VAS, visual analog scale; VSS, vancouver scar scale.

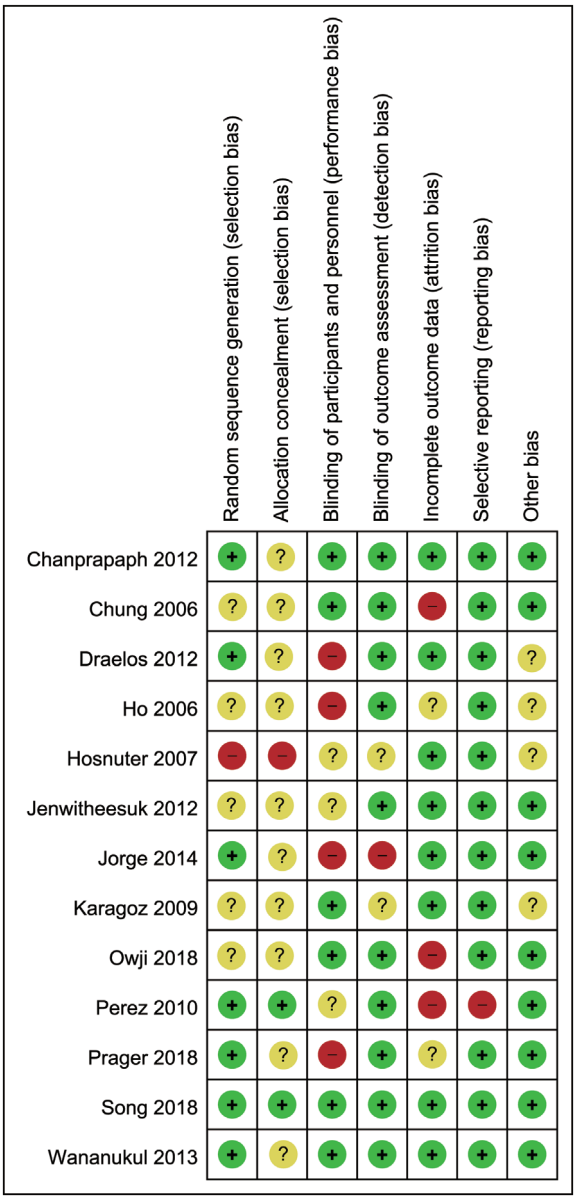

FIGURE 2 Risk-of-bias summary of the included studies

that OE gel is beneficial for scar management when compared with no treatment.

However, in this study, OE gel did not show superiority to other treatments, including petroleum ointment or jelly, silicone lotion, and silicone gel or gel sheet. This result is consistent with most of the included studies that concluded OE gel had similar effect with petroleum ointment or jelly, silicone lotion, and silicone gel or gel sheet. Furthermore, subgroup analysis of scars assessed by investigators found OE gel had a lower total improvement score than other treatments; Karagoz et al[1] concluded that OE gel was inferior to silicone gel and silicone gel sheet on scar treatment; one non-RCT[24] found petrolatum ointment was better than OE gel on scar treatment. In summary, OE gel is not superior to those treatment (petroleum ointment or jelly, silicone lotion, and silicone gel or gel sheet) on scar management, but the TSA of OE gel versus other treatments indicates more trails are needed to confirm this conclusion.

Furthermore, this meta-analysis found OE in silicone gel significantly increased the total improvement scores than placebo gel and silicone gel sheet, which is consistent with all of three included RCTs that OE in silicone gel was superior to placebo gel and silicone gel sheet. One similar RCT[25] reported that topical silicone gel plus herbal extract gel (*Allium cepa*, *Centella asiatica*, *Aloe vera*, and paper mulberry) had better vascularity and pigmentation than silicone gel. Although topical silicone gel beneficial for scar prevention has been concluded by two meta-analyses with weak evidence,[26,27] the performance of topical silicone gel and other non-silicone topical treatment is also similar.[27] Thus, OE in silicone gel seems an optimal choice for scar treatment, but still needs more studies to strength this evidence.

Concerning the safety, although OE gel had a potential to increase the incidence of total adverse effects when

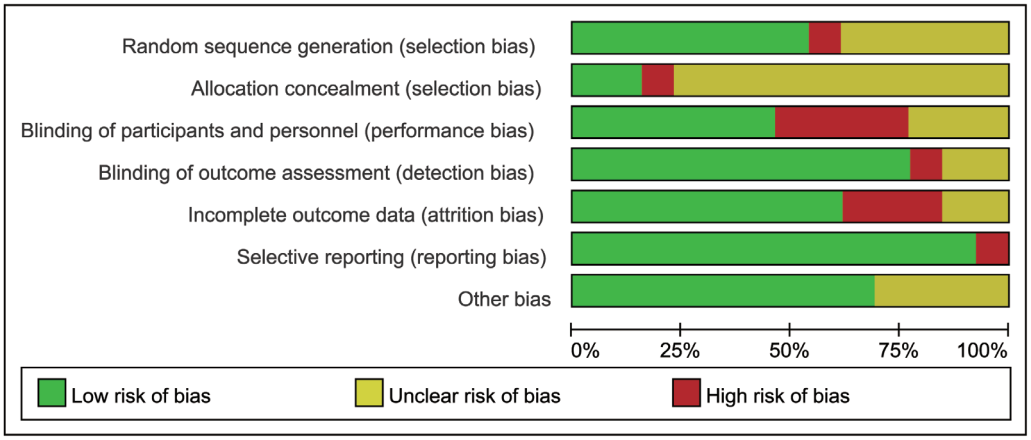

FIGURE 3 Risk-of-bias graph of the included studies

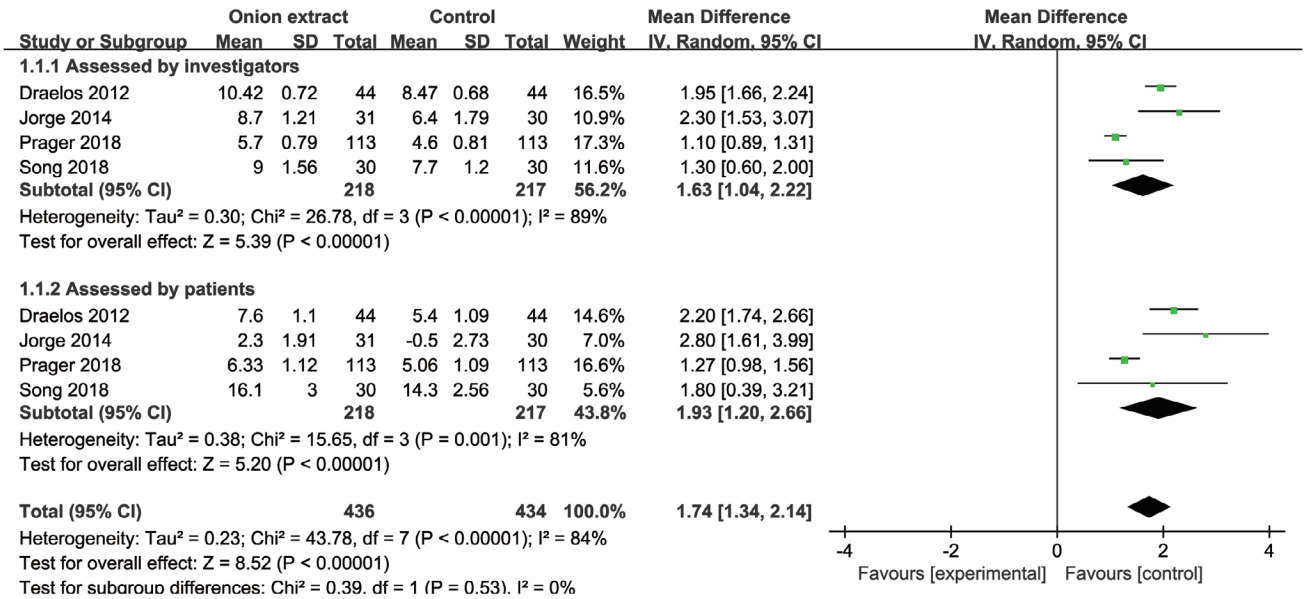

FIGURE 4 Forest plot diagram showing the total improvement scores between onion extract gel and no treatment

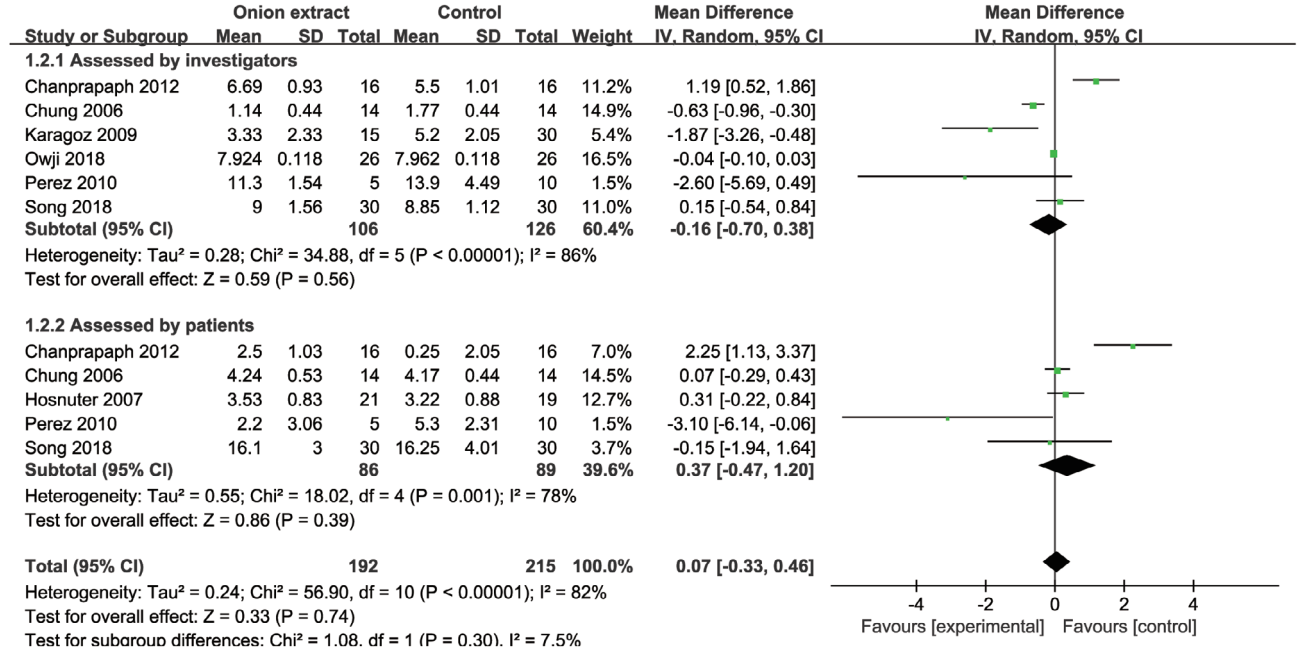

FIGURE 5 Forest plot diagram showing the total improvement scores between onion extract gel and other treatments

compared with no treatment and other treatments, most of the adverse effects were itching, burning, stinging, or contact dermatitis at the site of application, mild to moderate in severity, and resolved spontaneously. However, the increased incidence of dropping out caused by the intolerance of OE gel, indicating that OE gel is not suitable to all patients and the optimal topical choice for scar treatment should base on the topical reactions.

The limitations in our meta-analysis: (a) only three studies assessed the effect of OE in silicone gel; thus, the sample size was small to reach firm conclusion about OE in silicone gel in scar management. Moreover, TSA indicates more trails are needed to strength the conclusion about OE gel vs other topical treatments. (b) Heterogeneity among the included studies was visible, especially the different scales to assess the scars, different controls (no treatment, placebo gel, petroleum ointment or jelly, and silicone lotion, gel or gel sheet), and different study design (internally controlled or split-scar study). (c) Scales including different items, such as redness,

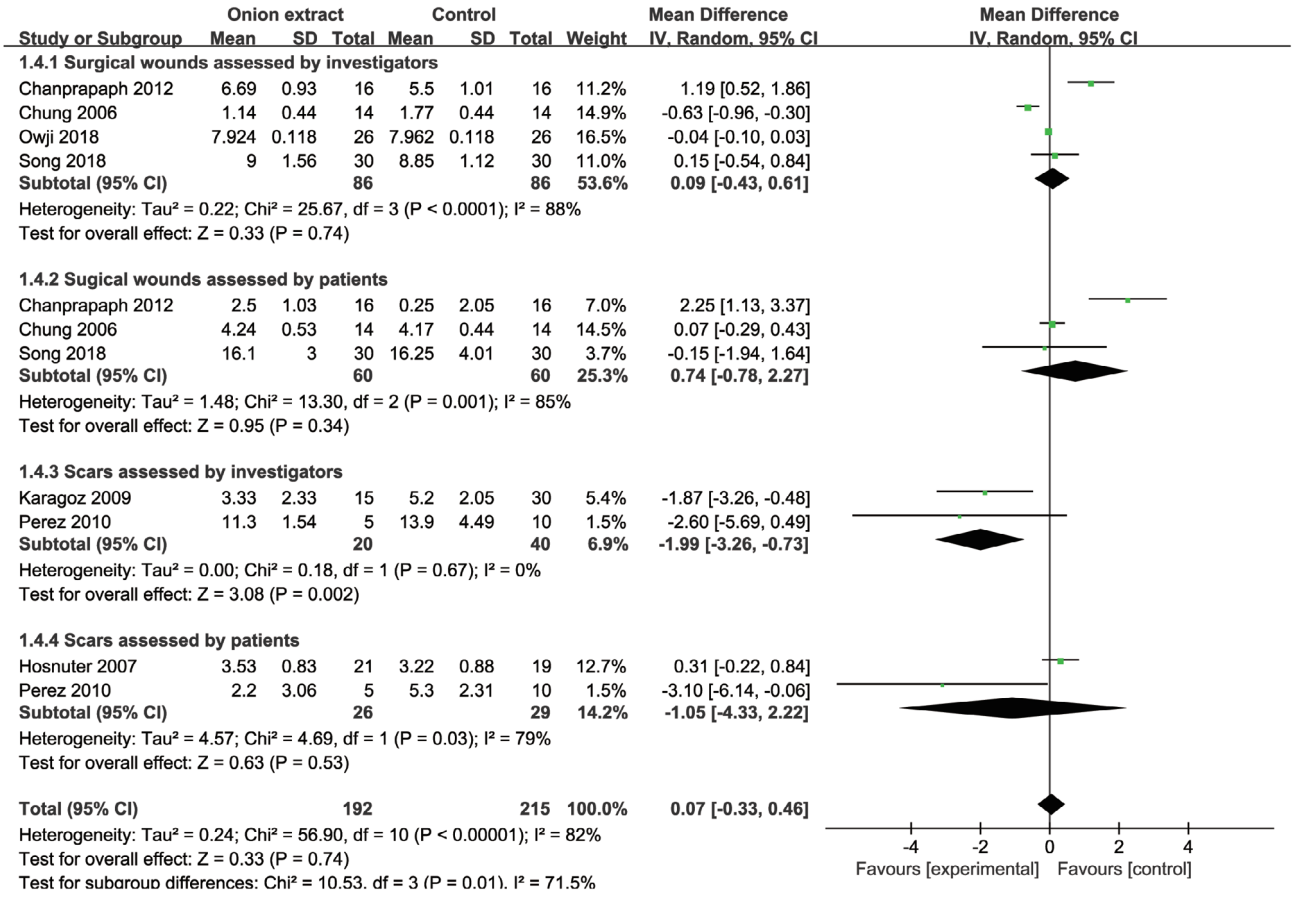

FIGURE 6 Forest plot diagram showing the subgroup analysis of total improvement scores between onion extract gel and other treatments

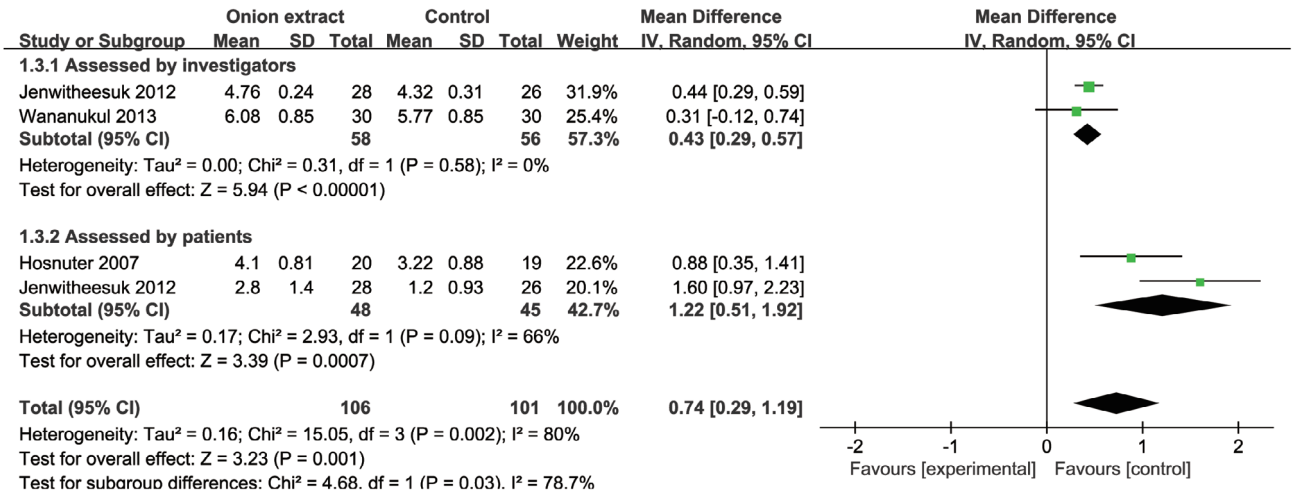

FIGURE 7 Forest plot diagram showing the total improvement scores between onion extract in silicone gel and other treatments

itchiness, burning, and pain, were used to evaluate the scars in the enrolled studies, and these items could not be meta-analysed separately to get more detailed information. (d) The asymmetrical funnel plot diagrams indicated that there were potential risks of publication bias in the included studies.

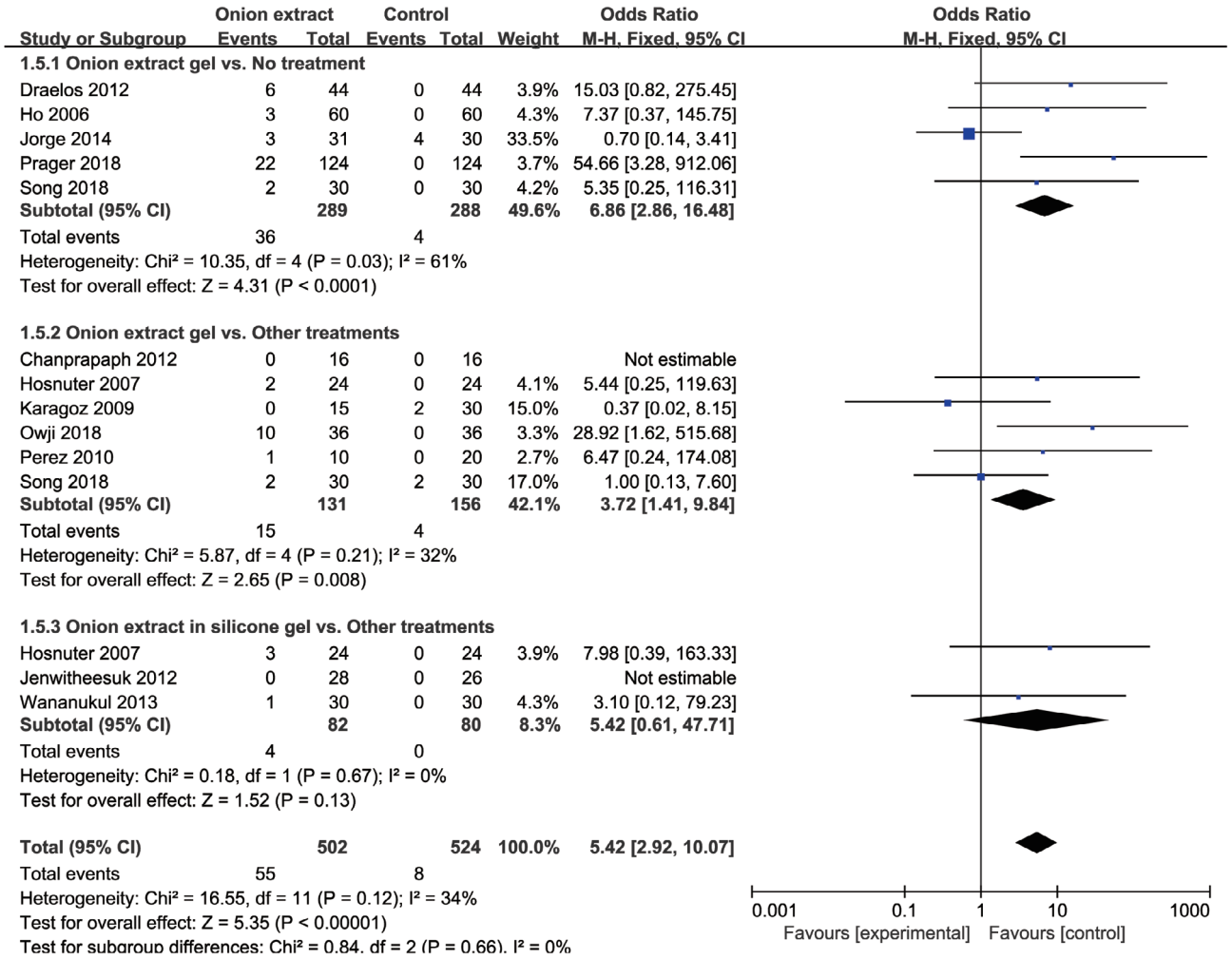

FIGURE 8 Forest plot diagram showing the incidence of total adverse effects by a fixed-effects model

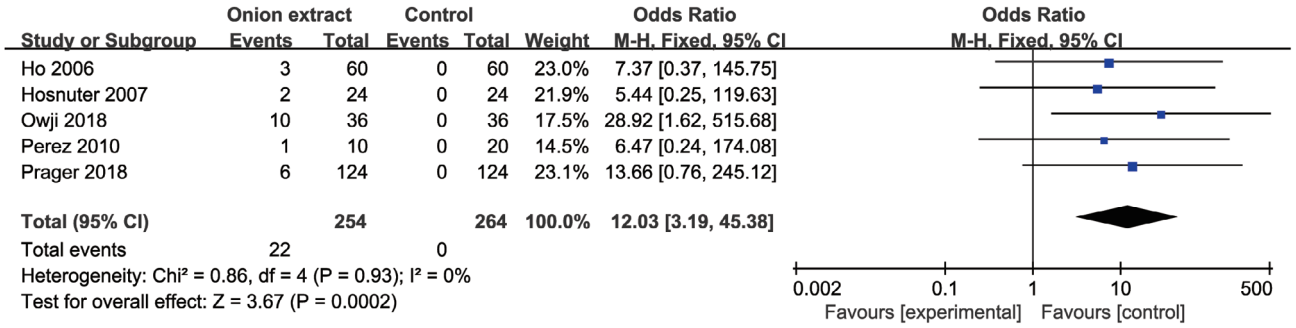

FIGURE 9 Forest plot diagram showing the incidence of dropping out caused by the intolerance of treatments

5 | CONCLUSIONS

Based on this meta-analysis of RCTs, OE gel not only has no superiority to commonly used topical treatments, but also has the potential to increase the incidence of adverse effects on scar management; OE in silicone gel might be the optimal topical choice for scar treatment; however, more evidences are needed to strength these conclusions.

ACKNOWLEDGEMENTS

This study was supported by Youth Talent Supported Program of Southwest Hospital (No. SWH2018QNLC-11).

CONFLICT OF INTEREST

None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are included within the article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Yuan X, Shen J, Chen L, Wang L, Yan Q, Zhang J. Onion extract gel is not better than other topical treatments in scar management: A meta-analysis from randomised controlled trails. *Int Wound J*. 2021;18:396–409. https://doi.org/10.1111/iwj.13542

APPENDIX A: Appendices (Search Strategy)

PubMed

#1 Allium cepa[TIAB] OR onion[TIAB] OR onions [TIAB] OR onion extract[TIAB]

#2 scar[TIAB] OR scars[TIAB] OR cicatrix[TIAB] OR cicatrice[TIAB] OR cicatrices[TIAB] OR keloid[TIAB] OR keloids[TIAB] OR cicatricle[TIAB]

#3 #1 AND #2

Medline

#1 TS=(Allium cepa) OR TS=(onion) OR TS=(onions) OR TS=(onion extract)

#2 TS=(scar) OR TS=(scars) OR TS=(cicatrix) OR TS=(cicatrice) OR TS=(cicatrices) OR TS=(keloid) OR TS=(keloids) OR TS=(cicatricle)

#3 #1 AND #2

Embase and Cochrane Library

#1 Allium cepa:ti,ab,kw OR onion:ti,ab,kw OR onions:ti,ab,kw OR onion extract:ti,ab,kw

#2 scar:ti,ab,kw OR scars:ti,ab,kw OR cicatrix:ti,ab,kw OR cicatrice:ti,ab,kw OR cicatrices:ti,ab,kw OR keloid:ti,ab,kw OR keloids:ti,ab,kw OR cicatricle:ti,ab,kw

#3 #1 AND #2