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Anti-nociceptive efficacy of essential oil-based extracts for the management of orofacial pain: a systematic review of available evidence

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Abstract. – OBJECTIVE: Experimental studies have shown that essential oil (EO)-based extracts derived from medicinal plants exhibit antinociceptive activity. The aim of the present systematic review was to assess the anti-nociceptive efficacy of EO-based extracts for the management of orofacial pain (OFP).

MATERIALS AND METHODS: To address the focused question "Are EO-based formulations effective for the management of OFP disorders?", indexed databases were searched without time and language restrictions using the preferred reporting items for systematic reviews and meta-analysis guidelines. Risk of bias (ROB) was assessed.

RESULTS: Eight studies were included and processed for data extraction. Two studies were clinical (one in adults and one in children) and 6 were performed in rodents. Results from one clinical study showed that inhalation of EO-extracts does not affect subjective toothache scores; and results from the study on children reported that inhalation of lavender oil reduces anxiety and pain during and after tooth extraction. Results from all experimental studies showed that administration of EO-extracts reduces orofacial nociceptive behavior. The ROB was high in 50% and 83.3% of the clinical and experimental studies, respectively.

CONCLUSIONS: The anti-nociceptive efficacy of EO-extracts for the management of OFP remains debatable. Further well-designed and power-adjusted randomized clinical trials are needed in this regard.

Key Words:
Essential-oil, Formalin test, Lavender, Nociception, Orofacial pain.

Abbreviations
EO: Essential oil; FT: Formalin test; NSAIDS: Non-steroidal anti-inflammatory drugs; OFP: Orofacial pain; PICO: Patients, Intervention, Control, Outcome; ROB: Risk of bias; *Syzygium cumini*: *S. cumini*; *S. cordifolia: Sida cordifolia.*

Introduction

Orofacial pain (OFP) is prevalent in the areas innervated by the trigeminal nerve[1]; and its prevalence in the United States ranges between 20 and 25%[2]. According to a recent report published by the committee of the International Classification of Orofacial Pain (ICOP), the categorization of OFP is complex and extensive[3]. Briefly, the ICOP has classified OFP as pain attributed to myofascial musculature, temporomandibular joint, psychosocial factors, diseases/lesions of dentoalveolar structures, cranial nerves, and idiopathic reasons[3]. This reflects that OFP has a multifaceted pathophysiology and psychosocial comorbidity, which may challenge accurate diagnosis and management protocols. Medications such as non-steroidal anti-inflammatory drugs (NSAIDS), opioids and endocannabinoids and anticonvulsants are often used to alleviate acute and chronic OFP[4-6]. However, their use is restricted due to withdrawal side effects[7]. Moreover, efficacy of anticonvulsants for the management of OFP remains debatable[4]. Furthermore, complications such as gastric ulcer and bleeding, and liver damage that are associated with prolonged use of NSAIDS cannot be overlooked[8,9].

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An innovative approach for the management of pain is using extracts or essential oil (EO) derivatives from medicinal plants[10-12]. EO-derivatives are organic compounds that possess anti-inflammatory, antimicrobial, anti-nociceptive and analgesic properties[13-17]. According to a study in mice[11], linalool, a monoterpene compound present in EO-derivates of several aromatic plant species exhibits antinociceptive properties. In a study on Swiss mice, the authors[10] assessed the effect of extracts from *Sida cordifolia* leaf (*S. cordifolia*) on the orofacial nociceptive response. In this experiment[10], orofacial nociception was induced using glutamate and formalin. The results showed that extracts of *S. cordifolia* significantly reduced the orofacial nociception and the treatment did not promote motor activity changes in the animals. The authors[10] concluded that *S. cordifolia* has a distinct antinociceptive activity on orofacial nociception. Similarly, another study[18] on rodents investigated the antinociceptive activity of *Syzygium cumini* (*S. cumini*) leaves on orofacial nociception. The results showed a significant inhibition of glutamate-induced orofacial nociception in mice treated with *S. cumini* extracts compared with mice in the control-group[18]. These experimental results[10,18] suggest that use of EO-extracts from medicinal plants is a potential therapeutic strategy for the management of OFP in susceptible patients. However, clinical results by Lehrner et al[19] showed no statistically significant effect of EO-extracts of *Citrus sinensis* on the perception of OFP. This demonstrates that there is a controversy over the effectiveness of EO-extracts for the treatment of OFP. A vigilant review of pertinent indexed literature demonstrated that there are no studies that have systematically reviewed the efficacy of EO-based extracts for the management of OFP. It is also alluring to review pertinent literature to determine whether the anti-inflammatory, anti-nociceptive and/or analgesic potency of EO-based extracts is similar to traditional pharmaceutical preparations that are commonly used for the management of OFP.

With this background, the aim of the present systematic review was to assess the antinociceptive efficacy of EO-based extracts for the management of OFP disorders.

Materials and Methods

Focused Question

The focused question was "Are EO-based extracts effective for the management of OFP?".

Inclusion and Exclusion Criteria

The inclusion criteria were as follows (a) original studies; (b) clinical prospective studies; (c) studies performed on animal models; and (d) case-reports/series. *In-vitro* and ex-vivo studies, retrospective clinical studies, editorials, and commentaries were excluded.

Literature Search Protocol

The present systematic review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[20]. Indexed databases (PubMed/Medline, SCOPUS, EMBASE, Ovid, ISI web of knowledge and Google-Scholar) were searched by two trained and experienced researchers (FJ and FOBC) without time and language restrictions. Different combinations of the following key words were used during the literature search: (a) antinociceptive; (b) Lavender; (c) Lippia grata; (d) neuropathic; (e) orofacial pain; (f) Vanillosmopsis arborea Baker. These keywords were combined using Boolean operators (AND, OR) to expand the search results. Both investigators (FJ and FOBC) independently screened the titles and abstracts of studies identified; and independently read full texts of relevant studies. Databases were searched up to and including October 2021. Reference lists of potentially relevant original studies were hand-searched to identify studies that could have been missed during the initial search. Disagreements related to inclusion of studies were resolved via discussion and consultation with a third and fourth examiner (AN and DM).

Patients, Interventions, Control and Outcome

The Patients, Interventions, Control and Outcome (PICO) format was based on the following: (a) P=Patients/subjects with OFP; (b) I=management of OFP using EO-based extracts; C= management of OFP without EO-based extracts; (d) O=improvement in OFP.

Data Collection and Data Items

Two authors (FJ, FOBC) independently extracted data from eligible studies; and the following information was documented: (a) authors et al/reference; (b) study design; (c) subject characteristics and study groups; (d) methods of induction of OFP; (e) methods of assessment of OFP; (f) study duration; (g) primary outcomes; (g) EO-extract administration-related characteristics; (h) orofacial nociception-related characteristics; (i) risk of bias (ROB); and (j) main study outcomes.

Table I. General characteristics of included clinical studies.

Authors et al	Study design	Participants (n)	Mean age (range)	Gender	Study groups	Duration/ history of OFP	Assessment of OFP	Follow-up
Lehrner et al[19]	Prospective controlled	72 adult patients	NR (22-57 years)	32 males 40 females	Test-group: Exposure to EO-extract odor Control-group: No exposure	NA	Self-reported; using an 11-point Likert scale	NR
Arslan et al[23]	Prospective controlled	126 children	NR (6-12 years)	72 males 54 females	Test-group: Exposure to EO-extract odor Control-group: NA No exposure		Self-reported; using the Wong-Baker pain rating scale	NR

NA: Not applicable NR: Not reported OFP: Orofacial pain EO: essential oil.

Disagreements were again addressed through consensus discussion.

Risk of Bias Assessment

The ROB was assessed by two authors (FJ and FOBC) using the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) and the Cochrane ROB tools[21,22]. Briefly, subsequent sections are considered for experimental studies: groups being similar at baseline, adequate allocation concealment, random housing of the animals, blinding of the performance of caregivers and/or investigators, selection of animals at random for outcome assessment, blinding of outcome assessor(s) and address of incomplete outcome data. Each point was rated as high, low or unclear.

Results

General Characteristics

In total, 8 studies[17-19,23-27] were included and processed for data extraction (Figure 1). Two prospective controlled clinical studies[19,23] and 6 studies[17,18,24-27] performed in rodents were assessed.

One clinical study[19] was performed in 72 adults (32 males and 40 females) and 1[23] was performed in 6-12 years old children (72 males and 54 females). None of the clinical studies[19,23] reported the mean age and duration/history of OFP of the participants. In both studies[19,23], individuals in the test-group were exposed to EO odor; and patients in the control-group comprised of individuals that were not exposed to EO odor[19,23]. In these studies OFP was assessed using self-reported pain scales[19,23] (Table I). Five[17,18,25-27] experimental studies were performed in male and 1[24] in male and female rodents. The number of animals ranged between 80 and 120 rodents. None of the experimental studies[17,18,24-27] reported the mean age of the rodents, which ranged between 2 and 3 months. In all experimental studies[17,18,24-27] OFP was induced using subcutaneous injections of 2% formalin, capsaicin, or glutamate. In these studies[17,18,24-27], orofacial nociception was induced prior to treatment using subcutaneous injections of 2% formalin, capsaicin and glutamate. In these studies[17,18,24-27] formalin was used to induce a biphasic nociceptive response (phase-1: 0-5 minutes and phase-2: 15-40 minutes). Quantification of orofacial nociceptive behavior was assessed as the time spent by animals rubbing the injected area of the face[17,18,24-27] (Table II).

EO-based Characteristics

In clinical studies[19,23], EOs were extracted from *Citrus sinensis* and *Lavandula angustifolia*. In the study by Lehrner et al[19], 5 drops (0.25 ml) of the extract were added to a diffuser every morning and noon in the waiting room of a dental office. Arslan et al[23] poured 2 drops (0.1 cc per drop) of 100% lavender oil on med patches, and children inhaled the oil without skin contact in a separate room prior to the oral therapeutic interventions. The duration of exposure to EO-extract vapor

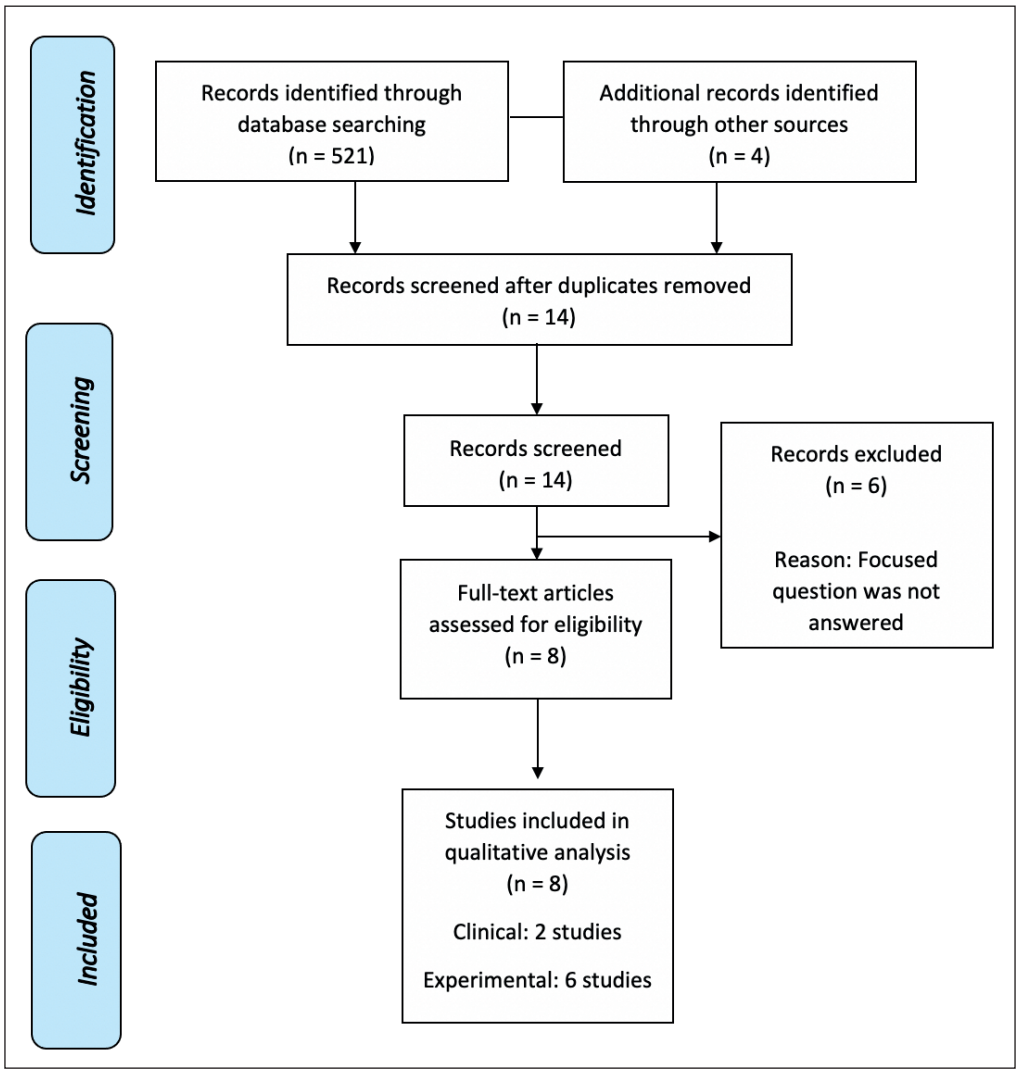

Figure 1. Data extraction.

ranged between 3 and 20 minutes and the participants were exposed once to the EO-extract vapor (Table III). Animals in the test-group were treated for induced OFP using Citronellol EO-extracts in 3 studies[25,26,28]. In the studies by Barreto et al[27] and Leite et al[24], pretreatment was done with EO-extracts from *Stachys lavandulifolia* and *Vanillosmopsis arborea*, respectively. In 1 study[17], antinociceptive efficacy of Carvacrol was assessed. In all studies[17,24-28], animals in the control-group were pretreated with morphine and distilled water (Table II). In 3 studies[17,26,28], EO-extracts were administered through the intraperitoneal route 30 minutes before induction of OFP. In 2 studies[18,24], EO-extracts were administered through the oral route 1 hour before OFP induction. In the study by Barreto et al[27], EO-extracts were administered via the oral or intraperitoneal routes 30 minutes or 1 hour before induction of OFP (Table III).

Outcomes of Studies and Risk of Bias Assessment

Results from one clinical study[19] showed that inhalation of EO-extracts does not affect subjective toothache scores; whereas, results from a study[23] on children reported that inhalation of lavender oil reduces anxiety and pain during and after tooth extraction (Table IV). Results from all experimental studies[17,18,24-27] showed that administration of EO-extracts reduces orofacial nociceptive behavior (Table IV). Among the clinical investigations, 1 study[19] had a high and 1[23] had a

Table II. Characteristics of studies on animal-models.

Authors	Subjects (n)	Weight in grams	Mean age (range) in months	Gender	Pretreatment	Induction of OFP	Duration of induced pain	Quantification of orofacial nociceptive behavior
Guimarães et al[17]	Swiss mice (120)*	25-33 g	NR (NR)	Male	Test-group: Carvacrol Control-group: morphine or distilled water (vehicle)	Injection† of 2% formalin, capsaicin, or glutamate into the right upper lip (perinasal area)	Formalin: Phase-1: up to 5 minutes; Phase-2: 15–40 minutes Capsaicin: 10–20 minutes Glutamate: 15 minutes	Time (in seconds) spent face-rubbing the injected area
Leite et al[24]	Swiss mice (and Wistar rats (120)*	20-30 g 150-200 g	NR (NR)	Males and females	Test-group: *Vanillosmopsis arborea* Control-group: distilled water	Injection† of 2% formalin, capsaicin, acidic saline, or glutamate into the right upper lip (perinasal area)	Formalin: Phase-1: up to 5 minutes; Phase-2: 15–40 minutes Capsaicin: 10–20 minutes Glutamate: 15 minutes	Time (in seconds) spent face- and eye rubbing the injected area
Siqueira-Lima et al[25]	Swiss mice (90)*	27–35 g	3 months old (NR)	Male	Test-group: Citronellol Control-group: morphine or distilled water (vehicle)	Injection† of 2% formalin, capsaicin, or glutamate into the right upper lip (perinasal area)	Formalin: Phase-1: up to 5 minutes; Phase-2: 15–40 minutes Capsaicin: 10–20 minutes Glutamate: 15 minutes	Time (in seconds) spent face-rubbing the injected area
Brito et al[26]	Swiss mice (90)*	28–32 g	NR (NR)	Male	Test-group: Citronellol Control-group: morphine or distilled water (vehicle)	Injection† of 2% formalin, capsaicin, or glutamate into the right upper limb	Formalin: Phase-1: up to 5 minutes; Phase-2: 15–40 minutes Capsaicin: 10–20 minutes Glutamate: 15 minutes	Time (in seconds) spent face-rubbing the injected area
Barreto et al[27]	Swiss mice (108)*	28-33 g	NR (NR)	Male	Test-group: *Stachys lavandulifolia*, bisabolol, Control-group: morphine or distilled water (vehicle)	Injection† of 2% formalin, capsaicin, or glutamate into the right upper limb	Formalin: Phase-1: up to 5 minutes; Phase-2: 15–40 minutes Capsaicin: 10–20 minutes Glutamate: 15 minutes	Time (in seconds) spent face-rubbing the injected area
Quintans-Júnior et al[28]	Swiss mice (40)* Wistar rats (40)*	30-36 g 230-260 g	NR (2-3 months) NR (2-3 months)	Male Male	Test-group: citronellal, Control-group: morphine or distilled water (vehicle)	Injection† of 2% formalin, capsaicin, or glutamate into the right upper lip (perinasal area)	Formalin: Phase-1: up to 5 minutes; Phase-2: 15–40 minutes Capsaicin: 10–20 minutes Glutamate: 15 minutes	Time (in seconds) spent face-rubbing the injected area

Calculated according to the number of animals included in each group; †Subcutaneous; NR: Not reported; OFP: Orofacial pain.

Table III. Characteristics of the essential-oil extracts.

Clinical studies					
Authors	**EO-extract plant**	**Composition of EO-extract**	**Directions of use**	**Frequency of exposure**	**Duration of exposure**
Lehrner et al [19]	*Citrus sinensis*	Orange (limonene 88.1%, myrcene 3.77%, and a-pinen 1.19%)	Five drops (0.25 ml) applied to the diffuser in the waiting room of the dental clinic.	Once	Up to 20 min
Arslan et al[23]	*Lavandula angustifolia*	Lavender (100% pure)	Two drops (0.1 cc per drop) of 100% lavender oil were poured on medical patches, and patients inhaled the oil without skin contact in a separate room prior to the interventions.	Once	3 min
Studies on animal models					
Authors	**EO-extract plant**	**Pharmacological name**	**Concentration of extract**	**Route of administration**	**Frequency of exposure**
Guimarães et al[17]	*Origanum* and *Satureja* species	Carvacrol	25, 50, and 100 mg/kg	Intraperitoneal; 0.5 hours before OFP induction	Once
Leite et al[24]	*Vanillosmopsis* arbórea *Baker*	*Vanillosmopsis arbórea*	*Vanillosmopsis* arbórea (50 mg/kg), *Vanillosmopsis* arbórea -βCD (10 or 50 mg/kg).	Oral; 1 hour before OFP induction	Once
Siqueira-Lima et al[25]	*Lippia grata*	Lippia grata leaf essential oil	6, 12 or 24 mg/kg	Oral; 1 hour before OFP induction	Once
Brito et al[26]	*Cymbopogon citratus*	Citronellal	25, 50 and 100 mg/kg,	Intraperitoneal; 0.5 hours before OFP induction	Once
Barreto et al[27]	*Stachys lavandulifolia var. lavandulifolia*	Lamiaceae	25 and 50 mg/kg	Oral or intraperitoneal; 0.5 or 1 hour before OFP induction	Once
Quintans-Júnior et al[28]	*Cymbopogon citratus*	Citronellal	50, 100, and 200 mg/kg,	Intraperitoneal; 0.5 hours before OFP induction	Once

EO: Essential oil; OFP: Orofacial pain

low ROB. Five studies on animal models had a high ROB[17,18,24,26,27]. The study by Siqueira-Lima et al[25] demonstrated a low ROB (Table V).

Discussion

Studies[29-31] have shown that EO have cytotoxic and anti-inflammatory effects on oral cancer cells and periodontal tissues, respectively. However, from an orofacial perspective, the literature search showed that there are a limited number of studies[17,24-26] that have assessed the contribution of EO-based extracts towards the management of OFP. The authors explored relevant indexed literature to identify studies that assessed the efficacy of EO-based extracts for the management of OFP disorders. Traditionally, case-reports and case-series are excluded during the literature search for systematic reviews. However, since merely 2 clinical prospective studies[19,23] were identified following an exhaustive literature search, the authors considered including case-reports/series in an attempt to gather as much clinical evidence as possible in relation to the focused question. To date, there are no case-reports/series that have assessed

Table IV. Main outcomes and conclusions of the included studies.

Clinical studies		
Authors	**Main results**	**Conclusion**
Lehrner et al [19]	There was no significant difference in subjective toothache scores among patients in the test- and control-groups.	Inhalation of EO-extracts does not affect subjective toothache scores.
Arslan et al[23]	Anxiety and pain scores after tooth extraction were significantly lower in the lavender compared with the control-group.	Inhalation of lavender oil reduces anxiety and pain during and after tooth extraction.
Studies on animal models		
Authors	**Main outcomes**	**Conclusion**
Guimarães et al[17]	CARV significantly reduced nociceptive face-rubbing behavior in both phases of the formalin test. CARV produced significantly antinociceptive effect at all doses in the capsaicin- and glutamate-tests.	CARV reduces orofacial nociceptive behavior.
Leite et al[24]	VA reduced the intensity of facial rubbing induced by formalin, capsaicin, and acidic saline, but not by glutamate.	VA reduces orofacial nociceptive behavior.
Siqueira-Lima et al[25]	β-CD significantly reduced nociceptive face-rubbing behavior in both phases of the formalin test. β-CD produced significantly antinociceptive effect at all doses in the capsaicin- and glutamate- tests.	β-CD reduces orofacial nociceptive behavior.
Brito et al[26]	CT reduced orofacial nociceptive behavior in mice induced by formalin, Capsaicin or Glutamate.	CT reduces orofacial nociceptive behavior.
Barreto et al[27]	SL reduced the orofacial nociceptive behavior in mice induced by formalin, Capsaicin or Glutamate. Bisabolol had a more proficient antinociceptive effect.	SL reduces orofacial nociceptive behavior.
Quintans-Júnior et al[28]	CT significantly reduced nociceptive face-rubbing behavior in both phases of the formalin test. CT produced significantly antinociceptive effect at all doses in the capsaicin- and glutamate- tests.	CT reduces orofacial nociceptive behavior.

EO: Essential oil βCD: beta-cyclodextrins; CARV: Carvacrol; CT: Citronellol; SL: *Stachys lavandulifolia;* VA: *Vanillosmopsis arbórea.*

the efficacy of EO-extracts for the management of OFP. Authors of the present study speculated that the analgesic, anti-inflammatory and/or anti-nociceptive activity of EO-extracts is comparable to that of the traditional medications (such as NSAIDS, anticonvulsants and opioids) that are frequently used for the management of OFP. The authors intended to perform a meta-analysis on the studies[17-19,23-27] assessed. Two clinical studies[19,23] despite assessing the influence of EO-extracts on perceived OFP demonstrated a heterogenicity in their methodology and demographics of the targeted patient populations. With reference to the studies performed on animal-models[17,18,24-27] a vigilant review of their methodology and statistical analysis revealed that data on the effect-size was reported in none of them. Based upon these limitations, the data could not be quantitively

Table V. Risk of bias assessment.

Clinical studies						
Authors	**Allocation concealment**	**Blinding**	**Randomization**	**Sample-size estimation**	**Other biases controlled?**	**Overall risk**
Lehrner et al [19]	Yes	Yes	Yes	No	No	High
Arslan et al[23]	Yes	Yes	Yes	Yes	No	Low
Studies on animal models						
Authors	**Allocation concealment**	**Blinding**	**Randomization**	**Sample-size estimation**	**Other biases**	**Overall risk**
Guimarães et al[17]	No	No	Yes	No	No	High
Leite et al[24]	No	No	Yes	No	No	High
Siqueira-Lima et al[25]	No	Yes	Yes	Yes	No	Low
Brito et al[26]	No	No	Yes	No	No	High
Barreto et al[27]	No	Yes	No	No	No	High
Quintans-Júnior et al[28]	No	No	Yes	No	No	High

evaluated. Following a vigilant review of pertinent indexed literature, the authors observed that although the clinical studies[19,23] assessed relation between self-reported pain in the orofacial region and contribution of EO-extracts towards its management; the precise details related to the origin of pain remained unclear. In other words, none of the patients had a history of OFP disorders such as trigeminal neuralgia. Moreover, methodology of these studies[19,23] reflected that the participants were exposed once to EO-extract vapors during their dental visits. It has been claimed that EO-extracts from medicinal plants such as *Lavandula angustifolia* (Lavender) exhibit analgesic, antidepressant, carminative and anxiolytic properties[32,33]. It is speculated that in the clinical studies[19,23] EO-extract vapors inhaled by participants temporarily reduced their anxiety levels; which, in turn provisionally modulated levels of self-rated OFP. However, from the authors' perspective, such findings may not necessarily coincide with the intensity and severity of OFP experienced by patients with neuropathic disorders such as facial migraine and trigeminal neuropathy. Therefore, further well-designed and power-adjusted randomized clinical trials on patients with OFP disorders are needed to assess the influence of EO-extracts on pain reduction in these patients.

A homogeneity in the methodology for the induction and quantification of orofacial nociceptive behavior was observed in the experimental studies[17,18,24-27]. For instance, OFP was induced in animals via subcutaneous injections of 2% formalin. It has been reported that the orofacial formalin test (FT) induces a biphasic pain by inducing vocalization and thermal, electrical, chemical and mechanical stimulation of the orofacial region in rats[34,35]. In this context, the FT is a reliable method of producing and quantifying nociception in the orofacial region in rodents[34,35]. Interestingly, results from all studies on rodents[17,18,24-27] showed that administration of EO-extracts via oral and/or intraperitoneal routes significantly reduces nociceptive face-rubbing behavior. However, these results should be cautiously interpreted as a number of factors may have influenced the reported outcomes. Power-analysis for prior sample-size determination/power analysis is an essential factor that minimizes the ROB within studies[36]. A prior sample-size estimation was not performed in 50%[19] and >83%[17,18,24,26,27] of the clinical and experimental studies, respectively. Moreover, allocation concealment, blinding and other biases remained unaddressed in 100%[17,18,24-27], 66.7%[17,18,24,26] and 100%[17,18,24-27] of the studies performed on animal-models. According to Bello et al[37] lack of blinding of outcome assessors in experiments on animal-models suggests risk of observer bias. Furthermore, in all clinical[19,23] and experimental[17,18,24-27] studies EO-extracts were administered once to patients and subjects, respectively throughout the study duration. Based upon these confounding factors, the clinical significance of the reported studies remains questionable.

In summary, studies on experimentally-induced OFP may provide a better understanding of

the characteristics of the nerve fibers and synaptic circuitry that are associated with OFP; however, translation of results of experimental interventional studies (such as those assessing the influence of EO-extracts on OFP) into clinical settings (particularly among patients with neuropathic pain) is demanding.

Conclusions

The anti-nociceptive efficacy of EO-extracts for the management of OFP remains debatable. Further well-designed and power-adjusted randomized clinical trials are needed in this regard.

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Author Contributions

Fawad Javed (fawad_javed@urmc.rochester.edu): Designed the study, performed the literature search, wrote the manuscript and revised it prior to submission.
Fernanda Oliveira Bello-Correa (fernandabello@hotmail.com): Performed the literature search and wrote the manuscript
Aikaterini Nikolaidou (katynikola@hotmail.com): Performed the literature search and wrote the methods
P. Emile Rossouw (Emile_rossouw@urmc.rochester.edu): Wrote the manuscript and revised it prior to submission
Dimitrios Michelogiannakis (Dimitrios_michelogiannakis@urmc.rochester.edu): Performed the literature search wrote the manuscript and revised it prior to submission.

Conflicts of Interest

The authors declare no conflicts of interest.

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