Effects of Topical Application and Oral Intake of *Rosa Damascena* on Adults' Acute Pain: A Systematic Review and Meta-Analysis

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Abstract

Recent studies have reported conflicting results regarding the pain-alleviating effects of *Rosa Damascena* in topical and oral administration forms. Therefore, we evaluated the potential effects of topical application and oral intake of this herbal medicine on adults' acute pain severity in a meta-analysis. A systematic search was performed on the Cochrane Central Register of Controlled Trials, PubMed, Scopus, Web of Science Core Collection, Embase,

Cumulative Index to Nursing and Allied Health Literature, SID, and MagIran from inception to March 20, 2021. We included parallel-group and cross-over randomized controlled trials (RCTs) that compared the effects of any products of *Rosa Damascena* in oral and topical administration forms to placebo, non-treatment, or conventional treatment. Two independent researchers performed study screening and selection, data extraction, and risk of bias assessment. A random-effect model was used to pool the data. Of the 11 studies that met the inclusion criteria, four and seven administered *Rosa damascena* through topical application and oral intake, respectively. The oral intake of *Rosa damascena* reduced pain severity non-significantly [standardized mean difference (SMD): −0.55; 95% confidence interval (CI): −1.27, 0.17; P= 0.132]. However, the topical application of this treatment had no pain-alleviating effect [SMD: 0.10; 95% CI: −0.75, 0.96; P= 0.814]. Most studies (n= 6) had fair methodological quality, and one reported mild allergic rhinitis as an adverse effect of the treatment. Further robust RCTs are suggested to compare the effects of oral intake and topical application of *Rosa damascena* on the severity of different types of acute pain in adults.

***Keywords*:** Acute pain; Adult; Analgesics; *Rosa Damascena*; Review.

PROSPERO number: CRD42020205071

1. Introduction

Rosa Damascena (*R. Damascena*), commonly known as *Damask Rose*, is a medicinal herb belonging to the *Rosaceae* family [1]. This herb is cultivated in Iran, Bulgaria, Pakistan, Turkey, Morocco, and India [2]. *R. Damascena* is considered as the flower's king because it is the sign of purity, inspiration, love, happiness, and beauty [3]. In addition, *R. Damascena* is commonly known as *"Gole-Mohammadi"* by Muslims, because its fragrance reminds them of *"Prophet Muhammad"* [4].

R. Damascena is currently used in food, perfume, cosmetic, and pharmacological industries worldwide [3,5]. The pharmacological properties of this herb are attributed to a high percentage of glycosides, terpenes, flavonoids, and anthocyanins [2,6]. Traditionally, different products of *R. Damascena* have been used for managing erectile dysfunction, arthritis, hepatitis, cardiovascular disorders, respiratory tract infections, and digestive disorders [3,6,7]. Also, *R. Damascena* is suggested to alleviate pain in traditional and modern medicine [2,5,6,8]. In Persian traditional medicine, *R. Damascena* is used as one of the most popular analgesic agents [9,10]. Recently, *R. Damascena* has been evaluated for its pain-alleviating properties in both *in vivo* and *in vitro* studies [11-40].

Recent reviews have suggested positive effects of *R. Damascena* in aromatherapy form on reducing pain severity [5,6,8,41,42]. However, potential pain-alleviating effects of this herbal medicine in oral and topical forms have not yet been addressed in a comprehensive review. Based on the recent randomized controlled trials (RCTs), topical application or oral intake of *R. Damascena* induced alleviating effects in pregnancy-related low back pain, menstrual-related pain, post-operative pain, and aphthous stomatitis-induced pain [24,30,31,35,36,43]. On the contrary, two RCTs found no significant difference in sexual-related pain among women who received *R. Damascena* capsule compared to those who received placebo capsule [27,28]. Similarly, no significant difference was reported between students' menstrual-related abdominal pain when they received *R. Damascena* and Mefenamic acid capsules in a cross-over design [25]. In addition, oral intake of *R. Damascena* had a non-significant alleviating effect on menstrual-related abdominal pain and headache among females with primary dysmenorrhea (PD) and premenstrual syndrome (PMS) [26,29]. Moreover, topical application of this herbal medicine had no significant effects on pain induced by migraine headache and aphthous ulcers [32,34].

Although the results of recent RCTs are inconclusive on the pain-alleviating effects of *R. Damascena* in topical and oral administration forms, to the best of our knowledge, no review has yet synthesized the conflicting findings of these RCTs. Therefore, we aimed to systematically identify and summarize the results of recent RCTs regarding the effects of topical application and oral intake of *R. Damascena* on adults' acute pain severity and also to pool the obtained findings in a meta-analysis.

2. Methods

This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020205071). The review was also reported based on the statements presented by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [44].

2.1. Search strategy

A systematic search was performed on the Cochrane Central Register of Controlled Trials, PubMed, Scopus, Web of Science Core Collection, Embase, Cumulative Index to Nursing and Allied Health Literature, Scientific Information Database (http://www.sid.ir/), and MagIran (http://www.magiran.com). All data sources were searched by two independent researchers two times: initially from inception to October 30, 2020; and second from October 30, 2020, to March 20, 2021. Moreover, the Iranian Registry of Clinical Trials and the World Health Organization International Clinical Trials Registry Platform were searched to find other probable related clinical trials. The corresponding authors of the retrieved trials were contacted *via* email to get information on their trials. Likewise, the reference lists of the eligible trials were checked to avoid missing related studies.

A combination of the following keywords was used in the systematic search: (Rosa OR Rose OR Rosaceae OR Rosewater OR "Rose water" OR "Rose oil" OR "Rosa damascena" OR "R. Damascena" OR "R. X damascena" OR "Damask rose" OR "Rose damask" OR

"Damascus rose" OR "Gole Mohammadi" OR Gol-E-Muhammadi OR Gol-E-Mohammadi) AND (Oral OR Supplement* OR Syrup OR Suspension* OR Emulsion OR Linctus OR Drop* OR Solution OR Extract* OR Oil* OR Capsule* OR Tablet OR Spray OR Ointment* OR Gel* Or Cream OR Lotion OR Massage OR Topical) AND (Pain OR Analgesi* OR Antinocicepti*). To find all possibly related studies, no restrictions were applied with regard to studies' participants, clinical conditions, language, and publication date in the literature search.

2.2. Eligibility criteria and studies selection

The studies were included based on the elements of the PICOS question, including participants, intervention, comparison, outcomes, and study design (**Table 1**). Studies were excluded if they: (*a*) were without available English abstract; (*b*) were conference papers, theses, letters, comments, short communications, reviews, meta-analyses, and animal studies; (*c*) administered *R. Damascena* in aromatherapy form; (*d*) administered *R. Damascena* in combination with other herbal products; (*e*) administered other species of Rosa; (*f*) recruited individuals who experienced chronic pain; and (*g*) recruited individuals over 60 years of age. Also, if studies conducted over the same participants, once with limited data were excluded.

Table 1: Inclusion criteria for considering studies on the effects of topical application and oral intake of *Rosa Damascena* on adults' acute pain.

Items	Criteria
Participants	Individuals within the age range of 18-60 years who experienced any types of moderate to severe acute pain
Intervention	Administration of any products of *Rosa Damascena* (e.g., essential oil, extract, absolute or concrete, syrup or juice, *Jollab*, petal jam, *Gulkand*, rose water, tea, drop, capsule, mouthwash) in the form of topical application or oral intake for a treatment group
Comparison	Placebo treatment, non-treatment, and conventional treatment
Outcomes	Pain severity, analgesics use, adverse effects of the treatment
Study design	Parallel-group and cross-over randomized controlled trials

The studies' screening and selection were performed by two independent researchers. In total, 1429 records were found from the electronic search. Based on the screening of title and abstract of 953 records, 938 were removed and full-texts of the 15 remaining studies were assessed for compliance with the inclusion criteria. Of these, two redundant publications [43,45], and a single-group study [39] were excluded. Also, one study that recruited individuals over 60 years of age was excluded [34]. Finally, 11 studies were considered eligible for this review [24-32,34,36] **(Figure 1)**.

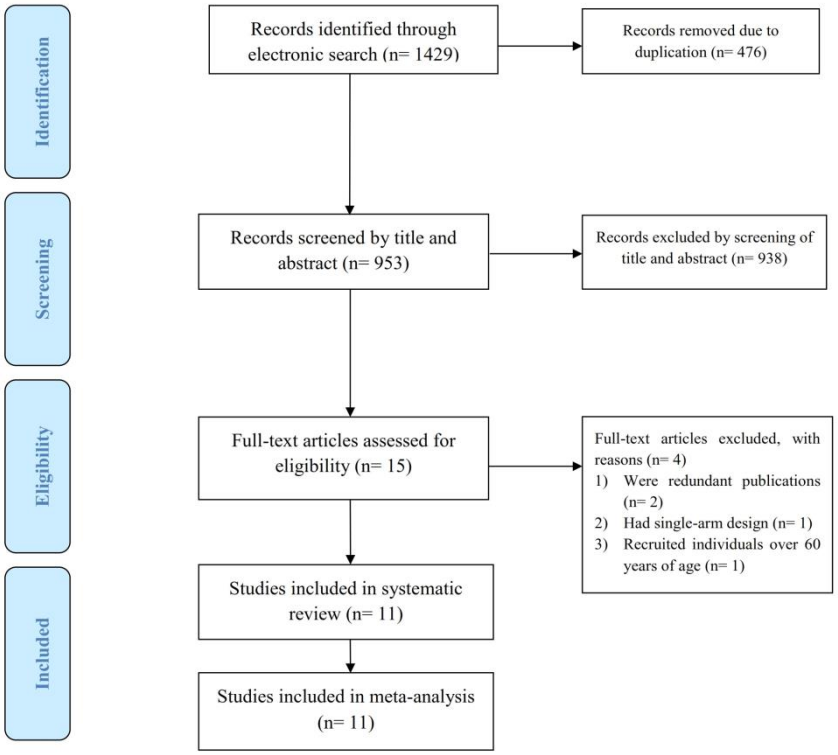

Figure 1: PRISMA flow diagram for identification of the studies and selection process.

2.3. Data extraction

The following data were extracted for each study by two independent researchers: *(a)* study details; *(b)* participants' characteristics; *(c)* intervention details; and *(d)* mean or mean changes and standard deviation (SD), as well as number and percentage for the measured outcomes. In four studies with multiple intervention groups, data were extracted from the *R. Damascena* and control groups [26,29,35,36]. Of these, one considered both placebo and non-treated groups; hence, data were extracted from the placebo group for comparison [36]. If the studies contained unclear or insufficient information, the study authors were contacted *via* email or phone call to get additional information on their studies. Any disagreement in data extraction between the researchers was resolved by discussion.

2.4. Assessment of risk of bias

The risk of bias for each included study was assessed by two independent researchers using the Cochrane Risk of Bias Assessment Tool, which consists of seven items: *(a)* random sequence generation (selection bias); *(b)* allocation concealment (selection bias); *(c)* blinding of participants and personnel (performance bias); *(d)* blinding of outcome assessment (detection bias); *(e)* incomplete outcome data (attrition bias); *(f)* selective reporting (reporting bias), and *(g)* other biases [46]. Disagreements between the researchers were resolved by consensus with a third researcher.

2.5. Data analysis

Studies recorded pain at different post-treatment times; hence, we calculated the changes of mean and SD in each study group by comparing the baseline and the end-of-trial values, using standard methods [42,47]. In a cross-over trial, the effect sizes of the first and second phases were pooled [25]. Also, the effect sizes of one study over the same participants were pooled before conducting the meta-analysis [26].

All effect sizes were reported as standardized mean difference (SMD) of outcomes with their 95% confidence interval (CI), using a random-effect model to take between-study heterogeneity into account. To assess heterogeneity, the I^2 statistic value of 50% or more and Cochran's Q test value of less than 0.05 were considered as significant heterogeneity. Subgroup analysis was performed to determine probable sources of heterogeneity and investigate any possible differences between studies about clinical condition, *R. Damascena* total administration dosage and duration as well as administration form, study tool, and study quality. To conduct a subgroup analysis based on total administration dosage, we converted *R. Damascena* products to a similar product or unit if possible. According to the administration dosage reported in the majority of included studies, 10 drops of *R. Damascena* was estimated as 1 mL. Also, we considered 1 mg of *R. Damascena* equal to 0.001 mL. To find the dependency of the overall estimate on the effect size from a single study, a sensitivity analysis was conducted. The Begg's and Egger's tests and also a visual inspection of funnel plots were used to assess potential publication bias. All statistical analyses were performed using Stata, version 11.2 (Stata Corp, College Station, TX). *P-values* were considered to be significant at the level of < 0.05.

3. Results

3.1. General characteristics

All included studies were conducted in Iran, and three were published in Farsi [24,29,32]. Studies were conducted on individuals within the age range of 18-40 years who experienced different painful conditions. All studies were recorded only pain severity, except one which recorded frequency and dosage of administrated analgesics in addition to pain severity [30]. Only one study reported mild allergic rhinitis in the *R. Damascena* group [35] (**Table 2**).

Table 2: Summary of included studies for the effects of topical application and oral intake of *Rosa Damascena* on adults' acute pain.

Authors	Study design	Participants	Sample size/ age	Intervention			Outcome/ study tool (measurement times)	Adverse events/ findings
				Study arms	Administration route	Administration dosage and duration†		
Shirazi et al. [35]	Triple-blind, placebo-controlled, 3-arm, parallel-group	Pregnant women with low back pain	I: 37/ 27.7 ± 0.8 C: 38/ 27.9 ± 0.7	I: R.D drop (essential oil in carrier of almond oil) + standard care C: Placebo drop (almond oil) + standard care	Topical application[1]	7 drops of each product (estimated as 0.7 mL), 2 times daily for 4 consecutive weeks [total dosage: 39 mL; total duration: 28 days]	Pregnancy-related low back pain/ VAS (baseline, 2nd week of intervention, 2 weeks after the end of intervention)	Mild allergic rhinitis/ Sig.
Khatibi et al. [32]	Double-blind, placebo-controlled, 2-arm, parallel-group	Individuals with minor aphthous ulcers	I: 50/ 30 ± 13.81 C: 50/ 24.5 ± 8.34	I: R.D drop + standard care C: Placebo drop (Diphenhydramine syrup) + standard care	Topical application[2]	10 drops of each product (estimated as 1 mL), 4 times daily for 1 week [total dosage: 28 mL, total duration: 7 days]	Aphthous ulcer pain/ VAS (baseline, 2nd, 4th, and 7th days of intervention)	nrep./ NS
Sadeghi Aval Shahr et al. [36]	Single-blind, placebo-controlled, 3-arm, parallel-group	College students with PD	I:25/ 26 ± 3.6 C:25/ 24.6 ± 3.1	I: R.D drop (essential oil in carrier of almond oil) C: Placebo drop (almond oil)	Topical application[3]	5 drops of each product (estimated as 0.5 mL) at the 1st day of menstruation for 2 subsequent MC [total dosage: 1 mL, total duration: 2 days]	Menstrual-related abdominal pain/ VAS (before and after intervention in 1st and 2nd MC)	nrep./ Sig. only at the 2nd MC
Hoseinpour et al. [31]	Double-blind, placebo-controlled, 2-arm, parallel-group	Individuals with minor aphthous ulcers	I: 25/ 34.4 ± 9.6 C: 25/ 33.6 ± 14.4	I: R.D mouthwash C: Placebo mouthwash	Topical application[4]	5 mL of each product, 4 times daily for 2 weeks [total dosage: 280 mL, total duration: 14 days]	Aphthous ulcer pain/ perceived pain rating scale (baseline and 4th, 7th, 11th and 14th days of intervention)	nrep./ Sig only at 4th and 7th days
Farnia et al. [28]	Double-blind, placebo-controlled, 2-arm, parallel-group	Opioid-dependent females with methadone-related sexual dysfunction	I: 25/ 38.92 ± 8.31 C: 25/ 38.72 ± 7.24	I: R.D soft gelatin capsule (filled with 2 mL essential oil) + standard care C: Placebo soft gelatin capsule (filled with 2 mL oil-water solution) + standard care	Oral intake	One capsule of each product (estimated as 2 mL), daily for 8 consecutive weeks [total dosage: 112 mL, total duration: 56 days]	Sexual-related pain/ FSFI (baseline, 4th and 8th weeks of intervention)	nrep./ NS
Davaneghi et al. [26]	Double-blind, placebo-controlled, 4-arm, parallel-group	Females with PD	I: 27/ 22.63 ± 0.47 C: 25/ 22.08 ± 0.39	I: R.D hard gelatin capsule (filled with 800 mg R.D extract) + fish oil soft gelatin capsule (placebo) C: R.D hard gelatin capsule (filled with placebo)+ fish oil soft gelatin capsule (placebo)	Oral intake	One capsule of each product (estimated as 0.8 mL), daily from the first day of menstruation until 60 consecutive days [total dosage: 48 mL, total duration: 60 days]	Menstrual-related headache and abdominal pain/ VAS (baseline, 30th and 60th days of intervention)	nrec./ NS
Ataollahi et al. [24]	Double-blind, placebo-controlled, 2-arm, parallel-group	College students with PD	I: 55/ 21.41 ± 1.49 C: 55/ 21.38 ± 1.72	I: R.D oral drop C: Placebo drop (water and sugar)	Oral intake	10 drops of each product (estimated as 1 mL), 2 times daily during first 3 days of menstruation for 2 subsequent MC [total dosage: 12 mL, total duration: 6 days]	Menstrual-related abdominal pain/ McGill (baseline, end of 2nd MC)	nrec./ Sig.
Farnia et al. [27]	Double-blind, placebo-controlled, 2-arm, parallel-group	Females with SSRI-induced sexual dysfunction	I: 25/ 32.45 ± 5.68 C: 25/ 34.02 ± 6.45	I: R.D soft gelatin capsule (filled with 2 mL essential oil) + standard care C: Placebo soft gelatin capsule (filled with 2 mL oil-water solution) + standard care	Oral intake	One capsule of each product (estimated as 2 mL), daily for 8 consecutive weeks [total dosage: 112 mL, total duration: 56 days]	Sexual-related pain/ FSFI (baseline, 4th and 8th weeks of intervention)	nrep./ NS
Bani et al. [25]	Double-blind, placebo-controlled, 2-arm, cross-over groups	College students with PD	I: 46/ 22.20 ± 2.11 C: 46/ 22.13 ± 2.06	I: R.D hard gelatin capsule (filled with 200 mg R.D extract) C: Mefenamic acid capsule (250 mg)	Oral intake	One capsule of each product (estimated as 0.2 mL), 4 times daily during first 3 days of menstruation for 2 subsequent MC (total dosage: 4.8 mL, total duration: 6 days)	Menstrual-related abdominal pain/ VAS (baseline and 1, 2, 3, 6, 12, 24, 48, 72 hours after taking the first drug during 1st and the 2nd MC)	nrep./ NS
Jamilian et al. [29]	Double-blind, placebo-controlled, 3-arm, parallel-group	Females with PMS	I: 40/ 25.93 ± 4.68 C: 40/ 26.56 ± 3.53	I: R.D oral drop C: Placebo drop (distilled water)	Oral intake	15 drops of each product (estimated as 1.5 mL), 2 times daily from 14 days before menstruation until end of menstruation for 3 subsequent MC [total dosage: 180 mL, total duration: 60 days]	Menstrual-related headache/ DSRS (baseline, end of 3rd MC)	nrec./ NS
Mostafa-Gharabaghi et al. [30]	Double-blind, placebo-controlled, 2-arm, parallel-group	Females undergoing C/S	I: 46/ 27.78 ± 4.04 C: 46/ 22.28 ± 5.04	I: R.D hard gelatin capsule (filled with 400 mg R.D extract) + standard care C: Placebo hard gelatin capsule (filled with 400 mg starch) + standard care	Oral intake	2 capsules of each product (each estimated as 0.4 mL), during 15 min before anesthesia [total dosage: 0.8 mL]	Post-operative pain/ VAS (baseline and 3, 6, 12, and 24 hours after surgery) Frequency and dosage of administrated analgesics (baseline, end of intervention)	nrep./ Sig.

Abbreviations: C: Control; C/S: Cesarean section; DSRS: Daily symptom rating scale; DW: Distilled water; FSFI: Female sexual function index; I: Intervention; MC: Menstrual cycle; McGill: McGill pain questionnaire; min: Minutes; nrep.: Not reported; nrec.: Not recorded; NS: Not significant; PD: Primary dysmenorrhea; PMS: Premenstrual syndrome; R.D: Rosa Damascena; Sig.: Significantly; SSRI: Selective serotonin-reuptake inhibitors; VAS: Visual analog scale.

† Ten drops and 1 mg of *R. Damascena* was estimated as 1 mL and 0.001 mL, respectively.

[1] Products were self-administered topically for 100 cm^2 of the painful part of the skin (without massage).

[2] Products were self-administered topically on the lesions using a sterile swab (without massage and after meals, and before sleep).

[3] Products were self-administered topically on the abdomen and then the abdomen was massaged by clockwise circular movements for 15 min.

[4 2] Products were swished around the mouth for 30 seconds and then were expelled (preferably after oral-hygiene procedures).

* Significantly lower in the intervention group compared to the comparison group after the intervention.

3.2. Topical application of R. Damascena

Of four studies that administered *R. Damascena* in topical form, three used 0.5-1 mL topical drop [32,35,36], and the other one administered 5 mL mouthwash [31]. The total administration duration of *R. Damascena* products varied from 2 to 28 days. The products were self-administered without massage in all studies, except one which applied abdomen massage with *R. Damascena* essential oil [36]. All studies had a parallel-group design and two recruited only females [35,36]. The total sample size of the placebo group (i.e., Diphenhydramine syrup and almond oil) and the *R. Damascena* group were 137 and 134 (**Table 2**).

Based on the combined effect sizes of four RCTs, topical application of *R. Damascena* had no pain-alleviating effect (SMD: 0.10; 95% CI: −0.75, 0.96; P= 0.814). Heterogeneity was significant between studies in the overall analysis (I^2: 91.3%, P< 0.001) (**Figure 2**). After excluding one study which applied *R. Damascena* using massage [36], a non-significant reducing effect of treatment was observed (SMD: -0.06; 95% CI: −1.13, 1.00; P= 0.906).

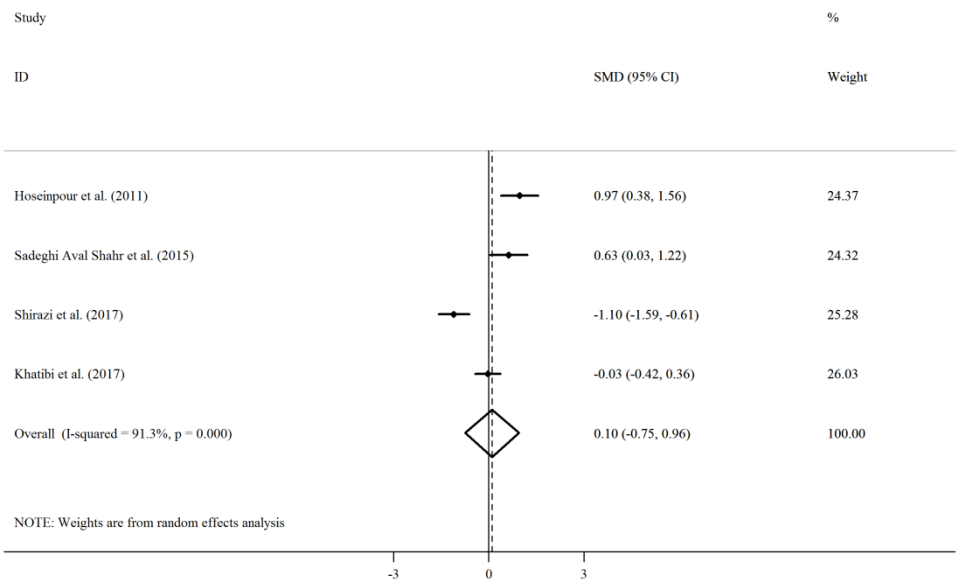

Figure 2: Forest plot for the effect of topical application of *Rosa Damascena* on adults' acute pain.

3.3. Oral intake of R. Damascena

Of seven studies that investigated *R. Damascena* in oral form, five administered soft or hard gelatin capsule containing either 200-800 mg extract [25,26,30] or 2 mL essential oil [27,28]. Two remaining studies used 1 mL or 1.5 mL oral drop [24,29]. The total administration duration of *R. Damascena* products varied from 1 day to 60 days. All studies were recruited only females and had a parallel-group design, except one which was conducted with a cross-over design [25]. The total sample size of the placebo/conventional treatment group (i.e., Mefenamic acid capsule) and the *R. Damascena* group were 308 and 310 (**Table 2**).

Based on the combined effect sizes of seven RCTs, oral intake of *R. Damascena* reduced pain severity non-significantly compared to the placebo or conventional treatment (SMD: −0.55; 95% CI: −1.27, 0.17; P= 0.132). A significant heterogeneity was found among the included studies for main analysis (I^2: 94.3, P< 0.001) (**Figure 3**). After excluding one cross-over study [25], the results of primary meta-analysis did not change (SMD: −0.68; 95% CI: −1.55, 0.20; P= 0.129). Based on subgroup analysis, pain severity was significantly reduced when *R. Damascena* was administered using oral drop (P= 0.024) (**Table 3**).

Table 3: Subgroup analysis for the effects of topical application and oral intake of *Rosa Damascena* on adults' acute pain.

Variables		Effect sizes (n)	I^2	Cochran's Q test	SMD (95%CI)	P-within
Topical application						
Clinical condition	Menstrual-related pain	1	-	-	0.63 (0.03, 1.22)	0.039
	Pregnancy-related low back pain	1	-	-	-1.10 (-1.59, -0.61)	<0.001
	Aphthous ulcer pain	2	87.0%	0.006	0.45 (-0.53, 1.42)	0.372
Total administration dosage	≤ 39 mL	3	90.6%	<0.001	-0.18 (-1.09, 0.74)	0.702
	280 mL	1	-	-	0.97 (0.38, 1.56)	0.001
Total administration duration	≤ 14 days	3	77.1%	0.013	0.49 (-0.14, 1.12)	0.125
	28 days	1	-	-	-1.10 (-1.59, -0.61)	<0.001
Administration form	Drop	3	90.6%	<0.001	-0.18 (-1.09, 0.74)	0.702
	Mouthwash	1	-	-	0.97 (0.38, 1.56)	0.001
Study tool	VAS	3	90.6%	<0.001	-0.18 (-1.09, 0.74)	0.702
	Perceived pain rating scale	1	-	-	0.97 (0.38, 1.56)	0.001
Study quality	Poor[1]	1	-	-	-0.03 (-0.42, 0.36)	0.818
	Fair[2]	3	94.2%	<0.001	0.16 (-1.17, 1.48)	0.883

Oral intake						
Clinical condition	Sexual-related pain	2	88.3%	0.003	-0.68 (-1.89, 0.53)	0.270
	Menstrual-related pain	4	95.9%	<0.001	-0.79 (-1.85, 0.27)	0.143
	Post-operative pain	1	-	-	0.62 (0.20, 1.04)	0.004
Total administration dosage	≤ 12 mL	3	93.8%	<0.001	-0.07 (-0.92, 0.78)	0.874
	≥48 mL	4	94.1%	<0.001	-0.94 (-2.12, 0.25)	0.121
Total administration duration	≤ 6 days	3	93.8%	<0.001	-0.07 (-0.92, 0.78)	0.874
	≥56 days	4	94.1%	<0.001	-0.94 (-2.12, 0.25)	0.121
Administration form	Soft or hard gelatin capsule	5	84.9%	<0.001	-0.07 (-0.60, 0.46)	0.793
	Oral drop	2	94.3%	<0.001	-1.71 (-3.20, -0.23)	0.024
Study tool	VAS, McGill (0-10 scales)	4	90.8%	<0.001	-0.03 (-0.69, 0.63)	0.927
	Other	4	94.2%	<0.001	-1.29 (-2.69, 0.12)	0.072
Study quality	Poor[1]	1	-	-	0.62 (0.20, 1.04)	0.004
	Fair[2]	3	95.0%	<0.001	-1.12 (-2.42, 0.19)	0.094
	Good[3]	3	88.6%	<0.001	-0.38 (-1.19, 0.44)	0.363

Abbreviations: CI: Confidence interval; McGill: McGill pain questionnaire; SMD: Standardized mean difference; VAS: Visual analog scale.

[1] Cochrane risk of bias assessment tool: High risk of bias in one item and unclear risk of bias in more than two items.

[2] Cochrane risk of bias assessment tool: High risk of bias in one item or unclear risk of bias in one item or two items.

[3] Cochrane risk of bias assessment tool: Low risk of bias in all items.

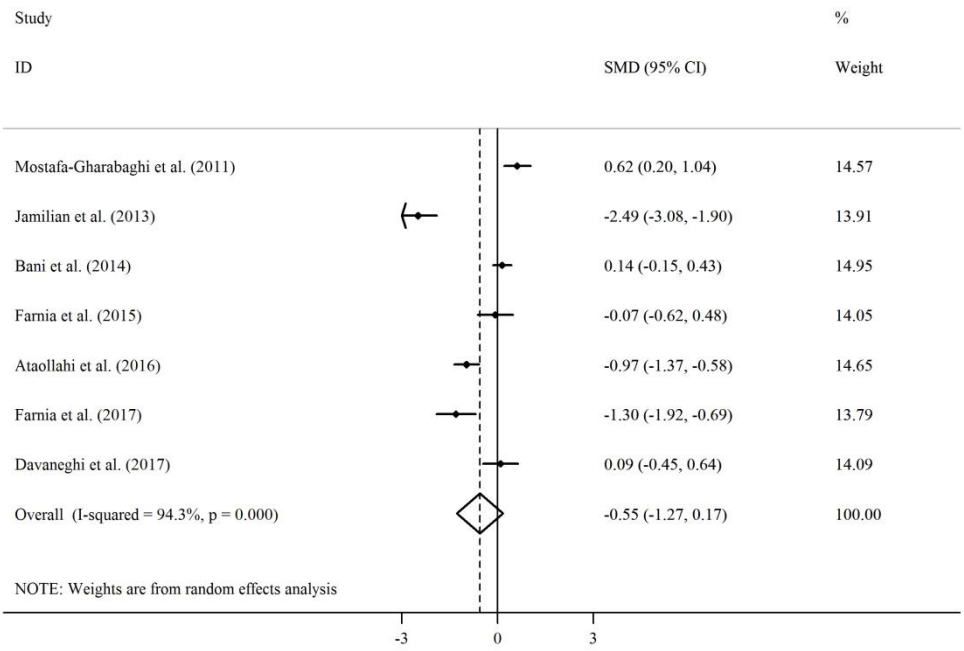

Figure 3: Forest plot for the effect of oral intake of *Rosa Damascena* on adults' acute pain.

3.3. Assessment of the risk of bias

Of the 11 included studies, three had good quality (low risk of bias for all items) [25,27,28], while two had poor quality (high risk of bias in one item and unclear risk of bias in more than two items) [30,32]. The remaining six studies had fair quality (high risk of bias in one item or unclear risk of bias in one item or two items) [24,26,29,31,35,36] (**Figures 4 and 5, Table 4**).

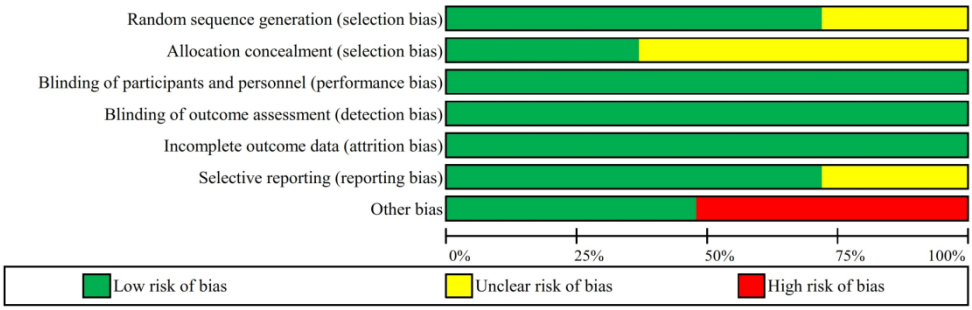

Figure 4: Risk of bias graph for studies on the effects of topical application and oral intake of *Rosa Damascena* on adults' acute pain.

Figure 5: Summery of risk of bias within studies on the effects of topical application and oral intake of *Rosa Damascena* on adults' acute pain.

Table 4: Assessment of risk of bias within studies with support for judgment.

Risk of bias items	Authors' judgment	Support for judgment
Shirazi et al (2017)		
Random sequence generation	Low risk	It was done using shuffling envelopes
Allocation concealment	Low risk	It was done using sequentially numbered drug containers of identical appearance
Blinding of participants and personnel	Low risk	Blinding of participants and key study personnel has been ensured
Blinding of outcome assessment	Low risk	Blinding of outcome assessment has been ensured
Incomplete outcome data	Low risk	Missing outcome data balanced in numbers across groups
Selective reporting	Low risk	The protocol is available (IRCT2014091419150N1) and all outcomes have been reported
Other bias	High risk	Measurement time is not well specified and is not based on the protocol
Khatibi et al (2017)		
Random sequence generation	Unclear risk	No specific information
Allocation concealment	Unclear risk	No specific information
Blinding of participants and personnel	Low risk	Blinding of participants and key study personnel has been ensured

Blinding of outcome assessment	Low risk	Blinding of outcome assessment has been ensured
Incomplete outcome data	Low risk	No missing outcome data
Selective reporting	Unclear risk	The protocol is not available
Other bias	High risk	The registered protocol does not exist, ethical approval does not exist, no specified funding source
Sadeghi Aval Shahr et al. (2015)		
Random sequence generation	High risk	No specific information
Allocation concealment	High risk	No specific information
Blinding of participants and personnel	Low risk	Blinding of participants has been ensured
Blinding of outcome assessment	Low risk	No blinding of outcome assessment, but the outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data	Low risk	No missing outcome data
Selective reporting	Low risk	The protocol is available (IRCT2012081310182N2) and all outcomes have been reported
Other bias	Low risk	No other sources of bias
Hoseinpour et al (2011)		
Random sequence generation	Low risk	It was done using a computer random number generator
Allocation concealment	Low risk	It was done using sequentially numbered drug containers of identical appearance
Blinding of participants and personnel	Low risk	Blinding of participants and key study personnel has been ensured
Blinding of outcome assessment	Low risk	Blinding of outcome assessment has been ensured
Incomplete outcome data	Low risk	No missing outcome data
Selective reporting	Unclear risk	The protocol is not available
Other bias	Low risk	No other sources of bias
Farnia et al (2017)		
Random sequence generation	Low risk	It was done using the drawing of lots
Allocation concealment	Low risk	It was done using sequentially numbered drug containers of identical appearance
Blinding of participants and personnel	Low risk	Blinding of participants and key study personnel has been ensured
Blinding of outcome assessment	Low risk	Blinding of outcome assessment has been ensured
Incomplete outcome data	Low risk	No missing outcome data
Selective reporting	Low risk	The protocol is available (IRCT2015091523705N2) and all outcomes have been reported
Other bias	Low risk	No other sources of bias
Davaneghi et al. (2017)		
Random sequence generation	Low risk	It was done using a random number table
Allocation concealment	Unclear risk	No specific information
Blinding of participants and personnel	Low risk	Blinding of participants and key study personnel has been ensured
Blinding of outcome assessment	Low risk	Blinding of outcome assessment has been ensured
Incomplete outcome data	Low risk	Missing outcome data balanced in numbers across groups
Selective reporting	Low risk	The protocol is available (IRCT201403105670N8) and all outcomes have been reported
Other bias	Low risk	No other sources of bias
Ataollahi et al. (2016)		
Random sequence generation	Low risk	It was done using block randomization
Allocation concealment	Unclear risk	No specific information
Blinding of participants and personnel	Low risk	Blinding of participants and key study personnel has been ensured
Blinding of outcome assessment	Low risk	No blinding of outcome assessment, but the outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data	Low risk	No missing outcome data
Selective reporting	Low risk	The protocol is available (IRCT201311216807N10) and all outcomes have been reported
Other bias	High risk	Outcome measurements have not been reported based on the protocol
Farnia et al (2015)		
Random sequence generation	Low risk	It was done using the drawing of lots
Allocation concealment	Low risk	It was done using sequentially numbered drug containers of identical appearance
Blinding of participants and personnel	Low risk	Blinding of participants and key study personnel has been ensured
Blinding of outcome assessment	Low risk	Blinding of outcome assessment has been ensured
Incomplete outcome data	Low risk	Missing outcome data balanced in numbers across groups
Selective reporting	Low risk	The protocol is available (IRCT2013100114333N9) and all outcomes have been reported
Other bias	Low risk	No other sources of bias
Bani et al. (2014)		
Random sequence generation	Low risk	It was done using block randomization

Allocation concealment	Low risk	It was done using sequentially numbered drug containers of identical appearance
Blinding of participants and personnel	Low risk	Blinding of participants and key study personnel has been ensured
Blinding of outcome assessment	Low risk	No blinding of outcome assessment, but the outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data	Low risk	No missing outcome data
Selective reporting	Low risk	The protocol is available (IRCT201207267618N2) and all outcomes have been reported
Other bias	Low risk	No other sources of bias
Jamilian et al. (2013)		
Random sequence generation	Low risk	It was done using a computer random number generator
Allocation concealment	Unclear risk	No specific information
Blinding of participants and personnel	Low risk	Blinding of participants and key study personnel has been ensured
Blinding of outcome assessment	Low risk	No blinding of outcome assessment, but the outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data	Low risk	No missing outcome data
Selective reporting	Low risk	The protocol is available (IRCT201108237405N1) and all outcomes have been reported
Other bias	High risk	Outcome measurements have not been reported based on the protocol
Mostafa-Gharabaghi et al (2011)		
Random sequence generation	Unclear risk	No specific information
Allocation concealment	Unclear risk	No specific information
Blinding of participants and personnel	Low risk	Blinding of participants and key study personnel has been ensured
Blinding of outcome assessment	Low risk	No blinding of outcome assessment, but the outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data	Low risk	No missing outcome data
Selective reporting	Unclear risk	The protocol is not available
Other bias	High risk	The registered protocol does not exist, ethical approval does not exist, no specified funding source

3.4. Publication bias and sensitivity analysis

With regard to topical application, no evidence of publication bias was found based on the visual inspection of the funnel plot as well as the Begg's test (P= 0.734) and Egger's test (P= 0.527)**.** Such findings were also obtained for oral intake based on the funnel plot and also the Begg's test (P= 0.230) and Egger's test (P= 0.236) (**Figure 6**).

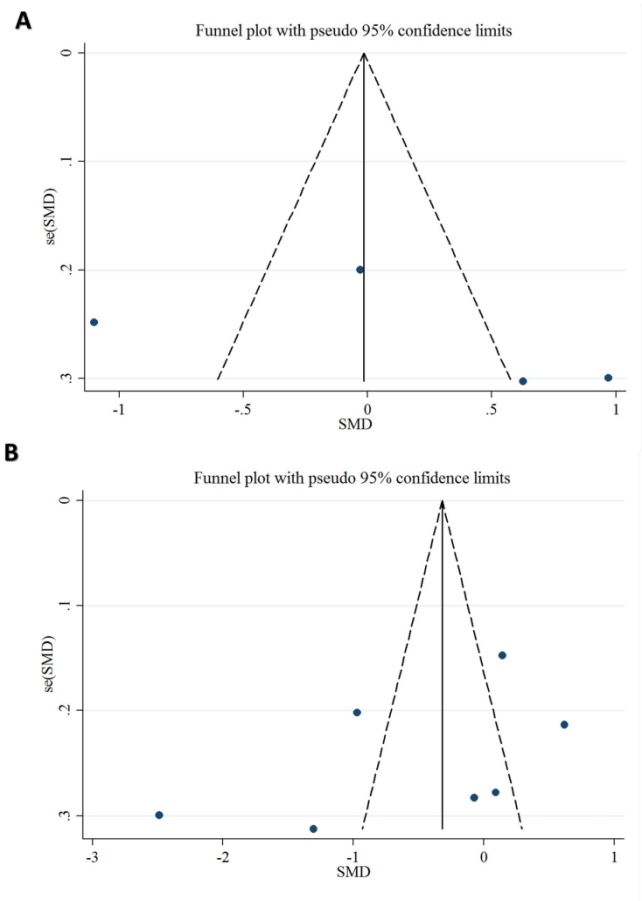

Figure 6: Funnel plots for the effects of topical application (A) and oral intake (B) of *Rosa Damascena* on adults' acute pain.

Sensitivity analysis showed that the pooled effect sizes obtained for topical application (lower CI limit: −1.17 to −0.06; upper CI limit: 0.73 to 1.48) and oral intake (lower CI limit: −1.55 to −0.79; upper CI limit: 0.01 to 0.34) did not depend on a particular study or group of studies (**Figure 7)**.

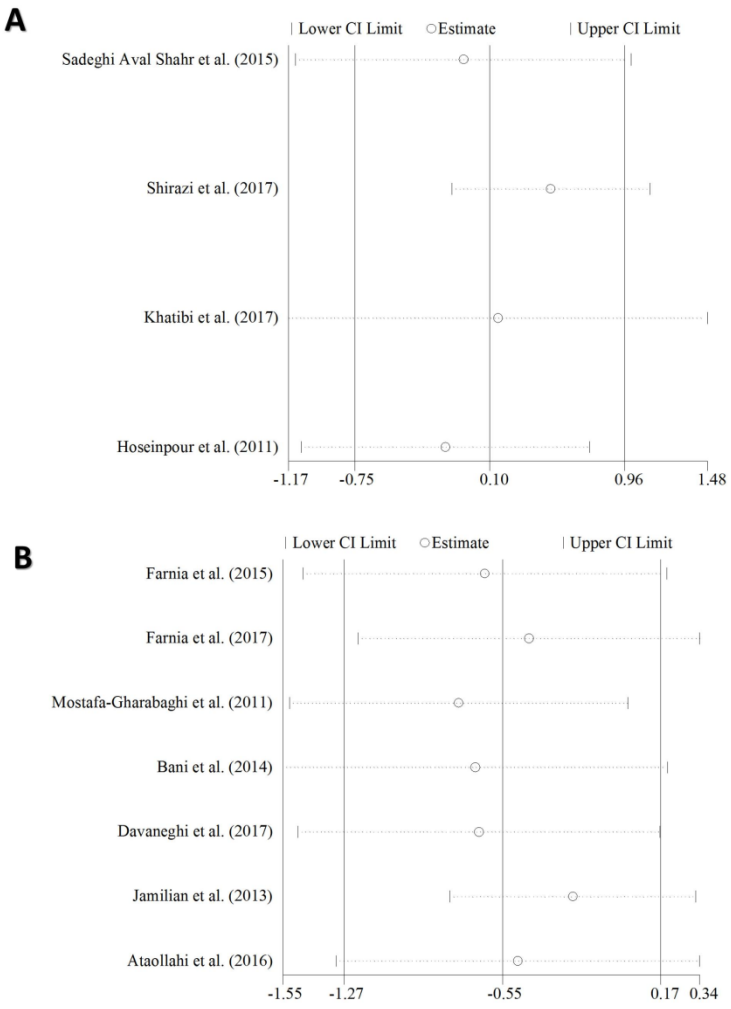

Figure 7: Sensitivity analysis for the effects of topical application (A) and oral intake (B) of *Rosa Damascena* on adults' acute pain.

4. Discussion

In Asian countries, different herbs are used in traditional and complementary medicine for alleviating different painful conditions [48,49]. Recently, different products of *R. Damascena* have been used in Asian countries for their pain-alleviating properties; however, there is a paucity of comprehensive evidence to support their applications [3,7,42]. Accordingly, we performed this review to summarize the effects of topical application and oral intake of this herbal medicine on treating acute pain in adults.

Based on the meta-analysis findings, administration of oral intake of *R. Damascena* reduced pain severity non-significantly. However, the topical application of this herbal medicine had no pain-alleviating effect, which might be due to the limited number of included studies and also their undesirable methodological quality. Also, it seems that the findings obtained for topical application were affected by one study that applied *R. Damascena* using massage [36]. After excluding this study, pain severity reduced non-significantly which can justify the observed findings.

The findings of this review update the available reviews regarding the analgesic effect of *R. Damascena*. In a recent meta-analysis by Koohpayeh *et al.*, the pooled analysis of five RCTs on the effects of oral intake and aromatherapy of *R. Damascena* reduced the menstruation-related pain non-significantly [weighted mean difference (WMD): -1.39; 95% CI: -3.21, 0.43; P= 0.133] [47]. Also, in a systematic review of herbal medications for post-operative pain, Arruda *et al.* found no significant reduction in the need for analgesics after oral intake of *R. Damascena* in combination with ginger [50]. However, Nayebi *et al.* reported the analgesic effects and safety of *R. Damascena* in the forms of inhalation aromatherapy, topical treatment, or massage application on pain induced by surgery, PD, pregnancy, and aphthous ulcer [2]. In another systematic review, Mohebitabar *et al.* found promising evidence for the effectiveness of inhalation use of *R. Damascena* on pain of menstruation, renal colic,

and surgery [8]. Moreover, Boskabady *et al.* and Mahboubi *et al.* reported the analgesic activities of *R. Damascena* based on the results of both *in vivo* and *in vitro* studies [5,6].

Different study objectives might be the main reason for the differences observed in the findings of previously mentioned reviews and current review. In this meta-analysis, we included only RCTs that addressed pain-alleviating effects of *R. Damascena* using oral or topical administration routes, while the above-mentioned systematic or narrative reviews neither focused specifically on the analgesic properties of *R. Damascena* nor they stratified the administration routes of this treatment. However, Nasiri *et al.* pooled 15 RCTs on the effect of aromatherapy with *R. Damascena* on adults' acute pain severity and found a promising pain-alleviating effect of treatment [WMD: -2.12; 95% CI: -2.85, -1.40; P < 0.001][42]. Nasiri *et al.* included studies that evaluated the effect of *R. Damascena* in form of aromatherapy; whereas we considered oral intake or topical application of *R. Damascena* which can justify the differences in the obtained findings.

The analgesic effects of *R. Damascena* induced by oral intake or topical application have been attributed to some ingredients of this herbal medicine. Hongratanaworakit has reported the analgesic effects of *R. Damascena* oil without olfactory stimulation, and she presumed that molecules of *R. Damascena* could enter the bloodstream by dermal absorption [51]. In a recent animal study, the non-water soluble ingredients of *R. Damascena* oil such as quercetin and kaempferol were reported as responsible for its analgesic effect [33]. Likewise, 2-phenylethanol found in *R. Damascena* might be a pain signal inhibitor that could block pain receptors [17]. Moreover, the topical effects of *R. Damascena* on reducing pain might be explained by the high tannin content of the extract of this herbal medicine [31]. Further studies are recommended to determine the biochemical mechanisms responsible for analgesic activities of oral intake and topical application of *R. Damascena*.

4.1. Implications of findings

The findings of the present review can increase our understanding of the value of *R. Damascena* as a holistic care approach and non-pharmacological agent. We found that oral intake of *R. Damascena* led to a 0.55 unit reduction in pain severity. Also, the administration of *R. Damascena* was reported to be free of side effects in most included RCTs. However, we confirmed a paucity of well-designed trials in this area as most included studies had a fair or poor methodological quality. Considering the low-cost and simple application of *R. Damascena*, future studies with improved methodological quality are suggested to evaluate the pain-alleviating potencies of this herbal medicine to reach an evidence-based conclusion.

Although we used subgroup analysis, we could not found a source of between-study heterogeneity or a significant difference within subgroups in most cases, which might be due to the limited number of included studies. Based on studies that evaluated the oral intake of *R. Damascena*, it seems that pain severity reduced more when the treatment was administrated in higher dosage and longer duration and form of an oral drop. On the contrary, it seems that shorter administration duration and lower dosage could lead to more reduction in pain severity when *R. Damascena* was administrated using the topical application. Further studies are suggested to compare the effects of oral intake and topical application of *R. Damascena* on pain severity in different groups of participants with different administration durations, dosages, and forms.

4.2. Limitations

Initially, we did not receive any response or feedback from corresponding authors of the published studies in some cases when we requested further information *via* email. In the following, contact was made with the authors *via* phone call and the required details were obtained. However, estimations were made based on discussion and consensus in one study [30], because phone call details were not available. Second, to pool data using meta-analysis, we compared the changes of baseline and end-of-trial values due to a minor variation in

assessment time of pain severity after treatment. Hence, different choices of an endpoint may lead to different effect sizes or heterogeneities. Third, the results obtained by subgroup analysis might be affected by the limited number of studies in each subgroup. Forth, we could not perform a dose-response analysis due to the limited number of included studies and the low variations of *R. Damascena* administration dosages and durations. Finally, all studies were conducted in Iran and most recruited females; hence, the findings may not be generalized to all participants and countries.

5. Conclusion

Although the growing trend of recent RCTs about pain-alleviating effects of topical application and oral intake of *R. Damascena* provides a scientific rationale for its clinical properties, the present meta-analysis indicated that oral intake of this herbal medicine had a non-significant alleviating effect on adults' acute pain severity. Also, the topical application of *R. Damascena* had no pain-alleviating effect. Therefore, further robust RCTs are needed to elicit reliable conclusions in this regard.

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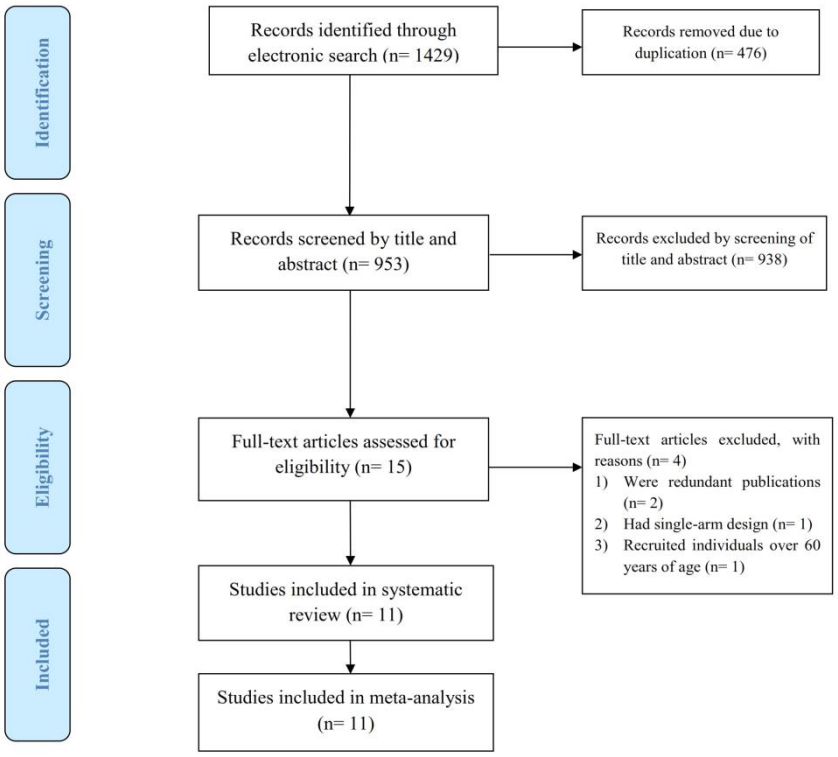

Graphical abstract