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Is the topical application of sesame oil (*Sesamum indicum* L.) combined with standard care valuable and safe for managing infusion-related phlebitis: Evidence from a systematic review with meta-analysis of randomized controlled trials

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ABSTRACT

Objectives: Recent randomized controlled trials (RCTs) have studied the potential effect of the topical use of sesame oil (SO), obtained from the sesame plant seeds (*Sesamum indicum L.*, Pedaliaceae family), in preventing or alleviating the symptoms of infusion-related phlebitis (IRP); nevertheless, their data are inconsistent. Thus, this review sought to qualitatively and quantitatively synthesize data from all available RCTs concerning the effect of the topical administration of SO on managing IRP.

Methods: The online databases were searched up to July 13, 2024. Studies were eligible if they compared administering standard care plus topical SO to applying an alternative modality and/or standard care. The Cochrane risk-of-bias tool and GRADE framework were employed to appraise the quality of the evidence.

Results: Eight studies of 755 records in the initial search met the inclusion criteria, which investigated inpatients and/or outpatients with chemotherapy-induced phlebitis (n = 6) and amiodarone-induced phlebitis (n = 2). According to the quantitative analysis, adults who had received coadministration of standard care and topical SO on the infusion site were significantly less affected by IRP than those who had received a control condition (effect sizes= 5, risk ratio= 0.54; 95 % confidence interval[0.32, 0.92]; $P = 0.025$). Also, based on the qualitative syntheses, SO can potentially prevent the formation of advanced stages of IRP, delay the appearance of IRP symptoms, and reduce IRP-induced pain severity.

Conclusion: Topical SO had a favorable effect on caring for adults with IRP. However, uncertainty remains because the evidence quality was moderate, some RCTs needed better methodological rigor, and most required to address the safety of the intervention or independent verification of SO used in terms of purity and potency. Thus, to build a valid conclusion about the efficacy and safety of SO in managing IRP, more high-quality RCTs must be conducted considering an active placebo control intervention along with a well-designed randomization and blinding approach, as well as a better description of safety parameters and the quality control information of the SO used.

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1. Introduction

Infusion-related phlebitis (IRP) is one of the considerable complications of intravenous infusion therapies, characterized by the inflammation of the tunica intima of a superficial vein.[1] The incidence of IRP with peripherally inserted central and midline catheters was reported to be 3.41 % and 1.52 %, respectively.[2] A combination of chemical, mechanical, and bacterial sources can cause the IRP. Risk factors for this condition are solution concentration and medication irritation, venous catheter size and location, venipuncture impairment, and microbial contamination.[3,4] Patients with IRP commonly experience local pain, tenderness, erythema, swelling, and induration on the venous tract, as well as a palpable cord-like vein around the infusion area.[5] The occurrence of these signs and symptoms makes it challenging to persist with the intravenous therapies, potentially leading to patient discomfort.[6] Moreover, this condition requires rapid interruption of the infusion, relocation and removal of the venous catheter, as well as it can cause clotting, thrombophlebitis, and even death.[7] IRP may also permanently affect the venous endothelium, reducing the probability of effectively applying any future intravenous treatment through the injured vein. Besides, patients experiencing IRP with first catheterization are more susceptible to developing post-IRP upon subsequent catheterizations.[8] Therefore, the prevention and early treatment of IRP by implementing an appropriate caring protocol is essential to the nursing profession's healthcare work.

Currently, different caring interventions have been suggested to prevent or lessen the severity of IRP, including but not limited to administering heparin, saline lock, nitroglycerin ointment, prophylactic antibiotics, anti-inflammatory drugs or corticosteroids, transparent dressings, and hot or wet compress, as well as rapid dilution and injection of drugs and catheter removal.[1,9,10] However, none of these interventions are without complications, and there is no agreement regarding the optimal methods despite the variety of known approaches, making it a fundamental concern at a clinical level.[8,11] Consequently, it is inevitable and crucial to investigate the application of proper, low-cost, and unique approaches to prevent or minimize the potential complications of the standard preventive and therapeutic methods of IRP management.

Traditionally, herbal preparations have been applied to alleviate inflammation and pain caused by different conditions.[12–14] In recent decades, different phytotherapeutic products (e.g., chamomile, notoginseng, and Aloe vera) have attracted attention to prevent or alleviate IRP symptoms because of their low cost, comfortable usage, and scarcity of unfavorable effects.[15,16] Sesame oil (SO), obtained from the sesame plant seeds (*Sesamum indicum L.*, Pedaliaceae family), has been long utilized in traditional medicine due to its anti-inflammatory and analgesic activities.[17,18] Also, in recent trials, SO has been a focus of interest to prevent or treat skin injuries and inflammatory conditions such as phlebitis.[19–22] The anti-inflammatory properties of this herbal product are attributed to its chemical compositions, which are assumed to play an action similar to that of opioids and non-steroidal anti-inflammatory medications. It has considerable portions of unsaturated fatty acids, which induce anti-inflammatory consequences on prostaglandins and leukotrienes and inhibit pain transmission pathways.[23] Likewise, SO contains various lignans, which should be accountable for this product's anti-inflammatory, anti-swelling, and analgesic properties by preventing the release of pro-inflammatory indices (i.e., interleukin-8 and endothelin-1).[24]

Recently, randomized controlled trials (RCTs), especially in the nursing field, demonstrated a significant interest in investigating the potential consequence of the external application of SO in preventing or alleviating the symptoms of IRP; yet, their data are conflicting. A recent trial reported no meaningful difference in the incidence of chemotherapy-induced phlebitis (CIP) between three groups of SO, alcohol-betadine solution, and nitroglycerin ointment.[25] However, in three other trials, topical application of SO on the infusion site significantly diminished the incidence of CIP compared to the control condition.[26–28] Besides, the application of SO on the phlebitis site with/without massage was more effective in decreasing the pain of clients with CIP compared to the administration of massage solely/alcoholic solution on the phlebitis site.[29,30] Another trial also indicated that the topical SO remarkably decreased the severity, incidence, and onset of amiodarone-induced phlebitis (AIP) compared to the topical placebo.[31] However, another study reported no statistically significant difference in AIP incidence, severity, and onset in the SO and control groups.[32]

Recent reviews of animal and human experiments regarding the sesame properties also documented favorable evidence of the anti-inflammatory effect of SO.[18,24,33,34] Likewise, current reviews proposed the potential effectiveness of topical use of SO for clients with IRP.[1,35] Nonetheless, based on available information, no review has ever specifically evaluated the effect of SO on the management of IRP, making it demanding to suggest this reasonable complementary method in phlebitis control guidelines. Thus, considering the conflicting findings of related trials, the current review sought to synthesize and appraise RCTs concerning the effect of the external use of SO on managing IRP. Moreover, it aimed to evaluate the potential impact of intervention by a pooled-analysis approach. We considered IRP incidence and severity as the primary outcome and time of IRP development and IRP pain severity as the secondary outcomes.

2. Methods

2.1. Review registration

The Institutional Ethics Committee of Abadan University of Medical Sciences (Abadan, Iran) supported the present study (Ethics Approval No. IR.ABADANUMS.REC.1403.054). Similarly, the study protocol was publicized in the International Prospective Register of Systematic Reviews (PROSPERO; No. CRD42024542497).

2.2. Information sources

A systematic search was accomplished on five top electronic data sources for biomedical research, including the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Web of Science, and Scopus. Google Scholar was also searched for grey literature. Moreover, a search was conducted in the WHO International Clinical Trials registry forum to obtain unpublished documents and ongoing trials. Likewise, the bibliographic references of the eligible articles and previous related reviews were screened meticulously to find potentially pertinent records that could have been overlooked during the systematic searches.

2.3. Search strategies

We determined primary investigations utilizing a specific strategy adjusted for each data source. To this end, in the first stage, appropriate medical subject headings (MeSH) and key terms were selected; then, the most common Boolean operators were used for the highest specificity and sensitivity. A detailed search formula for each database is obtainable in Supplementary Table 1. Two investigators (MN and LA) searched all data sources independently, without publication time and language restrictions, in April 2024. Also, a complementary search was accomplished on July 13, 2024, to recover appropriate new eligible reports. The investigators reached a consensus during the systematic search via in-depth discussion.

2.4. Eligibility criteria

The criteria for including studies were as follows: 1) Participants: both genders, with no age restriction, who were susceptible to or experienced IRP induced by any intravenous therapies; 2) Intervention

group: receiving routine hospital care in addition to topical SO on the infusion site to prevent or treat IRP; 3) Comparison group: administrating routine hospital care or/and the topical alternative products on the infusion site to prevent or treat IRP; 4) Outcomes: phlebitis incidence and severity, time of phlebitis development, or pain severity of phlebitis; and 5) Study designs: cross-over or parallel-group RCTs published in any time and language.

The studies that had the following criteria were excluded: 1) were animal studies, preclinical trials, letters, theses, case reports, conference proceedings, redundant publications, and reviews; 2) considered SO as a part of a herbal mixture (e.g., MEBO: moist exposed burn ointment, including SO plus Chinese herbal remedies, β-sitosterol, and berberine); 3) considered IRP in addition to the phlebitis of any other etiology; and 4) addressed IRP induced by a combination of different intravenous therapies (i.e., chemotherapy agents, arrhythmia reversion treatments, and antineoplastic drugs), without presenting data of each therapy separately.

2.5. Study selection and data collection

The research team was in persistent contact during screening, selecting eligible studies, and extracting data from the included documents. First, these processes were executed by two investigators independently (FY and SZ); then, disagreements were resolved with the help of two other research team members (MT and MoA). The reliability of the study selection process was confirmed by obtaining a coefficient of 0.86 based on Cohen's Kappa.

The search results from all data sources were imported into reference management software (i.e., Endnote© version X8, Thomson Reuters, New York, NY). Consequently, after eliminating the duplications, all remaining documents' titles and abstracts were screened. After that, the full texts of the qualified articles were scrutinized for eligibility criteria. Eventually, the needed details were extracted for each included paper utilizing a data extraction layout. To prepare data for pooled analysis, the number with percentage was obtained for the categorical outcomes. At the same time, mean/mean change with standard deviation/standard error was extracted for the numerical variables. Additionally, any reported adverse events/effects of treatments were documented. In case of ambiguous information, the necessary data was acquired by emailing the responsible authors. Likewise, the register entries of the eligible studies were scanned to obtain more information when the studies had indefinite data.

2.6. Quality appraisal

The selected studies' risk-of-bias (RoB) was evaluated utilizing the revised version of the Cochrane RoB tool for randomized trials (RoB 2).[36] The GRADE framework (grading of recommendations, assessment, development, and evaluation) was also employed to consider the overall evidence quality.[37] Three independent investigators (ESM, MeA, MaA) recorded the RoB 2 and GRADE, and further consultations resolved their disagreements.

2.7. Synthesis of results

Data on phlebitis incidence, which were partially comparative and homogenous, were aggregated via a random-effects approach utilizing Stata (Stata Corp., College Station, TX, USA). To this end, the effect sizes (ESs) were declared as risk ratio (RR) with a related 95 % confidence interval (CI). The I-squared statistic (I^2) and Cochran's Q test were employed to estimate the degree of inconsistency and heterogeneity. Supplementary analyses were also accomplished when required, including meta-regression, sub-group, and sensitivity.[38] Finally, Egger's linear regression test was run to address the potential for publication bias.[39]

3. Results

3.1. Search results

The flow diagram of study identification and selection is visualized in Fig. 1. In the initial search, 745 records were detected from data sources. Additionally, the manual search resulted in selecting a further ten records, totaling 755. After eliminating duplicates (n = 285), 470 articles were examined based on their titles and abstracts, with only 162 were eligible for inclusion. Based on an investigation of the full text of 12 documents that met the selection criteria, four were excluded due to the following reasons: 1) administered SO combined with other herbal preparations,[20,40] 2) followed a case report design,[19] and 3) was a redundant publication of an included trial.[41] Finally, eight articles were deemed eligible for the present review.[25–32]

3.2. Studies characteristics

An overview of the leading characteristics of the reviewed RCTs is summarized in Table 1. The studies were performed in Iran (n = 5), Egypt (n = 1), Indonesia (n = 1), and Turkey (n = 1), and were published from 2012 to 2024 in English. All eight included RCTs were conducted with a parallel arm design. Also, all used a two-arm design except one, which considered three groups.[25] We extracted the data from the control and SO groups for this three-arm study, which investigated an extra intervention arm of nitroglycerin ointment.

Studies were conducted on inpatients and/or outpatients who had received intravenous infusions of either chemotherapy agents in the oncology ward (n = 6) or amiodarone in a coronary care unit (n = 2). All studies recruited adults, except one investigated children aged 2–14 years.[27] In all studies, a peripheral intravenous line was established in the healthy upper extremities using a similar approach in the study groups. Also, the study intervention was presented by a professional nurse in the participating unit in all studies, except three, in which the intervention was administered only by the patients[26,28] or by an expert nurse during hospitalization/one of the patient's family members after hospital discharge.[27]

The study sample size of the intervention and comparison arms varied from 18 to 50. Patients in the intervention arm received routine hospital care plus administrating topical SO on the phlebitis site, with a superficial massage (n = 2) or without any massage (n = 6). Considering the control condition, one study administered routine hospital care in addition to massage of the phlebitis site without a topical agent.[29] In three other studies, the control group received no specific interventions except routine care.[26,28,32] The remaining four studies applied routine hospital care in addition to using topical alternative products on the infusion site in the same quantity and approach to the SO administration (i.e., alcoholic solution= 2, paraffin liquid as placebo= 2). The administration dosage of SO/alternative products varied from 3 to 10 drops (about 1–3 mL) in each intervention; the most used was 10 drops (n = 4), followed by 5 drops (n = 2). The shortest intervention period was also six hours,[30] while the longest lasted 30 days post-discharge.[27] Besides, the total administration times varied from 1 to 60; the most administered frequency was twice daily.

3.3. Phlebitis incidence and severity

Six trials measured the incidence and severity of IRP after administering SO or control conditions.[25–28,31,32] All studies used the Visual Infusion Phlebitis Scale (VIPS), a numerical scale from 0 (i.e., a healthy intravenous site, no sign of phlebitis) to 5 (i.e., thrombophlebitis). However, there were some variations in the frequency of completing this scale. Two studies collected data at three 24-h periods after infusion,[25,32] one trial measured outcomes two times after infusion (i.e., the final day of intervention and 30 days after study initiation),[28] and one study addressed a five-time point during 30 h and 10 min after infusion.[31] The

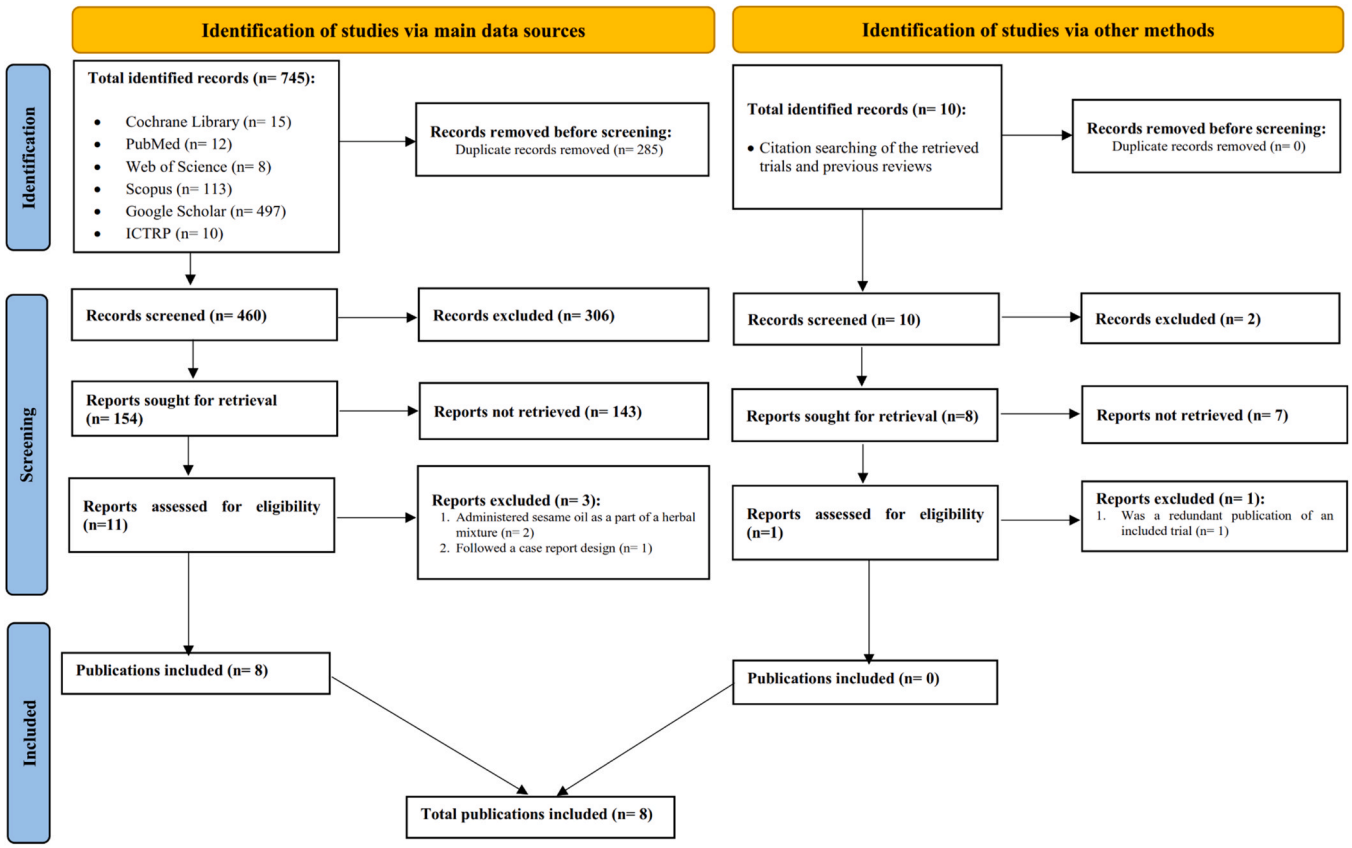


Fig. 1. Flow diagram for the process of studies screening and selection.

other two studies documented the outcomes only once after the intervention (i.e., 14 or 30 days post-intervention).[26,27] Accordingly, to make data uniformity for meta-analysis, the data was summed up in four studies that reported outcomes at more than one endpoint.[25,28,31,32]

Considering the severity of IRP, data were inconsistent for meta-analysis. However, a qualitative synthesis revealed that SO can potentially prevent the formation of advanced stages of IRP (Table 1). Also, of six studies that addressed the IRP incidence, one was not considered in the meta-analysis as it was conducted among children.[27] Finally, the ESs of five RCTs among adults were suitable for meta-analysis of phlebitis incidence.

Based on the pooled analysis, adults who had received coadministration of routine hospital care and topical SO on the infusion site were significantly less affected by IRP than those who had received routine hospital care alone or in addition to alternative products on the infusion site (ESs= 5, RR= 0.54; 95 % CI[0.32, 0.92]; $P = 0.025$). However, data stratification based on the type of IRP revealed no substantial between-group difference regarding the impact of the intervention on reducing the incidence of CIP among adults with cancers as well as AIP among adults with cardiac disorders (ESs= 3, $P = 0.264$; ESs= 2, $P = 0.424$, respectively) (Fig. 2). Also, according to the sensitivity analysis, the overall pooled ES depended on four specific RCTs,[26,28,31,32] as excluding each of these studies from the primary meta-analysis altered the effectiveness of the intervention to non-effective (Supplementary Figure 1). Similarly, removing the only research that applied SO plus massage[28] modified the substantial effect of the intervention to non-significant for the remaining RCTs that administered SO without any massage (ESs= 4; $P = 0.215$) (Supplementary Figure 2). However, after excluding the only three-arm RCT,[25] the pooled ES for two-arm studies was consistent with the overall finding (ESs= 4; $P = 0.037$) (Supplementary Figure 3).

A high between-study heterogeneity was found in the overall analysis (I^2: 91.7 %, $P < 0.001$). According to the sub-group analyses, the study's country of origin (Iran vs. others) and the control conditions (routine hospital care alone vs. routine hospital care plus topical alternative products) could be a basis of heterogeneity (Supplementary Table 2). However, none of the continuous variables was the origin of observed heterogeneity, according to the meta-regression (Supplementary Table 3). The Egger's linear regression test also showed no publication bias ($P = 0.143$).

3.4. Time of phlebitis development

Four RCTs compared the time of IRP development between the study arms.[26,27,31,32] Of these, one investigated children,[27] and running a pooled analysis was impossible for the remaining three studies on adults due to the heterogeneity of reporting data. However, two studies among adults showed that the appearance of IRP symptoms was significantly delayed in the SO arm in comparison with the control condition.[26,31] Such a finding was also observed among children.[27] However, one study among adults discovered no statistically significant between-group difference[32] (Table 1).

3.5. Pain severity of phlebitis

Out of eight included RCTs, three addressed the pain severity of IRP among adults.[29,30,32] However, data inconsistency made it impossible for these studies to be pooled in the meta-analysis. Two RCTs reported a more substantial decrease in the mean of CIP pain severity after administrating topical SO compared to the control conditions.[29,30] Nevertheless, the remaining study that described the percentage of AIP pain severity after the topical use of SO and control condition showed a non-significant difference between groups[32] (Table 1).

Table 1
Characteristics of the included randomized controlled trials on the effect of topical administration of sesame oil on management of infusion-related phlebitis.

Study ID (country)	Design (blinding)	Participants (hospital unit)	Venipuncture/ phlebitis site	Groups	Sample size (years: mean ± SD/ range with %)	Intervention protocol (frequency; duration/time)	Outcomes (measures, time)	Findings*	RoB**
Gülşen and Arslan[32] (Turkey)	2-arm RCT (non-blinded)	Cardiac inpatients, aged ≥ 18 y, who received IV infusion of amiodarone (CCU)	Forearms	IG: SO + RC CG: RC	IG: 22 (56.7 ± 7.0) CG: 22 (56.0 ± 7.3)	10 drops of SO (1 drop per min, about 3 mL) were applied within the 10 cm radius of the infusion site for 10 min, then the area was dressed and fixed with anti-allergenic adhesives (three times: every 8 h during the 24-h amiodarone infusion)	AIP incidence and severity (VIPS, three 24-h periods after catheterization, at the end of every 24 h) Time of phlebitis development (researcher's observations, over 3 d) Adverse effects (nrep., over 3 d)	N/S N/S nrep.	Low
El-Sayad et al.[28] (Egypt)	2-arm RCT (nrep.,)	Cancer outpatients/ inpatients (adults), who received IV infusion of chemotherapeutic agents (oncology ward)	Anterior forearms, backside of hands, or wrist	IG: SO massage + cold compress + RC CG: Cold compress + RC	IG: 50 (49.4 ± 9.5) CG: 50 (50.2 ± 8.1)	A 5-min circular massage with 10 drops (about 3 mL) of SO was applied within the 10 cm radius of the phlebitis site (14 times: BID, every 12 h; from the 1st d of admission up to the 7th d of intervention)	CIP incidence and severity (VIPS, three-time points: T1, 1st d of intervention; T2, 7th d of intervention; T3, 28th d of study)	Sig. ↓ at T1, T2, T3	Some concern
Safikhani Mohammadzadeh et al.[25] (Iran)	3-arm RCT (single-blinded)	Cancer inpatients, aged 18–65 y, who received IV infusion of chemotherapeutic agents (oncology ward)	Anterior forearms or backside of hands	IG: SO + RC CG: Alcoholic solution + RC	IG: 46 (46.9 ± 14.7) CG: 46 (45.8 ± 15.8)	SO or alcoholic solution was applied on the distal catheter area at a length of 1.5 cm and width of 2 × 4 cm, then the area was dressed and fixed with anti-allergenic adhesives (once: following IV catheterization; before the injection of chemotherapeutic agents)	CIP incidence and severity (VIPS, three 24-h periods after catheterization, at the end of every 24 h)	N/S	Low
Bigdeli Shamloo et al.[29] (Iran)	2-arm RCT (non-blinded)	Cancer outpatients/ inpatients (i.e., colorectal), aged 20–60 y, who experienced CIP with a degree of 2 on VIPS and pain of phlebitis site with scores of 1–3 on VAS (oncology ward)	Metacarpal, cephalic, basilic, or median cubital vein	IG: SO massage + RC CG: Massage solely + RC	IG: 28 (41–55: 50.0 %) CG: 30 (41–55: 46.7 %)	A 5-min massage solely or with 10 drops (about 3 mL) of SO was applied within the 10 cm radius of the phlebitis site; then the area was dressed and fixed with anti-allergenic adhesives (14 times: BID, every 12 h; from the 1st d of admission up to the 7th d of intervention)	CIP pain severity (VAS, four-time points: T1, 1st d of intervention; T2, 3rd d of intervention; T3, 5th d of intervention; T4, 7th d of intervention) Adverse effects (researcher's observations and the patient's reports, daily after catheterization)	Sig. ↓ at T1, T2, T3, as well as T1 vs. T2, T1 vs. T3, T1 vs. T4 nrep.	Some concern
Damanik[30] (Indonesia)	2-arm RCT (nrep.)	Cancer inpatients (adults), who experienced CIP with degrees of ≥ 2 on VIPS (oncology ward)	nrep.	IG: SO + RC CG: Alcoholic solution + RC	IG: 20 (47.5 ± 12.4) CG: 20 (50.3 ± 10.3)	About 3 drops (1 mL) of SO or alcoholic solution was applied on the phlebitis site for 30 min (twice with 3 h intervals; nrep.)	CIP pain severity (VAS, two-time points: T1, before the intervention; T2, after the intervention)	Sig. ↓ at T2	Some concern
Mosayebi et al.[27] (Iran)	2-arm RCT (double-blinded)	Cancer inpatients (i.e., ALL), aged 2–14 y, who received IV infusion of chemotherapeutic	nrep.	IG: SO + RC CG: Placebo (liquid	IG: 30 (7.5 ± 3.8) CG: 30	10 drops (about 3 mL) of SO or placebo was applied on the anterior forearm within the	CIP incidence and severity (VIPS, daily after catheterization)	Sig. ↓	Some concern

(*continued on next page*)

Table 1 (*continued*)

Study ID (country)	Design (blinding)	Participants (hospital unit)	Venipuncture/ phlebitis site	Groups	Sample size (years: mean ± SD/ range with %)	Intervention protocol (frequency; duration/time)	Outcomes (measures, time)	Findings*	RoB**
		agents (oncology ward)		paraffin) + RC	(6.2 ± 2.9)	10 cm radius of the infusion site (60 times: BID, every 12 h; from the 1st d of chemotherapy up to the 30 d later)	Time of phlebitis development (researcher's observations, over 30 d)	Sig. ↑	
Bagheri-Nesami et al.[31] (Iran)	2-arm RCT (double-blinded)	Cardiac inpatients, aged ≥ 18 y, who received IV infusion of amiodarone (CCU)	Wrists, forearms, or median cubital vein	IG: SO + RC CG: Placebo (liquid paraffin) + RC	IG: 18 (68.5 ± 13.0) CG: 18 (70.2 ± 13.5)	5 drops (about 1.5 mL) of SO or placebo was applied within the 10 cm radius of the infusion site (five times: once following IV catheterization and before the 1st injection of amiodarone, four times in 24 h with the onset of amiodarone infusion)	AIP incidence and severity (VIPS, five-time points after catheterization; a total of 30 h and 10 min: T1, the first 10 min; T2, from the first 10 min to 6 h and 10 min; T3, from 6 h and 10 min to 24 h and 10 min; T4, from 24 h and 10 min to 30 h and 10 min)	Sig. ↓ at T2 and T4, as well as totally	Some concern
							Time of phlebitis development (researcher's observations, over 30 h and 10 min after catheterization)	Sig. ↑	
Nekouzad et al.[26] (Iran)	2-arm RCT (non-blinded)	Cancer inpatients (i.e., colorectal), aged 30–70 y, who received IV infusion of chemotherapeutic agents (oncology ward)	nrep.	IG: SO + RC CG: RC	IG: 30 (nrep.) CG: 30 (nrep.)	5 drops (about 1.5 mL) of SO were applied on the anterior forearm within the 10 cm radius of the infusion site (28 times: BID, every 12 h; from the 1st d of chemotherapy up to the 14th d later)	CIP incidence and severity (VIPS, daily over 14 d)	Sig. ↓	Some concern
							Time of phlebitis development (researcher's observations, over 14 d)	Sig. ↑	

Abbreviations: AIP: Amiodarone-induced phlebitis; ALL: Acute lymphoblastic leukemia; BID: Two times a day; CCU: coronary care unit; cm: Centimeter; CG: Control group; CIP: Chemotherapy-induced phlebitis; d: Days; h: Hour (s); IG: Intervention group; IV: Intravenous; min: Minutes; mL: Milliliter; nrep.: Not reported; RCT: Randomized control trial; RoB: Risk of bias; RC: Routine care; SD: Standard deviation; SO: Sesame oil; VAS: Visual analog scale; VIPS: Visual Infusion Phlebitis Scale; y: Years; %: Percentage; ↑: longer; ↓: less.

* Intervention group vs. control group

** The revised Cochrane's RoB tool for randomized trials (RoB2): 1) Low: the study is believed to be at low RoB for all domains, and 2) Some concern: the study is deemed to raise some concerns in one or two domains, but not to be at high RoB for any domain.

3.6. Safety

Three studies investigated potential adverse consequences of the treatment; however, all reported its safety[27,29,32] (Table 1).

3.7. Risk of bias

Fig. 3 demonstrates details on assessing the RoB of the included articles. Besides, the details of the authors' judgments about the RoB of each included article are presented in Supplementary Table 4. The included RCTs had a low RoB in all aspects except the domain of bias arising from the randomization process. Two studies adequately generated the randomization sequence and concealed the randomization process,[25,32] while the remaining studies had concerns about this risk, primarily due to unclear information about allocation concealment. Hence, only two RCTs had an excellent methodological quality,[25,32] whereas the remaining RCTs had a moderate quality.

3.8. Evidence quality

Based on the GRADE method, the evidence quality for phlebitis incidence was moderate. Inconsistency was the leading rationale for lowering the evidence rate (Table 2).

4. Discussion

Catheter-related phlebitis is a frequent and fatal complication that affects more than half of the hospitalized patients with peripheral intravenous therapies.[3] Various interventions are utilized globally to control this complication; however, it is still an unresolved significant problem as it might hurt patients' safety due to its association with venous catheterization.[11] Therefore, recent clinical practice guidelines underscore this issue, requiring further investigation.[32] Accordingly, it is necessary for healthcare specialists, particularly nurses, to understand the significance of commonly related interventions and scrutinize

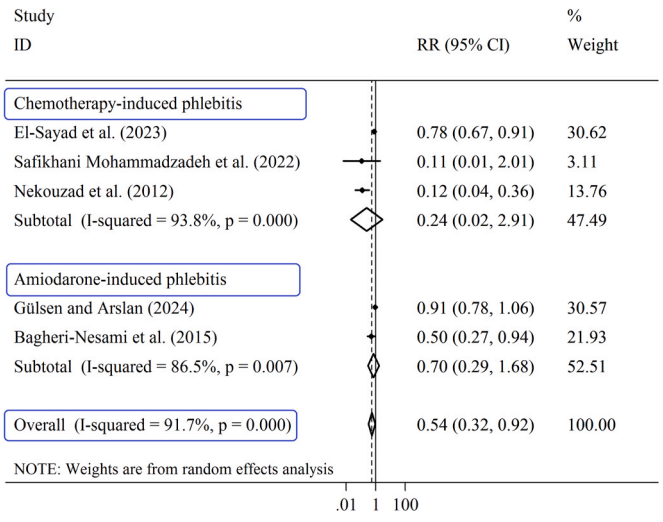
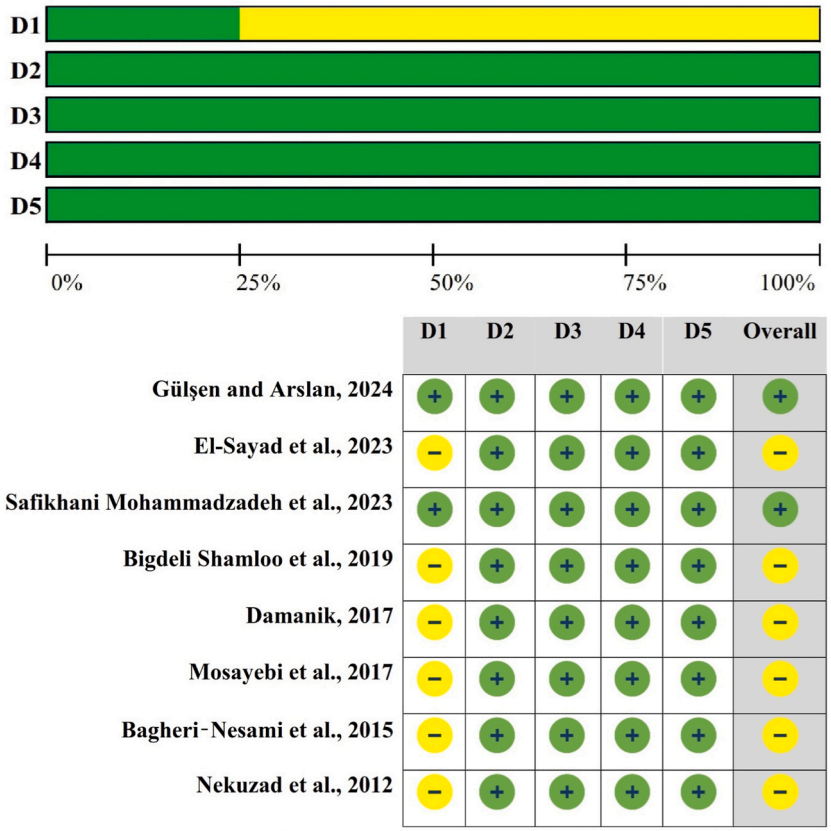


Fig. 2. Forest plot for the effect of topical sesame oil and routine care coadministration on the incidence of adults' infusion-related phlebitis (data are stratified based on the type of infusion-related phlebitis: chemotherapy-induced phlebitis vs. amiodarone-induced phlebitis).

available evidence to determine best practices, as this promotes clinical decision-making and optimizes results for the patients.[9] Although the action mechanisms of pharmaceutical products in IRP management have been more extensively studied to establish their effectiveness, herbal-based products with roots from empirical knowledge are currently more popular to be incorporated into evidence-based care.[8] SO is one of the traditional herbal products investigated in recent studies for managing IRP; nevertheless, the results of related RCTs are controversial. Hence, we decided to synthesize these conflicting findings to establish a trustworthy evidence-based conclusion concerning the efficacy of topical SO on outcomes associated with IRP, including the incidence and severity of phlebitis, time of phlebitis development, and phlebitis pain severity.

In the present study, adult participants of the SO arm had 46% lower risks of IRP in comparison with those in the control arm. Also, based on the evidence synthesis, the degree of IRP severity in the control arm was substantially higher than that of the SO arm, indicating that SO can potentially prevent the formation of advanced stages of IRP. Besides, the development time of IRP in the SO group could be delayed compared to the control group. According to these findings, the coadministration of topical SO and routine care could be more effective than control conditions in preventing IRP. In line with these findings, a recent systematic review of 12 studies published in Spanish or English until April 2020 regarding different topical interventions for preventing IRP reported that SO could substantially reduce the frequency of all symptoms related to IRP.[1] Besides, in a systematic review of 13 RCTs published between 1998 and 2019 regarding the efficacy of different topical interventions in preventing IRP, SO was suggested for preventing this condition.[8] Likewise, a meta-analysis of 38 Chinese RCTs published until September 2016 concluded that MEBO (i.e., a Chinese burn ointment containing SO), compared to conventional therapies, remarkably decreased the incidence of IRP.[42]



Abbreviations: *D1*, bias arising from the randomization process; *D2*, bias due to deviations from intended interventions; *D3*, bias due to missing outcome data; *D4*, bias in measurement of the outcome; *D5*, bias in selection of the reported result.
Symbols: *yellow circles*, some concern in risk of bias; *green circles*, low risk of bias.

Fig. 3. Summary of the authors' judgments about the risk of bias domains across and within the included randomized controlled trials regarding the effect of topical administration of sesame oil on management of infusion-related phlebitis.

Table 2
GRADE evidence profile: the effect of topical sesame oil and routine care coadministration on the incidence of adults' infusion-related phlebitis.

Outcome (number of studies)	Quality assessment					Summary of findings			
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Number of participants		Effect (95 % CI)	Quality of evidence
						Experimental group	Control group		
Phlebitis incidence (5 RCTs)	No serious[1]	Serious[2]	No serious[3]	No serious[4]	Undetected[5]	166	166	RR: 0.54 lower (0.32 lower to 0.92 lower)	⊕⊕⊕⊖ Moderate[6]

Abbreviations: CI: Confidence interval; RCTs: Randomized controlled trials; RR: Risk ratio.
[1] The higher percentage of risk of bias domains across the studies was low.
[2] I-squared statistic (I^2) = 91.7 %.
[3] Studies were sufficiently directed regarding population, intervention, comparator, and outcome.
[4] The boundaries of the confidence interval included the overall treatment effect, but the optimal information size was met.
[5] Egger's linear regression test ($P = 0.143$).
[6] We are moderately confident in the effect estimate: The actual effect is likely to be close to the estimate of the impact, but there is a possibility that it is substantially different.

Based on the standards of nursing professionals, the presence of pain at the insertion area of a peripheral intravenous catheter is the primary clinical sign for diagnosing IRP.[43] The evidence synthesis in the current review showed that SO might alleviate the severity of adults' IRP pain. Thus, besides the preventive effect, SO has a therapeutic impact on IRP pain severity. In line with this finding, a scoping review aimed to provide a practical view of the topical treatments of IRP documented that SO could be an effective phytotherapeutic agent for the control of IRP pain.[44] Also, according to a recent narrative review on clinical trials of sesame for pain management, topical administration of SO could effectively suppress pain induced by CIP.[35] Besides, a systematic review suggested SO for reducing the local pain severity of IRP.[8] Furthermore, in a pooled analysis of two studies, SO was introduced as a treatment that led to the most substantial decline in IRP-induced pain among different topical interventions (mean difference: 5.83, $P < 0.001$).[1] In the current study, we did not perform a meta-analysis for pain severity because of the three included studies; only two were homogenous for pooled analysis, which were the same as those pooled in the previously mentioned meta-analysis.

4.1. Research implications

The importance of using a topical rather than an oral or intravenous medication when preventing or treating phlebitis is to decrease unwanted side effects of chemical drugs (e.g., hepatic toxicity and organ overload), increase patients' independence, and allow them to follow the treatment at non-clinical settings easily.[8] According to the results of this review, the coadministration of topical SO and routine care could reduce the incidence and progress of IRP as well as alleviate the pain severity induced by this condition. Thus, it seems that SO is influential in preventing and treating IRP. Since this oil is found abundantly in most countries and is relatively cheap compared to pharmacological agents, and also considering that the patients have welcomed it due to its easy application, this herbal remedy could be used as a simple non-pharmacological modality in complementary and alternative medicine for patients with peripheral intravenous therapies who are susceptible to or experienced IRP. Also, the findings could be incorporated into nursing care to improve the outcomes of IRP, in line with a scoping review that suggested the applicability of SO administration as an evidence-based nursing intervention for preventing and treating IRP.[9] Yet, further RCTs are required to guarantee the usefulness of SO as an evidence-based practice.

In addition to clinical implications, this review can update and augment previous reviews and help investigators to plan a suitable RCT. One of the notable findings of this study was the methodological flaws of included RCTs, which need to be fixed in future studies to boost the validity of the evidence. Based on the GRADE, the evidence quality for IRP incidence was moderate; inconsistency was the leading cause of evidence downgrading. Moreover, we found the paucity of RCTs performed with a well-designed approach. Of eight included RCTs, only two had reasonable methodological quality based on the Cochrane RoB tool.[25,32] The reason for observing RoB arose from the randomization process, as six studies did not adequately generate or conceal the randomization sequence. Also, in terms of blinding, two studies assumed an active control group of a placebo intervention; however, none addressed the success of blinding.[27,31] The remaining studies could not blind patients and interventionists regarding the materials used due to SO's waxy nature, odor, or color. Yet, in these studies, there was no evidence of deviations from the intended interventions likely to impact the outcome. Furthermore, only three RCTs recorded potential adverse effects of the intervention (e.g., any signs of sensitivity or allergy, infection, and bleeding).[27,29,32] These studies reported no significant adverse effects, implying that topical use of SO is well-tolerated and safe for IRP management. However, some evidence, although limited, reported adverse events after using sesame, such as allergenicity.[35] Besides, only one of the included RCTs reported independent biochemical testing of the SO used in terms of potency (i.e., amount of critical standardized chemical constituents),[29] while none addressed the purity of product (i.e., presence, absence, or amounts of adulterants with pharmaceuticals or contamination with wrong herbs or heavy metals), which believed to be a potential source of bias.[45] Thus, we recommend future studies with improved methodological quality and minimized RoB, especially in the randomization domain, to consider the safety and usefulness of SO among patients with a high risk of IRP by measuring safety laboratory parameters, conducting independent verification of the SO for potency and purity, and using an active placebo control intervention.

Other noticeable findings of this review were revealed by sub-group and sensitivity analyses. We found that the intervention significantly reduced the IRP incidence, while this effect was non-significant when stratifying data based on the type of IRP. This finding could be attributed to low ESs in each sub-group (CIP= 3 and AIP= 2). Moreover, based on the sensitivity analysis, after excluding four specific studies from the primary meta-analysis,[26,28,31,32] especially the trial of El-Sayad *et al.*,[28] the beneficial impact of the intervention changed to non-significant. Also, the sub-group analysis indicated the study's country of origin (Iran vs. others) and the control conditions (routine care alone vs. routine care plus topical alternative products) as potential sources of heterogeneity. Since IRP is a worldwide issue and three of five synthesized RCTs of phlebitis incidence were conducted in Iran, further studies in other regions, where IRP continues to be an unresolved problem, are of merit. Also, it is recommended to perform three-arm trials to compare the long-term effect of the coadministration of SO and routine care with routine care alone and routine care plus topical alternative products (e.g., chemical medications or placebo agents).

The other outstanding finding of the present study was variation in

dosage, frequency, and duration of administrated SO, as well as the interventionists and endpoints, causing it problematic to suggest a definitive caring protocol to reach the optimum effects. In two reviewed studies, a 5-min massage with 10 drops (about 3 mL) of SO was applied within the 10 cm radius of the phlebitis site twice a day for seven consecutive days,[28,29] while the others administered 3–10 drops (about 1–3 mL) of SO on the affected area without any massage considering different endpoints and durations. After excluding the only RCT that applied SO plus massage,[28] the influential impact of the intervention on declining IRP incidence changed to non-significant, implying that the SO could be more effective when administered with massage. However, according to the sub-group analyses, we could not uncover any difference between RCTs in terms of interventionist, study duration, as well as total dosage and frequency of SO administration, which could be because of a low number of included studies. Thus, additional investigations are strongly suggested to compare diverse administration frequencies and dosages as well as different intervention durations to establish the optimal protocol that must be followed to obtain the most significant consequences. Likewise, comparing the intervention's effectiveness when applied with and without massage or by different interventions (i.e., nursing experts and patients) is of merit.

4.2. Research strengths

SO has been used frequently in recent RCTs as an adjunctive treatment method to IRP; however, as far as we know, this paper is the first systematic review with meta-analysis to investigate the pooled impact of SO compared to conventional or alternative measures on IRP. We focused specifically on SO, while previous reviews addressed SO along with different topical treatments. To this end, we performed a comprehensive search with more specific and sensitive key terms to discover all the available studies. Besides, we included only RCTs, while most earlier reviews synthesized the results of studies with different designs. Also, we stratified data based on the IRP type to present more accurate results.

4.3. Research limitations

The main limitation of the current review is the heterogeneity in methodology and reporting data, as well as the low number of available studies regarding pain severity and development time of phlebitis, making a related pooled analysis impossible. Also, concerning phlebitis incidence, the quality of evidence was moderated, and a high level of statistical heterogeneity was detected, which could undermine the validity of the reported results. Similarly, most of the included RCTs utilized an inappropriate method for randomization or needed to report it appropriately. Likewise, we considered different endpoint choices for pooled analysis of phlebitis incidence, which may be a potential source of observed heterogeneity. Finally, the findings might be generalized to only some regions, as most of the reviewed RCTs were performed in Iran.

5. Conclusions

The quantitative analysis showed the substantial impact of topical SO and routine care coadministration on reducing the incidence of adults' IRP. Also, qualitative synthesis suggested topical SO as an intriguing choice for preventing the formation of advanced stages of IRP, delaying the appearance of related symptoms, and lowering the pain severity of this complication. However, due to some concerns about the methodological quality of most RCTs and the paucity of studies that address the safety of the intervention or independent verification of SO used in terms of purity and potency, undertaking more RCTs with more excellent methodological quality and in various international contexts is suggested to reach an evidence-based conclusion on efficacy and safety of topical SO in preventing or treating IRP. Besides, forthcoming studies are recommended to explore an optimal caring protocol to reach the ultimate beneficial effect of the intervention.

CRediT authorship contribution statement

Morteza Nasiri: Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Leila Amirmohseni:** Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mohammad Farzollah Abbasi:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Fatemeh Yarahmadi:** Writing – review & editing, Project administration, Methodology, Investigation, Conceptualization. **Sahar Zonoori:** Writing – review & editing, Project administration, Methodology, Investigation, Conceptualization. **Mahya Torkaman:** Writing – review & editing, Validation, Project administration, Methodology, Investigation, Conceptualization. **Elham Sadeghi Moghimi:** Writing – review & editing, Validation, Project administration, Methodology, Investigation, Conceptualization. **Mehrnaz Ardaneh:** Writing – review & editing, Software, Project administration, Methodology, Investigation, Conceptualization. **Masoomeh Asadi:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ctim.2024.103122.

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