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

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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.

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 antinociceptive 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.

Introduction

Orofacial pain (OFP) is prevalent in the areas innervated by the trigeminal nerve; and its prevalence in the United States ranges between 20 and 25%. 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. 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. 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. However, their use is restricted due to withdrawal side effects. Moreover, efficacy of anticonvulsants for the management of OFP remains debatable. Furthermore, complications such as gastric ulcer and bleeding, and liver damage that are associated with prolonged use of NSAIDS cannot be overlooked.
An innovative approach for the management of pain is using extracts or essential oil (EO) derivatives from medicinal plants10-12. EO-derivatives are organic compounds that possess anti-inflammatory, antimicrobial, anti-nociceptive and analgesic properties13-17. According to a study in mice11, linalool, a monoterpenep compound present in EO-derivatives of several aromatic plant species exhibits antinociceptive properties. In a study on Swiss mice, the authors10 assessed the effect of extracts from Sida cordifolia leaf (S. cordifolia) on the orofacial nociceptive response. In this experiment10, 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 authors10 concluded that S. cordifolia has a distinct antinociceptive activity on orofacial nociception. Similarly, another study18 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-group18. These experimental results10,18 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 al19 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-Analyses20. 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) independently screened the titles and abstracts of studies identified; and independently read full texts of relevant studies. 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.
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\textsuperscript{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\textsuperscript{17-19,23-27} were included and processed for data extraction (Figure 1). Two prospective controlled clinical studies\textsuperscript{19,23} and 6 studies\textsuperscript{17,18,24-27} performed in rodents were assessed.

One clinical study\textsuperscript{19} was performed in 72 adults (32 males and 40 females) in 6-12 years old children (72 males and 54 females). None of the clinical studies\textsuperscript{19,23} reported the mean age and duration/history of OFP of the participants. In both studies\textsuperscript{9,23}, 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\textsuperscript{19,23}. In these studies OFP was assessed using self-reported pain scales\textsuperscript{9,23} (Table I). Five\textsuperscript{17,18,24-27} experimental studies were performed in male and 1\textsuperscript{24} in male and female rodents. The number of animals ranged between 80 and 120 rodents. None of the experimental studies\textsuperscript{17,18,24-27} reported the mean age of the rodents, which ranged between 2 and 3 months. In all experimental studies\textsuperscript{17,18,24-27} OFP was induced using subcutaneous injections of 2\% formalin, capsaicin, or glutamate. In these studies\textsuperscript{17,18,24-27}, orofacial nociception was induced prior to treatment using subcutaneous injections of 2\% formalin, capsaicin and glutamate. In these studies\textsuperscript{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\textsuperscript{17,18,24-27} (Table II).

**EO-based Characteristics**

In clinical studies\textsuperscript{9,23}, EOs were extracted from *Citrus sinensis* and *Lavandula angustifolia*. In the study by Lehrner et al\textsuperscript{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\textsuperscript{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

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

NA: Not applicable NR: Not reported OFP: Orofacial pain EO: essential oil.
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. In the studies by Barreto et al. and Leite et al., pretreatment was done with EO-extracts from Stachys lavandulifolia and Vanillosmopsis arborea, respectively. In 1 study, antinociceptive efficacy of Carvacrol was assessed. In all studies, animals in the control-group were pretreated with morphine and distilled water (Table II). In 3 studies, EO-extracts were administered through the intraperitoneal route 30 minutes before induction of OFP. In 2 studies, EO-extracts were administered through the oral route 1 hour before OFP induction. In the study by Barreto et al., 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 showed that inhalation of EO-extracts does not affect subjective toothache scores; whereas, results from a study on children reported that inhalation of lavender oil reduces anxiety and pain during and after tooth extraction (Table IV). Results from all experimental studies showed that administration of EO-extracts reduces orofacial nociceptive behavior (Table IV). Among the clinical investigations, 1 study had a high and 1 had a

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**Figure 1. Data extraction.**
### Table II. Characteristics of studies on animal-models.

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

Calculated according to the number of animals included in each group; †Subcutaneous; NR: Not reported; 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**

Studies29-31 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 studies24,26 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 studies19,23 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.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Main results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lehrner et al 19</td>
<td>There was no significant difference in subjective toothache scores among patients in the test- and control-groups.</td>
<td>Inhalation of EO-extracts does not affect subjective toothache scores.</td>
</tr>
<tr>
<td>Arslan et al 23</td>
<td>Anxiety and pain scores after tooth extraction were significantly lower in the lavender compared with the control-group.</td>
<td>Inhalation of lavender oil reduces anxiety and pain during and after tooth extraction.</td>
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</table>

### Clinical studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Main outcomes</th>
<th>Conclusion</th>
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<tbody>
<tr>
<td>Guimarães et al 17</td>
<td>CARV significantly reduced nociceptive face-rubbing behavior in both phases of the formalin test.</td>
<td>CARV reduces orofacial nociceptive behavior.</td>
</tr>
<tr>
<td></td>
<td>CARV produced significantly antinociceptive effect at all doses in the capsaicin- and glutamate-tests.</td>
<td></td>
</tr>
<tr>
<td>Leite et al 24</td>
<td>VA reduced the intensity of facial rubbing induced by formalin, capsaicin, and acidic saline, but not by glutamate.</td>
<td>VA reduces orofacial nociceptive behavior.</td>
</tr>
<tr>
<td>Siqueira-Lima et al 25</td>
<td>β-CD significantly reduced nociceptive face-rubbing behavior in both phases of the formalin test.</td>
<td>β-CD reduces orofacial nociceptive behavior.</td>
</tr>
<tr>
<td></td>
<td>β-CD produced significantly antinociceptive effect at all doses in the capsaicin- and glutamate-tests.</td>
<td></td>
</tr>
<tr>
<td>Brito et al 26</td>
<td>CT reduced orofacial nociceptive behavior in mice induced by formalin, Capsaicin or Glutamate.</td>
<td>CT reduces orofacial nociceptive behavior.</td>
</tr>
<tr>
<td>Barreto et al 27</td>
<td>SL reduced the orofacial nociceptive behavior in mice induced by formalin, Capsaicin or Glutamate.</td>
<td>SL reduces orofacial nociceptive behavior.</td>
</tr>
<tr>
<td></td>
<td>Bisabolol had a more proficient antinociceptive effect.</td>
<td></td>
</tr>
<tr>
<td>Quintans-Júnior et al 28</td>
<td>CT significantly reduced nociceptive face-rubbing behavior in both phases of the formalin test.</td>
<td>CT reduces orofacial nociceptive behavior.</td>
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<tr>
<td></td>
<td>CT produced significantly antinociceptive effect at all doses in the capsaicin- and glutamate-tests.</td>
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</table>

**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 assessed. Two clinical studies of the efficacy of EO-extracts on perceived OFP demonstrated a heterogeneity in their methodology and demographics of the targeted patient populations. With reference to the studies performed on animal-models, 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 assessed.
evaluated. Following a vigilant review of pertinent indexed literature, the authors observed that although the clinical studies\textsuperscript{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\textsuperscript{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 \textit{Lavandula angustifolia} (Lavender) exhibit analgesic, antidepressant, carminative and anxiolytic properties\textsuperscript{32,33}. It is speculated that in the clinical studies\textsuperscript{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\textsuperscript{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\textsuperscript{34,35}. In this context, the FT is a reliable method of producing and quantifying nociception in the orofacial region in rodents\textsuperscript{34,35}. Interestingly, results from all studies on rodents\textsuperscript{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\textsuperscript{36}. A prior sample-size estimation was not performed in 50\%\textsuperscript{19} and >83\%\textsuperscript{17,18,24,26,27} of the clinical and experimental studies, respectively. Moreover, allocation concealment, blinding and other biases remained unaddressed in 100\%\textsuperscript{17,18,24-27}, 66.7\%\textsuperscript{17,18,24,26} and 100\%\textsuperscript{17,18,24-27} of the studies performed on animal-models. According to Bello et al\textsuperscript{37} lack of blinding of outcome assessors in experiments on animal-models suggests risk of observer bias. Furthermore, in all clinical\textsuperscript{19,23} and experimental\textsuperscript{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 manuscript. Dimitrios Michelogiannakis (Dimitrios_michelogiannakis@urmc.rochester.edu): Performed the literature search and revised it prior to submission.

Conflicts of Interest

The authors declare no conflicts of interest.

References


