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Review

Natural products assessed in animal models for orofacial pain – a systematic review

Pollyana S. Siqueira-Lima[a,b], Juliane C. Silva[a,c], Jullyana S.S. Quintans[a], Angelo R. Antoniolli[a], Saravanan Shanmugam[a], Rosana S.S. Barreto[a], Márcio R.V. Santos[a], Jackson R.G.S. Almeida[b,c], Leonardo R. Bonjardim[d], Irwin R.A. Menezes[e], Lucindo J. Quintans-Júnior[a,*]

[a] *Laboratório de Neurociências e Ensaios Farmacológicos, Universidade Federal de Sergipe, São Cristóvão, SE, Brazil*
[b] *Departamento de Farmácia, Universidade Estadual de Feira de Santana, Feira de Santana, BA, Brazil*
[c] *Colegiado de Ciências Farmacêuticas, Universidade Federal do Vale do São Francisco, Petrolina, PE, Brazil*
[d] *Faculdade de Odontologia de Baurú, Universidade de São Paulo, Baurú, SP, Brazil*
[e] *Departamento de Quimica-Biologica, Federal University of Cariri, Crato, CE, Brazil*

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ABSTRACT

Orofacial pain is related to tissues of the head, face, neck and all the intraoral structures; it is rather debilitating to the patient and also difficult to treat. There are relatively few studies dedicated to the use of natural products to alleviate orofacial pain in preclinical experiment models (performed in experimental animals which provide support for clinical trials). Main objectives of the present systematic review summarize the studies on natural products assessed in animal models for orofacial pain seeking to give evidence to future development of new pharmaceutical products to manage the orofacial pain. Our review includes a thorough search of literature using the terms of orofacial pain, facial pain, medicinal plants and natural products. This search was performed using to retrieve English language articles in Medline-PubMed, Scopus and Web of Science. A total of eighteen studies were included in our survey for the inclusion criteria. Firstly, this review identified 210 citations from electronic search, after removal of duplicates and screening for relevant titles and abstracts, a total of eighteen articles were selected to the inclusion criteria established. Our findings suggest that natural products can be a promising or a trump tool for the development of new drugs to treat orofacial pain conditions, but the researchers that deal with experimental preclinical trials of new drugs (including natural products or synthetic drugs) for orofacial pain conditions urgently need to show translational evidence (with clinical approach) of these compounds.

Introduction

Orofacial pain is related to tissues of the head, face, neck and all the intraoral structures determined by the American Academy of Orofacial Pain (AAOP). This pain condition represents a highly prevalent spectrum of disorders with pain intensity involving anatomical, biochemical and molecular aspects which are associated with psychosocial components (Hargreaves, 2011; Fan et al., 2012). The orofacial region is one of the most densely innervated areas of the body, and the trigeminal nerve plays an important role in this process. An orofacial pain encompasses a wide range of conditions including temporomandibular joint disorders, periodontal pain, trigeminal neuralgia, atypical facial pain, burning mouth syndrome, dental surgical pain, head and neck cancer pain, pain due to oral infections, and other neuropathic and inflammatory pain (Gilbert et al., 2001). It is also the site of frequent chronic post-herpetical neuralgia, migraine and referred pains (Pelissier et al., 2002; Raboisson and Dallel, 2004). Therefore, orofacial pain is often rather debilitating to the patient and many difficulties in the management of acute and chronic orofacial pain conditions stem from a lack of recognition and understanding of pain mechanisms (Miranda et al., 2009; Krzyzanowska and Avendaño, 2012).

Up to the present date, several animal models have been used to study orofacial pain. These include infraorbital nerve ligation or axotomy, injection of inflammatory agents into the vibrissal pads, temporomandibular joint or masseter muscle, as well as intradental or dural application of irritants (Ren and Dubner, 1999). Clavelou et al. (1989) reported that the adaptation of the formalin model of pain for the orofacial region provides an important contribution to the mechanisms of trigeminal pain and analgesic response

* Corresponding author.
E-mail: lucindo@pq.cnpq.br (L.J. Quintans-Júnior).

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(Mittal et al., 2009). Other orofacial pain animal models have been more recently proposed and have contributed with clinical studies, such as the assessment of neuropathic and inflammatory pain (Krzyzanowska and Avendaño, 2012). Despite the importance of these animal models, according to Khan and Hargreaves (2010), they pose some limitations that should always be taken into account in the choice of models for the testing of new drugs. Thus, these animal models have great an importance to the study, such as a better understanding, development of therapeutic proposals and advances in the treatment of orofacial pain.

The management of pain is still a major challenge to both the medical practitioners and the patients (Krzyzanowska and Avendaño, 2012). Opioids, antidepressants, anticonvulsants and non-steroidal anti-inflammatory drugs (NSAID) remain as the main agents used to relieve acute and chronic pain, including orofacial pain (Pace et al., 2006), but the wide range of side-effects aligned with low adherence has been a stimulus in the constant search for new drugs to treat orofacial pain (Quintans-Júnior et al., 2010). An actual approach is to develop a new biological compound that inhibits pain from natural products (NP), such as medicinal plants or their secondary metabolites, which could enhance efficacy, produce minimal side effects and operate in unusual ways compared to the synthetic drugs (Holanda-Pinto et al., 2008; Venâncio et al., 2011; Oliveira et al., 2012).

The present systematic review was designed to summarize the current studies on NP tested in animal models for attenuating the orofacial pain. Our main focus aimed to make the reader aware, through a systematic way, of which the main aspects of NP researched to orofacial pain are, in experimental protocols.

Methods

Search strategy

Three internet sources were used to search for appropriate papers that met the study purpose. These included the National Library of Medicine, Washington, D.C. (Medline-PubMed), Scopus and, Web of Science using different combinations of the following keywords: Orofacial pain, Facial pain, Medicinal plants, natural products. The databases were searched for studies conducted in the period up to and including April 30, 2015. The structured search strategy was designed to include all published papers that evaluated the use of natural products in orofacial pain. Citations were limited to animal studies. Additional papers were included in our study after the analyses of all references from the selected articles. We did not contact investigators and did not attempt to identify unpublished data.

Study selection

All electronic search titles, selected abstracts, and full-text articles were independently reviewed by a minimum of two reviewers (JSSQ and PSSL). Disagreements in study inclusion/exclusion were resolved with a consensus meeting with more reviewers. The following inclusion criteria were applied: orofacial pain studies, animal models and the use of NP for reducing nociception. Studies were excluded according to the following exclusion criteria: studies in humans, review articles, meta-analyses, abstracts and conference proceedings.

Data extraction

Data were extracted by one reviewer using standardized forms and were checked for completeness and accuracy by a second reviewer. Information collected included data regarding the study substance (natural products), animal, dose (route), model, receptors/mediators, antagonists and results.

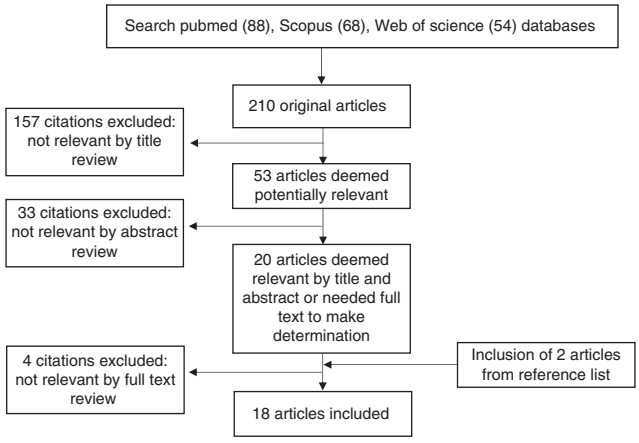


Fig. 1. Flow diagram for literature searching and screening.

Methodological quality assessment of studies

The risk of bias and quality of the study design were assessed using a 12-point checklist. The use of these questions has enabled the assessment of important aspects that contribute to the quality of the study, such as randomization of the treatment allocation, blinded drug administration, blinded outcome assessment and outcome measurements. Studies that reported randomization of animals, blinding and outcome measurements were considered of higher methodological quality (Zeng et al., 2015).

Results and discussion

The preliminary review of the present study identified 210 citations from electronic search, with 88 from Pubmed, 68 from Scopus, 54 Web of Science. After removal of duplicates and screening for relevant titles and abstracts, a total of eighteen articles were selected to the inclusion and exclusion criteria established (Fig. 1).

Curiously, from eighteen final studies selected, most of that research, particularly NP, was conducted in Brazil (88%) (Table 1) and 12% in India and USA. Details of the included studies are described in Table 1. That could be because we limit our inclusion criteria to orofacial pain animal models. However, if this survey sought clinical studies and/or ethnopharmacological search, it probably showed a wider range of countries (Tapsoba and Deschamps, 2006; Taheri et al., 2011). Another factor may have contributed to this finding because Brazil has the extensive ethical, cultural and greatest biodiversity in the world, which has historically been a source of exploration and study (Maciel et al., 2002; Oliveira et al., 2012). The result shows the scientific growth of Brazil in the area of NP corroborating with the potential of biological diversity (Peixoto and Morim, 2003) that has about 19% of earth's total diversity (Giulietti et al., 2005). Also, it is estimated that 49,000 plant species have already been described (Shepherd, 2002).

Traditionally, people believe that the NP from plants used in folklore medicine for therapeutic purposes have contributed over the years to obtain various drugs widely used in a clinical purpose (Cechinel-Filho and Yunes, 1998). Actually, about half of the drugs used are derived from natural sources (Kumari et al., 2012). The medical prescriptions of the United States prescribe 25% of natural substances as active ingredients obtained from plants of temperate and tropical regions; from as estimate of $900 million, about half of

Table 1
Characteristics of studies inserted in the review.

Authors, year, country	Substance/chemical group/(natural product)	Animals (strain/sex)	Dose (route)	Method of induction of orofacial pain	Parameters assessed		R	B
					Behavior	Biochemical/ molecular		
Gilbert et al., 2001, USA	Epibatidine	Rats (*SD*/M)	1–5 μg/kg	50 μl subcutaneous injection of formalin (5%) into one vibrissal pad	Grooming, rubbing and/or scratching face	–	N	Y
Mittal et al., 2009, India	Curcumin (*Curcuma longa*)	Rats (*W*/M)	1–600 mg/kg (i.p.)	50 μl subcutaneous injection of formalin (5%) into one vibrissal pad	Grooming, and/or scratching face	–	N	N
Holanda-Pinto et al., 2008, Brazil	α,β-amyrin (*Protium heptaphyllum*)	Rats (*W*/M)	10–100 mg/kg (i.p.)	20 μl subcutaneous injection of formalin (1.5%), capsaicin (1.5 μg) into one vibrissal pad	Face-rubbing	–	N	N
Siqueira et al., 2010, Brazil	Atranorin (AT)/Liquen (*Cladina kalbii* Ahti)	Mice (*S*/M)	100–400 mg/kg (i.p.)	20 μl subcutaneous injection of formalin (2%), capsaicin (2.5 μg) into the right upper lip (perinasal area)	Face-rubbing	–	N	N
Quintans-Júnior et al., 2010, Brazil	Citronellal (*Cymbopogon* genus)	Mice (*S*/M)	50–200 mg/kg (i.p.)	20 μl subcutaneous injection of formalin (2%), capsaicin (2.5 μg), 40 μl glutamate (25 μM) into the right upper lip (perinasal area)	Face-rubbing	Single sucrose gap electrophysiologic assays	Y	N
Bonjardim et al., 2011, Brazil	Ethanol, chloroform, methanol extract fractions (*S. cordifolia*)	Mice (*S*/M)	100–400 mg/kg (p.o.)	20 μl subcutaneous injection of formalin (2%), 40 μl glutamate (25 μM) into the right upper lip (perinasal area)	Face-rubbing	–	N	N
Venancio et al., 2011, Brazil	(*Ocimum Basilicum*) and (−)-linalool	Mice (*S*/M)	50–200 mg/kg (i.p.)	20 μl subcutaneous injection of formalin (2%), capsaicin (2.5 μg), 40 μl glutamate (25 μM) into the right upper lip (perinasal area)	Face-rubbing	Field potential recordings. electrophysiologic assays	N	N
Santana et al., 2011, Brazil	*p*-Cymene	Mice (*S*/M)	25–100 mg/kg (i.p.)	20 μl subcutaneous injection of formalin (2%), capsaicin (2.5 μg), 40 μl glutamate (25 μM) into the right upper lip (perinasal area)	Face-rubbing	–	N	N
Brito et al., 2013, Brazil	Citronellol (*Cymbopogon citrates*, C. *winterianus*)	Mice (*S*/M)	25–100 mg/kg (i.p.)	20 μl subcutaneous injection of formalin (2%), capsaicin (2.5 μg), 40 μl glutamate (25 μM) into the right upper lip (perinasal area)	Face-rubbing	Immunofluorescence	Y	N
Guimarães et al., 2012, Brazil	Carvacrol	Mice (*S*/M)	25–100 mg/kg (i.p.)	20 μl subcutaneous injection of formalin (2%), capsaicin (2.5 μg), 40 μl glutamate (25 μM) into the right upper lip (perinasal area)	Face-rubbing	–	Y	N
Paixão et al., 2013, Brazil	Aqueous extract (*Hyptis pectinata*)	Mice (*S*/M)	100–400 mg/kg (p.o.)	20 μl subcutaneous injection of formalin (2%), capsaicin (2.5 μg), 40 μl glutamate (25 μM) into the right upper lip (perinasal area)	Face-rubbing	TBARS DPPH	Y	N
Lima et al., 2013b, Brazil	Hydroethanol extract (*Hyptis fruticosa*)	Mice (*S*/M)	50–200 mg/kg (p.o.)	20 μl subcutaneous injection of formalin (2%), capsaicin (2.5 μg), 40 μl glutamate (25 μM) into the right upper lip (perinasal area)	Face-rubbing	TBARS	Y	N
Nomura et al., 2013, Brazil	Ethanolic extract (*Acmella oleracea)*	Mice (*S*/M)	10–100 mg/kg (i.p)	20 μl subcutaneous injection of formalin (2%), capsaicin (2.5 μg), cinnamaldehyde (13.2 μg) into the right upper lip (perinasal area)	Face-rubbing	–	N	N

Table 1
(*Continued*)

Authors, year, country	Substance/chemical group/(natural product)	Animals (strain/sex)	Dose (route)	Method of induction of orofacial pain	Parameters assessed		R	B
					Behavior	Biochemical/ molecular		
Quintans et al., 2014a, Brazil	Ethanolic extract (*Syzygium cumini*)	Mice (S/M)	100–400 mg/kg (p.o)	20 μl subcutaneous injection of formalin (2%), 40 μl glutamate (25 μM) into the right upper lip (perinasal area)	Face-rubbing	–	Y	Y
Siqueira-Lima et al., 2014, Brazil	β-Cyclodextrin complex containing essential oil (*Lippia grata*)	Mice (S/M)	6–24 mg/kg (p.o)	20 μl subcutaneous injection of formalin (2%), capsaicin (2.5 μg), 40 μl glutamate (25 μM) into the right upper lip (perinasal area)	Face-rubbing	Immunofluorescence	Y	Y
Quintans et al., 2014b, Brazil	Hexanic extract (*Combretum duarteanum*) and friedelin	Mice (S/M)	100–400 mg/kg (p.o)	20 μl subcutaneous injection of formalin (2%), capsaicin (2.5 μg), 40 μl glutamate (25 μM) into the right upper lip (perinasal area)	Face-rubbing	–	Y	Y
Damascena et al., 2014, Brazil	Aqueous extract (*Anadenanthera colubrina*)	Mice (S/M)	100–400 mg/kg (p.o)	20 μl subcutaneous injection of formalin (2%), capsaicin (2.5 μg), 40 μl glutamate (25 μM) into the right upper lip (perinasal area)	Face-rubbing	DPPH, MDA, TBARS, AAPH, $FeSO_4$	Y	N
Nowacki et al., 2015, Brazil	Hydroalcoholic extract (*Hypericum perforatum*, *Valeriana officinalis*, *Piper methysticum*)	Mice (S/M)	NR	20 μl subcutaneous injection of formalin (2%) into the right upper lip (perinasal area)	Face-rubbing	Hematological and hepatic markers	N	N

Animals: SD, Sprague–Dawley; W, Wistar; S, Swiss.
Parameters assessed: DPPH, 2,2-diphenyl-1-picrylhydrazyl radical; MDA, malonaldehyde; TBARS, thiobarbituric acid-reactive substances; AAPH, 2,2′-azobis(2-methylpropionamidine) dihydrochloride; $FeSO_4$, ferrous sulphate; R, reporting of randomization; B, reporting of blinding; Y, yes; N, no.

the drugs used commercially and are nowadays around are derived from natural sources (Braz-Filho, 2010).

Regarding the NP used for the management of orofacial pain tabulated in the present study, (Table 1) shows isolated substance (47.25%), extracts (47.25%) and β-cyclodextrin (β-CD) complexes containing essential oil (5.5%). That interprets most reviews of isolated compounds as reflecting the importance of the pharmaceutical industry, since the drugs are, almost entirely, a single active ingredient which is responsible for its pharmacological effect. Neverthless, the plant extracts consist of multicomponent active mixtures, partially active and inactive substances, which often work in different pharmacological targets (Ferreira and Pinto, 2010; Ulrich-Merzenich et al., 2010).

Moreover, our findings demonstrated that it is necessary to increase the number of studies with NP to orofacial pain models because 100% of the included studies in the present review use mainly chemical stimuli to induce pain (formalin, glutamate, capsaicin or cinnamaldehyde) into the vibrissal pad. These characteristics of the studies found become obvious limitations because orofacial pain is derived from many unique target tissues, such as the meninges, cornea, tooth pulp, oral/nasal mucosa and temporomandibular joint (Hargreaves, 2011). Further, there are other orofacial pain animal models also established in the literature, such as orofacial neurophatic pain or chronic pain model in temporomandibular joint, which have not been explored in articles inserted in this systematic review. According to Raboisson and Dallel (2004), the mechanisms underlying orofacial pain are still poorly understood, partly due to the relative scarcity of investigation devoted to the face and the mouth, when compared with pain in body. In particular, there are relatively few behavioral models in laboratory animals dedicated to the study pain in the trigeminal region.

Regarding the analysis of quality of the studies inserted, we found that 50% of studies (9) mentioned randomization in the allocation of animals for testing. However, they did not describe how they performed randomization of animals. Moreover, only four studies (22%) were performed by double-blind manner, as it can be seen in Fig. 2. That limits the interpretation of the results obtained in our review, what shows a low quality in the studies found.

To better describe and understand the results, we summarized them as isolated compounds, plant species, essential oils and extracts, which are described below.

Isolated substance

*Epibatidine (**1**)*

Epibatidine is a strong toxic alkaloid that is secreted from the *Epipedobates anthonyi* (Noble) (synonym *Epipedobates tricolor*) frog, which lives in Central and Southern Ecuador (Fitch et al., 2010). Epibatidine isolated from these frogs showed an effective analgesic and anti-inflammatory effects and was further assessed in the orofacial pain induced by the formalin animal model (Gilbert et al., 2001). According to authors, the acute treatment with epibatidine can produce a neuronal nicotinic receptor-mediated antihyperalgesia in both dose- and time-dependent manner.

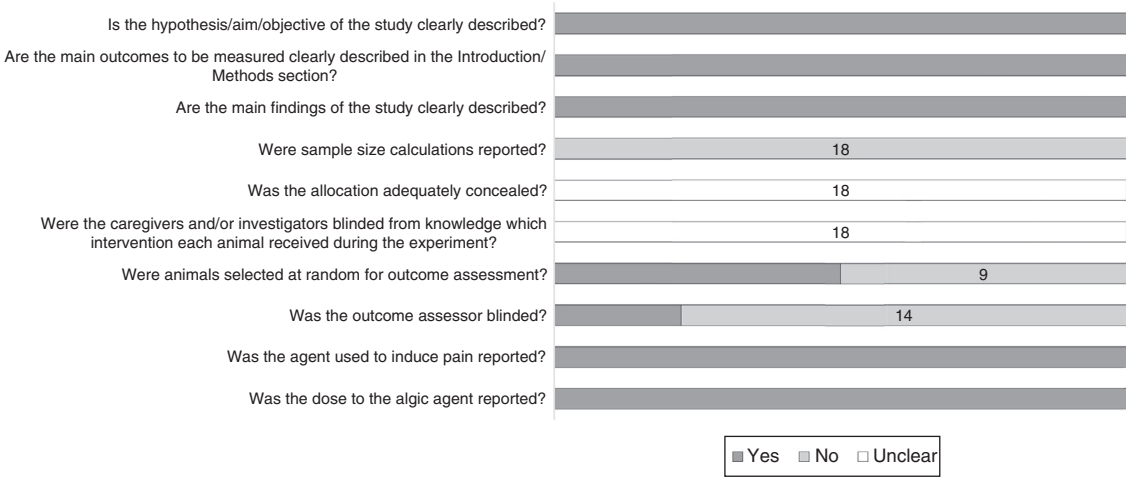
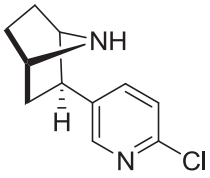


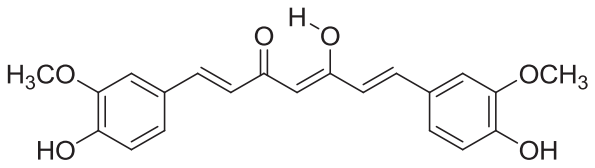
Fig. 2. Methodological quality of included studies. Dark gray bars indicate the proportion of articles that met each criterion; light gray bars indicate the proportion of studies that did not and white bars indicate the proportion of studies with unclear answers.



1

*Curcumin (**2**)*

The major bioactive constituent of the oleoresin of turmeric (*Curcuma longa* L., Zingiberaceae) demonstrated a significant reduction in grooming behavior induced with formalin in a dose-dependent manner in both phases. Curcumin has proven anti-inflammatory effect demonstrating its beneficial role for this pain condition (Mittal et al., 2009). Kim et al. (2003) explains the anti-inflammatory activity of curcumin due to its inhibitory action on Janus kinase (JAK) – STAT signaling pathway in brain microglial cells, which contributes to the attenuation of inflammatory response. Anti-inflammatory activity of curcumin may also be related to its ability to directly suppress nuclear factor-kappa B (NF-κB), leading to the inhibition of cellular COX-2 gene expression. Curcumin also causes an indirect suppression of the NF-κB an activity by inhibiting the degradation of the inhibitory unit I-κBα, which hampers subsequent nuclear translocation of the functionally active subunit of NF-κB (Surh et al., 2001). Also, it has been shown to overturn the synthesis of prostaglandin E2 (PGE2), which is known to be involved in mediating acute inflammation (Goel et al., 2001). There are also evidences of the inhibition of pro-inflammatory cytokine production (TNF-α, IL-1β, IL-8) by curcumin (Xu et al., 1997–1998; Banerjee et al., 2003; Jacob et al., 2007). Another study explains that the oxygen radical scavenging activity of curcumin has also been implicated to anti-inflammatory effects (Kunchandy and Rao, 1990). In addition to the anti-inflammatory profile, Sharma et al. (2006, 2007) demonstrated the efficacy of curcumin in the attenuation of diabetic neuropathic pain. According to Mittal et al. (2009), one needs to explain the mechanism of curcumin in the first phase of formalin, which occurs as a direct activation of A-delta and C-nociceptors as well as trigeminal and spinal nociceptive neurons, whereas anti-inflammatory action over the various mechanisms mentioned above might be responsible for reducing the grooming behavior during the tonic phase. Banafshe et al. (2014) explains that this antinociceptive effect may be due to the activation of the opioid system. Based on these reports, the compound curcumin represents a natural source for the treatment of orofacial and attenuating other pain- and inflammation-related disorders, which all need future clinical investigations.



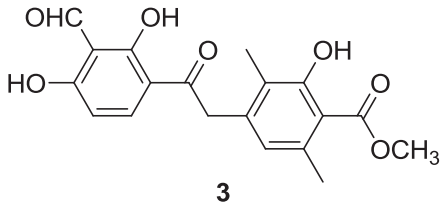
2

α,β-Amyrin

The effects of the pentacyclic triterpene isolated from *Protium heptaphyllum* (Aubl.) Marchand, Burseraceae, was investigated on rat model of orofacial pain induced by formalin or capsaicin. The results show that pretreatment with α,β-amyrin produces pronounced anti-nociception as evidenced by the decreased face rubbing behavior in capsaicin test and in the second phase of the formalin test (Holanda-Pinto et al., 2008). The inhibitory effect observed with α,β-amyrin on capsaicin and in the second phase of formalin-induced facial grooming may be a result of its possible inhibition on the Substance P release or due to a direct blocking action on its neurokinin-1 receptor (NK-1) (Holanda-Pinto et al., 2008). In this context, a previous study provided evidence for the tonic activation of NK-1 receptors during the second phase of the formalin test in the rat, and systemically administered, NK-1 receptor antagonist SR14033 blocks only the second phase of the orofacial formalin test (Henry et al., 1999; Luccarini et al., 2003). A recent study demonstrated the decreased NK-1 immunoreactivity in animals treated with α,β-amyrin in the rat model of visceral nociception induced by cyclophosphamide (Lima-Júnior et al., 2007). Silva et al. (2011) demonstrated that α,β-amyrin exhibits long-lasting antinociceptive and anti-inflammatory properties in models of CFA-induced inflammation and hyperalgesia *via* the activation of cannabinoid receptors and by inhibiting the production of cytokines, expression of nuclear factor κB (NF-κB) and cyclic adenosine monophosphate response element binding (CREB) and COX-2. Hence, from all these studies the α,β-amyrin involves in most of the central and peripheral mechanisms and exhibits antinociceptive and anti-inflammatory effects, offering themselves as a better candidature for clinical assessment of orofacial pain disorders.

*Atranorin (**3**)*

Siqueira et al. (2010) evaluated the antinociceptive effect of atranorin on formalin- and capsaicin-induced orofacial pain in mice. Their results showed that acute administration of atranorin (400 mg/kg, *i.p.*) in formalin-induced orofacial pain results in a pronounced anti-nociception as evidenced by decreased face-rubbing nociceptive behavior in the first and second phases of the formalin test. All doses of atranorin significantly inhibited the face-rubbing behavior at the second phase of the formalin test just as in the capsaicin test. Therefore, the study suggested a possible antinociceptive effect of this important lichen metabolite extracted from *Cladina kalbii* Ahti, in unspecific tests (Melo et al., 2008). This effect may have resulted from the inhibition of the Substance P release or due to a direct blocking action on its neurokinin-1 receptor (NK-1) (Holanda-Pinto et al., 2008). Melo et al. (2008) suggested a possible antinociceptive effect of atranorin to act peripherally on the inflammatory mediators, especially on prostaglandins. Bugni et al. (2009) showed that a part of the antinociceptive effect obtained with atranorin may be due to the COX inhibition. Additionally, it was demonstrated that atranorin effectively inhibited the biosynthesis of leukotriene B4 in bovine polymorphonuclear leukocytes, which could also lead to an anti-inflammatory effect (Kumar and Muller, 1999). The precise mechanisms through which atranorin exerts its action are currently under investigation, but they could possibly be related to the arachidonic acid cascade and/or modulation of pro-inflammatory molecule production (Siqueira et al., 2010).



3

Citronella

Reports from Quintans-Júnior et al., 2010, revealed the effects of citronellal, a monoterpene from the oils of *Corymbia citriodora* (Hook.) K.D. Hill & L.A.S. Johnson, Myrtaceae, *Cymbopogon nardus* (L.) Rendle, *C. citratus* (DC.) Stapf and *C. winterianus* Jowitt ex Bor, Poaceae, in the possible anti-nociceptive activity by using orofacial nociceptive tests (formalin-, capsaicin-, and glutamate-induced orofacial nociception) and investigated whether such effects might cause a change to neural excitability. Their results showed that an acute administration of citronellal caused pronounced antinociception as evidenced by decreased face-rubbing behavior in the first and second phases of the formalin test, suggesting that citronellal has a central analgesic effect. To confirm such an effect, the blocking effect of naloxone, a specific antagonist of μ morphinomimetic receptors, was tested on both phases of the formalin test (Belvisi et al., 1998). Its antagonist effects suggested the participation of the opioid system in the modulation of nociception induced by citronellal. Citronellal also inhibited nociceptive behavior induced by the capsaicin injection into the right upper lip. The inhibitory effect observed with citronellal on capsaicin- and formalin-induced face-rubbing behavior seems similarly act to α,β-amyrin, which can involve the inhibition of the Substance P release or the action on receptor neurokinin-1 (NK-1) (Holanda-Pinto et al., 2008). The results also showed that the intraperitoneal administration of the citronellal produced a significant inhibition of the nociceptive response induced by the right upper injection of glutamate into mice. That nociceptive response induced by glutamate seems to involve peripheral, spinal and supraspinal sites and its action is mediated by NMDA and non-NMDA receptors (Beirith et al., 2002). Thus, the suppression of glutamate-induced nociception by citronellal treatment can be associated with the interaction of citronellal with the glutamatergic system (Ferreira et al., 1999). The present study used the single sucrose gap method to show that citronellal could reduce the excitability of isolated nerves through a diminution of amplitude of compound action potential (CAP). It is possible that the antinociceptive effects of citronellal in the experimental models of nociception could be involved in voltage-gated Na^+ channel blocking, and may also have CNS effects (Quintans-Júnior et al., 2010). Quintans-Júnior et al. (2010, 2011) also proposed that the orofacial antinociceptive effect of citronellal could be related to the antioxidant profile since these monoterpenes exhibited a significant antioxidant activity as seen in TRAP/TAR assays, and scavenge NO and superoxide molecules which are widely accepted methods to reliably establish the ability of isolated molecules to act as general antioxidants *in vitro* (Salvemini et al., 2006; Guimarães et al., 2010). Thus, citronellal when clinically tested could form a promising source of drug for treating orofacial pain disorders.

p-*Cymene*

Santana et al. (2011) investigated the antinociceptive potential of *p*-cymene, a monoterpene biological precursor of carvacrol and one of the main constituents of the essential oil obtained from species of *Protium*. *p*-Cymene significantly reduced the nociceptive behavior in the first and second phases of orofacial nociception in all models induced by formalin, capsaicin and glutamate, suggesting an action in both neurogenic and inflammatory pain. Recently, Santana et al. (2015) demonstrate that *p*-cymene anti-hyperalgesic shows an effect against carrageenan, TNF-α, dopamine and PGE2 tests. The anti-hyperalgesic effect seems to be related to the capacity of *p*-cymene to decrease total leukocyte migration, TNF-α levels, act in opioid receptors and increased number of c-Fos-immunoreactive neurons in periaqueductal gray (PAG) area. Quintans et al. (2013) suggested that *p*-cymene could have its analgesic and anti-inflammatory effect enhanced by complexation with cyclodextrins probably by increasing the bioavailability of the terpenoid.

Citronellol

Brito et al. (2013) evaluated the antinociceptive effects of citronellol on orofacial nociception in mice and also investigated the central pathway system involved in the effect. This monoterpenoid alcohol is present in essential oils of various aromatic plant species such as *Cymbopogon citratus* and *C. winterianus*; its administration produced a reduction in the face rubbing behavior induced by formalin in first and second phases, which may be associated with the blockade of the voltage-dependent Na^+ channels (Butler, 2008; Gonçalves et al., 2008; De Souza et al., 2006). All test doses of citronellol significantly reduced the face rubbing behavior induced by the administration of capsaicin. This inhibition observed in the effect of the formalin and capsaicin tests has been suggested to result from an inhibition of substance P or by a blocking action on neurokinin-1 receptor (NK-1), because studies demonstrated the evidence for the activation of NK-1 receptors, through the NK-1 antagonist administration blocking the second-phase formalin test (Luccarini et al., 2003; Holanda-Pinto et al., 2008). The results of the orofacial nociception induced by the glutamate show that citronellol, in all doses, significantly decreased the face rubbing behavior compared with the control group, thus suggesting its interaction with the glutamatergic system. Brito et al. (2013) showed that citronellol significantly increased the average number of neurons in the olfactory bulb, piriform cortex, retrosplenial cortex (RSP) and in the PAG of the animal brains when compared with the control (vehicle). Thus, it can be suggested that citronellol produced orofacial antinociceptive effect probably by the inhibition

of peripheral mediators, as well as the activation, direct or indirect, of CNS regions.

Carvacrol

This monoterpene is predominant in many essential oils from the family Lamiaceae, including the *Origanum* and *Satureja* species. Guimarães et al. (2012) reported that acute treatment with carvacrol plays a protective role in reducing behavioral pain when screened for formalin-, capsaicin-, and glutamate-induced orofacial nociception in mice. According to the authors, carvacrol seems to produce anti-nociception in the orofacial formalin-, capsaicin- and glutamate-tests due to its effects in the reduction of the neuronal excitability and voltage-gated Na^+ channel (NaV) inhibition in peripheral neurons (Joca et al., 2015) or to produce analgesic and anti-inflammation effects by the modulation of cytokines, such as IL-10, IL-1β or TNF-α (Guimarães et al., 2014, 2015). Additionally, the carvacrol effects on the CNS were assessed through immunofluorescence for Fos protein. Furthermore, molecular docking studies were performed to evaluate intermolecular interactions of the carvacrol and muscimol, as ligands of IL-10 and $GABA_A$ receptors, which showed the neuromodulatory properties of carvacrol in the brain areas that comprise the descending-pain pathway control, such as PAG, nucleus raphe magnus (NRM) and locus ceruleus (LC). In addition, carvacrol complexed in β-cyclodextrin (β-CD) had prolonged analgesic effect and acted on descending-pain inhibitory pathway without showing tolerance and in a smaller dose than the carvacrol isolated as they were rendered highly bioavailable (Barreto et al., 2014; Guimarães et al., 2014, 2015).

Additionally, Lima et al. (2013a) evaluated the contribution of the cytokine modulation to the anti-inflammatory effects of carvacrol in complete Freund's adjuvant (CFA) model. Hence, the administration of this substance produced anti-inflammatory effects and attenuated the paw edema and reduced the IL-1β and PGE2, but not TNF-α, local levels. That effect suggested that carvacrol caused anti-inflammatory effects by reducing the production of inflammatory mediators, such as IL-1β and prostanoids, possibly through the induction of the IL-10 release. Banji et al. (2014) used the same model, CFA, as Lima et al. (2013a), but Banji et al. used a combination of carvacrol with methotrexate observing that this association enriches the therapeutic benefit enhancing its anti-arthritic action and minimizing its toxicity.

Plant species, essential oils and extracts

Sida cordifolia L., Malvaceae

This plant is a native species of Northeastern Brazil, popularly known as "malva-branca". Pharmacological activity of the extracts and fractions from *S. cordifolia* in two animal models of orofacial nociception has been previously reported (Bonjardim et al., 2011). Administration of ethanol extract (EE), chloroform (CF) and methanol (MF) fractions from *S. cordifolia* produced a reduction in the face rubbing behavior induced by formalin. All doses tested significantly increased anti-nociception both in the first and second phase compared with the control (vehicle). Morphine (MOR) was able to reduce nociceptive behavior in both phases. The effects of EE, CF, MF and MOR were antagonized by naloxone. The treatment with CF and MF significantly reduced the nociceptive behavior induced by glutamate in relation to the control group. Thus, it is suggested that the constituents of this fraction could interfere in the glutamatergic system, through the activation of NMDA receptors, which would limit the production of NO and other inflammatory mediators (Ribas et al., 2008). Henceforth, the antinociceptive effect of the ethanol extract from *S. cordifolia* and its chloroform and methanol fractions is probably due to the presence of alkaloids and flavones. Additionally, it seems at least in part that this antinociceptive action of EE, CF and MF involves the opioid and the glutamatergic systems (Bonjardim et al., 2011).

Hyptis pectinata (L.) Poit., Lamiaceae

Paixão et al. (2013, 2015) investigated the effect of the aqueous extract from *H. pectinata* (AEPH) on the orofacial nociceptive models and its antioxidant potential. The results of the present study showed that AEPH is active against neurogenic and inflammatory pain since it inhibits the mice face-rubbing nociceptive behavior in both phases. In addition, when the mechanism of AEPH action was investigated using naloxone, its effect was not reversed, suggesting that its analgesic activity does not involve opioid receptors. Bispo et al. (2001) found that naloxone (5 mg/kg, *i.p.*) markedly reversed the antinociceptive effect of the aqueous extract (200 mg/kg) and of morphine (10 mg/kg) in the hot-plate test. In order to better assess this aspect, Lisboa et al. (2006) evaluated the non-selective opioid antagonist naloxone (5 mg/kg, *i.p.*), which was co-administrated with chloroform (200 mg/kg), ethyl acetate (100 mg/kg) and hexane extracts (100 mg/kg), since naloxone reversed the antinociceptive effect. This mechanism is similar to that found in the volatile oil of *H. pectinata*, in which the administration (*i.p.*) of the opioid agonist naxolone (5 mg/kg body wt) completely reversed the antinociceptive effect of the volatile oils of all genotypes on the hot-plate test, suggesting that opioid receptors are involved in its antinociceptive action (Arrigoni-Blank et al., 2008; Raymundo et al., 2011). Other mechanisms of volatile oil of *H. pectinata* were also investigated. L-NAME significantly reversed the effects of the EO in the acetic acid-induced contortions and hot-plate models and atropine completely reversed in all models. Besides, the EO inhibited the inflammatory process induced by subcutaneous carrageenan injection by reducing cell migration, exudate volume, protein concentration and inflammatory mediators (nitric oxide, PGE2, IL-6, and TNF-α) (Raymundo et al., 2011).

To further investigate the mechanism through which AEPH acts against orofacial pain, capsaicin was used, and there was a reduction in the capsaicin nociceptive effect in a dose-dependent manner, which indicates AEPH is acting as an antagonist of vanilloid receptors, possibly by inhibiting the initial release of substance P or bounding into its neurokinin 1 receptor. AEPH exhibited significant antinociceptive activity when the glutamate model was used. Therefore, it can be suggested that it interferes with the glutamatergic system. *In vitro* studies of this study showed that AEPH has an important neurogenic and inflammatory orofacial antinociceptive effect, without interference in the motor performance (Paixão et al., 2013).

Recently, the literature has shown that the analgesic and anti-inflammatory effects of *H. pectinata* can be improved with the incorporation into complexing systems (as cyclodextrins) or vectorization of drugs, which can bring benefits to physicochemical or pharmacological aspects of pharmaceutical preparations containing extracts or essential oils of medicinal plants (Oliveira et al., 2015; Brito et al., 2015; Paixão et al., 2015; Menezes et al., 2015; Quintans-Júnior et al., 2016).

Hyptis fruticosa Salzm. ex Benth., Lamiaceae

Lima et al. (2013b) revealed the improvement of the knowledge of the antinociceptive activity of this plant by studying its potential to treat orofacial pain using formalin, glutamate and capsaicin pain models, as well as its possible antioxidant and anti-lipoperoxidative activity. The crude hydroethanol extract inhibited both nociceptive phases induced by formalin, suggesting the extract has central and peripheral antinociceptive activity, similarly to morphine, the standard drug used for nociception and differently from the essential oil of *Hyptis fruticosa*, which has antinociceptive peripheral activity (Menezes et al., 2007). Franco et al. (2011) has assigned the pharmacological effects of this plant

due to the variety of volatile compounds found in the leaves such as, α-pinene, β-pinene, 1,8-cineole and limonene.

The results of Lima et al. (2013b) showed that the hydroethanol extract of the *H. fruticosa* leaves (CHEE) inhibited the nociception caused by glutamate with significant results for the highest concentration used (200 mg/kg), suggesting that the extract can be active in inhibiting the painful stimulus induced by this amino acid. CHEE at 100 and 200 mg/kg was able to reduce the capsaicin nociceptive effect, suggesting that vanilloid receptors can be involved in the CHEE action.

Ocimum basilicum L., Lamiaceae*, and linalool*

Venâncio et al. (2011) evaluated earlier the effect of *O. basilicum*. Lamiaceae. The leaf essential oil from *O. basilicum* (LEO) and its major chemical constituent linalool (LIN) in formalin-, glutamate- and capsaicin-induced orofacial nociception in mice and were investigated for whether these substances could also interfere with the hippocampal neuronal excitability. In the formalin test, there was a reduction in face rubbing after intraperitoneal injection of LEO or linalool (LIN). Every dose of linalool tested produced significant antinociceptive action in the first and second phase compared to control group. LEO manifested its effect only in the high dose, while morphine decreased the pain behavior in both phases. In capsaicin test, LIN or LEO diminished the nociception evidenced by the suppression of the face-rubbing behavior. When assessed to glutamate test, LEO and LIN produced marked analgesia, but only in higher doses. Batista et al. (2008) demonstrated that the antinociceptive effect of LIN may have a relationship with glutamate receptors, namely α-amino-3-hydroxy-5-methyl-4-isoxasolepropionic acid (AMPA), NMDA and kainate. These results confirmed this hypothesis, since pretreatment with LIN significantly protected against the orofacial formalin test. A similar result was obtained by acute administration of LEO. It is suggest that LEO and LIN can be considered as non-NMDA glutamate antagonists (AMPA or Kainate blockers). Hence, these behavioral experiments suggest that most of the analgesic effects of LEO could be attributed to LIN, its major component. The stimulation of the hylar region of the dentate gyrus (antidromic stimulation) generated a field potential response in the granular layer, which is characterized by a major negative component (population spike) followed by a small positive phase. Since this response is a consequence of activation of voltage-dependent sodium channels in the axons of the granular cells (Andersen et al., 1971), antagonists of these channels were expected to block the response. Similar effects were seen for LEO and LIN, which inhibited the field potentials activated by the antidromic stimulation of the hylus.

Acmella oleracea (L.) R.K. Jansen, Asteraceae

Nomura et al. (2013) examined the antinociceptive effect of the ethanolic extract obtained from the flowers of *Acmella oleracea* (EEAO) and their results revealed that EEAO (10, 30 and 100 mg/kg) reduced both phases of the formalin-induced orofacial nociception. Besides, the results decreased the pain in capsaicin- and cinnamaldehyde-induced orofacial nociception. Furthermore, the study also suggested that the analgesic effect of EEAO on the orofacial nociception mediated by capsaicin and cinammaldehyde could be related to TRPV1 and TRPA1 receptor modulation and/or blockade.

Syzygium cumini *(L.) Skeels,* Myrtaceae

Quintans et al. (2014a) evaluated the antinociceptive effect of the ethanol extract (EE) from *S. cumini* leaves on orofacial nociception that produced significant anti-nociception in the inflammatory phase of the formalin and glutamate test. When glibenclamide and L-NOARG were administrated, the antinociception caused by EE was reversed. However, pretreatment with naloxone did not change the antinociceptive action. Muruganandan et al. (2001) investigated the ethanolic extract of the bark of *S. cumini* for its anti-inflammatory activity and their results show that this extract has a powerful anti-inflammatory action against distinct phases of inflammation without any side effect on the gastric mucosa. The anti-inflammatory activity of this species was even studied by Machado et al. (2013), who investigated the anti-inflammatory and apoptotic activity of the essential oil of *S. cumini* showing relevant anti-inflammatory activity *in vivo*, possibly due to the high percentage of β-caryophyllene identified.

Lippia grata Schauer, Verbenaceae

Siqueira-Lima et al. (2014) investigated the possible antinociceptive activity of β-cyclodextrin complex containing *Lippia grata* leaf essential oil (β-CD/EO) in animal models especially in orofacial pain. The results demonstrated that β-CD/EO was capable of reducing the nociceptive face-rubbing behavior in both phases of the formalin, glutamate and capsaicin induction, possibly due to the relationship with vanilloid, opioid and cannabinoid receptors. β-CD/EO appears to be very effective in activated descending pain-inhibitory mechanisms without untoward effects already described for morphine-like drugs (Siqueira-Lima et al., 2014, 2016). Additionally, this study was the first to show the chemical and pharmacological benefits caused by the complexation in cyclodextrins, which seems to be an advantageous approach to essential oils and non-polar compounds (Oliveira et al., 2015; Brito et al., 2015). The cyclodextrins (CD) uses to enhance biological and chemical characteristics of terpenes and related compounds, such as essential oils, have been widely explored in the study of new drugs to treat pain, inflammation and cancer because CD may promote increased bioavailability and pharmacological efficacy (Siqueira-Lima et al., 2016).

Combretum duarteanum Cambess., Combretaceae

Quintans et al. (2014b) demonstrated that the hexanic extract and friedelin main be a compound from the *Combretum duartenum*-reduced nociception of formalin (in both phases). Glutamate and capsaicin-induced orofacial nociception tests suggest a possible interaction with the glutamatergic system and a possible inhibition of the substance P release or due to a direct block of its neurokinin-1 receptor (NK-1). These results are supported by previous findings of Antonisamy et al. (2011) regarding friedelin, who attributed the analgesic profile due to the central and peripheral effects. However, none of the studies provide molecular evaluations as friedelin can act by central and peripheral ways.

Anadenanthera colubrina (Vell.) Brenan, Fabaceae

A. colubrina, popularly known as 'angico-branco', is native to the Brazilian Caatinga biome and used by the people to treat respiratory conditions (asthma, bronchitis, cough and flu), as a skin-healing agent, analgesic and against inflammatory processes (Damascena et al., 2014) due to its biological properties, Damascena et al. (2014) sought to assess whether the *A. colubrina* stem bark aqueous extract can inhibit orofacial pain induced by chemical agents (formalin, capsaicin and glutamate) and investigated the antioxidant potential. Thus, the *A. colubrina* stem bark aqueous extract reduced orofacial pain in all animal models assessed and this effect appears to be associated with its redox-active radical scavenging activities.

Hypericum perforatum *L. Hypericaceae,* Valeriana officinalis *L., Caprifoliceae, and* Piper methysticum *G. Forst., Piperaceae*

This particular study performed by Nowacki et al. (2015) assessed the association of hypericum (*H. perforatum*), valerian (*V. officinalis*) and kava (*P. methysticum*) seeking to evaluate their effects in reducing orofacial pain as well as the possible

hepatic, hematologic and biochemical alterations induced by regular administration of these extracts. The authors found that the composition of these three medicinal plants produced significant analgesic profile in formalin-induced orofacial pain in rodents, and also produced an outstanding hepatoprotective effect.

Animal models of orofacial pain

The importance in the field of orofacial pain assessment can be suggested by the sharp increase in publications over the recent decades (Hargreaves, 2011). This fact has also been accompanied by the increased number of studies using orofacial pain animal models, which have sought to better understand the pathophysiology of orofacial pain and to assess new drugs to treat it (Raboisson and Dallel, 2004). There are relatively few behavioral models in laboratory animals dedicated to the study of nociception in the trigeminal region (Raboisson and Dallel, 2004). Thus, the animal models of orofacial pain had sought to mimic symptoms or the disease *per se* (Khan and Hargreaves, 2010). However, the orofacial pain is multifactorial and too complex for a single model to incorporate all the nuances, so there is an increasing number of different types of animal models.

As in our survey most studies have sought access to orofacial pain by chemical stimuli, we made here a brief comment on the orofacial pain animal models induced by chemical stimuli, such as formalin, capsaicin and glutamate (animal models are based on the induction of pain by administration of algogen into the vibrissal pad of rodents).

As described by Hargreaves (2011), this type of animal model can bring limitations for the analysis of the results because the orofacial pain condition is not derived from a unique target tissue, but from a variety of sensitive tissues such as the meninges, cornea, tooth pulp, oral/nasal mucosa and temporomandibular joint. Thus, the choice of the appropriate method for investigating the physiological or pharmacological event is extremely important in the study design by the researcher.

For the formalin test, probably the best established and most reliable experimental protocol to assess quickly orofacial pain condition (it is known to be the subcutaneous, *s.c.*, injection of dilute formalin), which causes indeed tissue injuries and generates behavioral as well as electrophysiological responses that last from several minutes up to more than 1 h (Raboisson and Dallel, 2004). Similarly, as it happens with the administration of formalin into the rodents paw, the injection of formalin in the vibrissa pad (into the upper lip) produces a biphasic pain stage (Luccarini et al., 2006). It is a model that evaluates drugs that act centrally or by peripheral mechanisms mediated by local inflammation induced by formalin (Raboisson and Dallel, 2004; Hunskaar and Hole, 1987). However, it is not the best animal model to evaluate painful or analgesic routes.

Recently, two other animal models have been widely used to assess drugs with potential analgesic profile to orofacial pain: capsaicin and glutamate-induced orofacial pain tests. The application of capsaicin, the prototypical transient receptor potential vanilloid 1 (TRPV1) agonist, evokes neuropeptide release and induces primary and secondary hyperalgesia (Khan and Hargreaves, 2010). The administration of capsaicin into the vibrissa pad of mice induces significant nociceptive behaviors expressed as head flinching and rubbing of the orofacial tissues during at least 1 h (Holanda-Pinto et al., 2008). On the other hand, glutamate is one of the most important excitatory neurotransmitters in the production and management of pain (Mogil, 2009). Moreover, glutamate is present in both central and peripheral terminals of trigeminal and dorsal root ganglion neurons (Keast and Stephensen, 2000). According to Quintans-Júnior et al. (2010), the injection of glutamate (volume of 20 μl) into the right upper lip (perinasal area), using a 27-gauge needle, caused a persistent nociceptive behavior characterized by strong rubbing of the orofacial face and head flinching. Therefore, drugs that inhibit these behaviors, after administration of capsaicin or glutamate, are potentially useful as analgesics (Quintans-Júnior et al., 2010).

Now we briefly mention the most common animal models to assess orofacial pain induced by chemical stimuli. More information about animal models to study orofacial pain can be assessed in the excellence reviews published by Raboisson and Dallel (2004), Mogil (2009), Khan and Hargreaves (2010) and Hargreaves (2011).

Conclusion

This systematic review suggests that the natural compounds have a potential for the treatment of pain conditions in orofacial region, hoping to discover new biologically active substances that may offer a new possibility for the most appropriate treatment of orofacial pain, since there is no pharmacological treatments which may result in clinical improvement without significant side effects in these pathological conditions. Paradoxically, the studies found in our survey are very lead-off (basically screenings), which are not directly related to the possible clinical applicability. Therefore, it could be believed that pharmacokinetic studies, incorporation into modern pharmaceutical formulations and biotechnological product development seem to be a distant horizon in even the selected studies. Thus, our opinion is that the evidence found in the studies showed a possible use of these NP in the management of orofacial pain conditions. However, new studies are needed to prove their underlying mechanisms and effects on the molecular level and in clinical research in a near future.

Authors' contributions

PSSL, JCS, JSSQ, RSSB and JRGSA contributed with both the survey of the articles and the preparation of the manuscript. SS, MRVS, LRB, JSSQ, ARA, IRAM and LJQJ participated in the drafting, correction and with their expertise in the discussion and finalization of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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