http://dx.doi.org/10.5935/0103-5053.20150332

J. Braz. Chem. Soc., Vol. 27, No. 3, 435-474, 2016.
Printed in Brazil - ©2016 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

Review

Antinociceptive Effect of Essential Oils and Their Constituents: an Update Review

Eder J. Lenardão,[,a] Lucielli Savegnago,*[,b] Raquel G. Jacob,[a] Francine N. Victoria[a] and Débora M. Martinez[a]*

[a]*Laboratório de Síntese Orgânica Limpa, LASOL, CCQFA and* [b]*Grupo de Pesquisa em Neurobiotecnologia, GPN, CDTec, Universidade Federal de Pelotas, UFPel, CP 354, 96020-250 Pelotas-RS, Brazil*

Plants and essential oils (EOs) have been used for centuries in folk medicine to treat diverse disorders, including analgesic to pain relief. In this context, the antinociceptive activity of EOs has been attracted attention since the management of pain continues being a major challenge for medicine. This review provides an overview of published reports on the antinociceptive activity of EOs and their constituents from 2000 until the first half of 2015. In this review are compiled the data on the antinociceptive activity of 63 EOs and 26 of their constituents with a discussion about the nociception model used to access the analgesic effect. These data were also analyzed in relation to ethnopharmacological and toxicological data available in the literature. As can be seen by the analysis of more than 300 articles, EOs and their constituents show antinociceptive effects in different models and their action mechanism is quite variable. Although there are a few essential oils or their isolated constituents on the phytopharmaceuticals market, this review intends to put in evidence the often-underexploited vast source of natural compounds with therapeutic potential in pain relief.

Keywords: essential oil, antinociceptive, analgesic, natural compound, pain

1. Introduction

Over the past few decades, strategies of drug discovery have been generally focused on an approach based on single targets along with the rapid growth in genetics and molecular biology. Medicinal plants have been used in developing countries as alternative treatments to health problems.[1] Many plant extracts and essential oils (EOs) isolated from plants have shown *in vitro* and *in vivo* biological activities, which have inspired intense research on their use in traditional medicine.[2]

Natural products are fundamental to pain treatment. They yield new analgesics and play an important role in the study of pain mechanisms.[3] Historically, the majority of new drugs has been directly produced from natural products (secondary metabolites) or from semi-synthetic compounds.[4,5] In recent years, an increasing number of studies have demonstrated that natural products from folk remedies have contributed significantly to the discovery of modern drugs worldwide.[6-8] A successful example of a drug obtained from natural product is morphine, an opioid drug extracted from the plant *Papaver somniferum*.[9] In an excellent survey, 210 medicinal plants, involving 79 families, were summarized about their analgesic effects by Almeida *et al*.[6] More recently, Yunes *et al*.[8] revised the development of analgesic drugs from glycosides, alkaloids, flavonoids and terpenes.

Plant EOs are complex mixtures of volatile compounds, which are isolated by physical methods (pressing and distillation) from a whole plant or plant parts (leaf, bark, fruits, flowers, etc.). The major components of the EOs are derived from only three biosynthetic pathways: (*i*) the methylerythritol phosphate (mep) pathway, which leads to mono- and diterpenes; (*ii*) the mevalonate pathway, leading to sesquiterpenes; and (*iii*) the shikimate pathway to phenylpropenes.[10] The identity and the relative quantity of these volatile substances in the EO is quite variable and they have various ecological roles in the plant, including the attraction of pollinating insects, as internal messengers and as a protective substance against herbivores.[11]

The pharmacological effects of EOs and their major constituents have been focused by many research groups in the last years.[12-20] There are in the literature several excelent reviews dedicated to the pharmacological activities of these

*e-mail: lenardao@ufpel.edu.br, lucielli@ufpel.edu.br

natural occurring compounds, including antinociceptive,[16,17] antioxidant,[18] anti-cancer[19] and anti-inflamatory activities.[20]

Owing to the new attraction for natural products like EOs and their major constituents, despite their wide use as analgesic in folk medicine, it is important to develop a better understanding of their antinociceptive action for new applications in human health. In Brazil, an example of successful application is the EO obtained from *Cordia verbenacea* (Boraginaceae), an anti-inflammatory medicine for topical use (Acheflan®).[21] A very interesting review covering patents involving the use of terpenes and EOs like pain relievers was recently published by Guimarães *et al.*[22] In that comprehensive review, 17 patents were critically analyzed and it was showed that, despite the large and intensive research in academy on natural products-based drug-discovery, plant EOs and their constituents potential as analgesic drugs remains underexplored.

The high volatility, low stability, along with the hydrophobicity of most EOs and their major consituents are among the reasons of the discrepancy between the high number of articles on their *in vivo* and *in vitro* activities and the restrict number of commercial products using these natural compounds.[22] This picture started to change in the last years, since new approaches have been developed aiming to increase the therapeutic properties of EOs and their components, notedly the use of drug-delivery structures, like β-cyclodextrins (β-CD).[23-25] It was observed that the inclusion of EOs with β-CD protects the EO against oxidation, heat and light degradation and reduces losses due evaporation and moisture.[23] In this line, it is worth noting the work from Quintans and co-workers[25] which obtained excellent outcomes using β-CD/EO complex in studies on the antinociceptive activity of several EOs and also some of their constituents. These studies opened a new perspective on the use of EOs and other volatile compounds as antinociceptive agents, improving the stability and on water solubility, reducing the volatility and faciliting the handle of the EO and individual components.[24,25]

Based on these considerations, the goal of this paper is to provide an overview of the published data on the antinociceptive activity of EOs and their constituents compiling the published data from 2000 to the first half of 2015. We searched Scopus, Medline, DOAJ, Web of Science and SciFinder and the search terms were relevant to the review subject being limited to the use of EOs and/or their isolated constituents, mainly terpenoids, in pain relief.

Studies involving the use of aqueous or ethanolic extracts, as well as semi-synthetic compounds will not be discussed in this review. Similarly, those papers describing preliminary screening, using non-specific tests, such as acetic acid-induced writhings alone, with no additional evidences on the antinociceptive effect of the EO or their constituents, were not included.

The first part of this review is dedicated to the description of the concepts involved in the nociception, followed by the major clinical treatments used to treat pain and the main tests used to evaluate the antinociceptive activity; after that, the antinociceptive effect of EOs and their constituents is presented, in order to make the reading more understanding through the text.

2. Nociception

Nociceptive pain comprises the processes of transduction, conduction, transmission and perception. The nociceptive signaling in physiological pain is initiated by activation of the specialized pain receptors (nociceptors), which are polymodal sensory fibers of the primary sensory neurons located in trigeminal and dorsal root ganglia with unmyelinated (C-fiber) or thinly myelinated (Aδ-fiber) axons. The conversion of a noxious thermal, mechanical, or chemical stimulus into electrical activity in the peripheral terminals of nociceptor sensory fibers consists in the transduction phase. This process is mediated by specific receptor ion channels, expressed only by nociceptors.[26]

The conduction phase consists in the passage of action potentials from the peripheral terminal along axons to the central terminal of nociceptors in the central nervous system, along unmyelinated (C-fibers), slow conducting and more rapidly conducting primary sensory ones. This sensory inflow then activates secondary sensory neurons in the dorsal horn of the spinal cord through synaptic transfer, in the transmission phase, which project to the cortex via a relay in the thalamus. Therefore, the transmission is the synaptic transfer and modulation of input from one neuron to another.[26,27]

The dorsal horn of the spinal cord is the site where the primary afferent fibers synapse with second-order neurons. It is also, where complex interactions occur between excitatory and inhibitory interneuron and where descending inhibitory tracts from higher centers exert their effect.[3] Large fiber inputs from other sensory modalities and descending pathways can modulate the activity in the dorsal horn (Figure 1).[28]

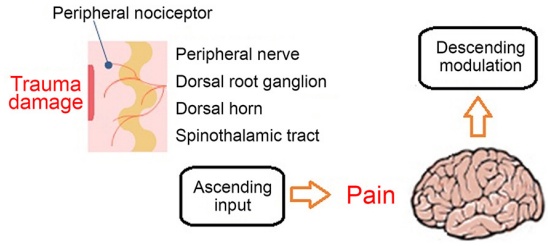

Figure 1. The pain pathway.

The multiplicity of events that occur during pain transmission in both, the peripheral and central nervous systems are arising from the direct or indirect action of chemical mediators. These include arachidonic acid metabolites (prostaglandins and leukotrienes), peptides (kinins, tachykinins, calcitonin gene related peptide, galanin, cholecystokinin, vasoactive intestinal peptide), serotonin, acetylcholine, cytokines, nerve growth factor, glutamate, nitric oxide, adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine and protons, among others. These mediators can be produced or released following tissue injury or by exogenous irritants (formalin, acetic acid, capsaicin, etc.).[29-31]

These mediators can act via a multiplicity of receptors that are widely distributed through central and peripheral nerves, many of which are coupled to heterotrimeric G-proteins and associated with the formation of multiple second messengers, such as protein kinases A, C and G, cAMP, cGMP and mobilization of intracellular calcium. Other neurotransmitters, such as excitatory amino acids and acetylcholine (acting at the nicotinic receptor), directly activate ion channels, and in turn control the membrane ion permeability.[32,33] Several factors, including physical damage to tissues, exposure to some inflammatory mediators, such as prostaglandin E_2, bradykinin, substance P, histamine, adenosine and serotonin are known to cause sensitization of nerve ending nociceptors to mechanical and thermal stimuli (Figure 2).[29-31]

3. Clinical Treatments

The drugs most often used to treat pain and inflammation are the non-steroidal anti-inflammatory (NSAIDs) and opioids, despite their well-known adverse effects.[34,35]

Opioid analgesics are used for the treatment of moderate to severe acute pain and currently are the most effective and frequently used drugs in patients with refractory malignant and non-malignant pain. Opioids include the broad category of compounds that are agonists of opioid receptors and that elicit actions typical of morphine.[36]

The term "opiate" typically includes the opioid alkaloids derived from the opium poppy seeds and includes the opium resin, codeine and morphine. The term opioid includes natural and semi-synthetic opiates (such as hydrocodone and oxycodone) and synthetic opioids (such as fentanyl and methadone).[36] Opioids can alter the central pain-related systems, resulting in opioid tolerance (a decrease in the analgesic effect of opioids), dependence (a behavioral state requiring continued use of opioids to avoid a series of aversive withdrawal syndromes) and withdrawal syndrome, which are the most predominant behavioral consequence of long-term usage of opioids; other effects are pruritus, nausea, slowing of gastrointestinal (GI) function, urinary retention and sexual dysfunction.[37,38] Therefore, repeated use of opiate analgesic drugs like morphine for the relief of chronic pain may result in the development of opiate tolerance and dependence. A consequence of these effects is a narrowing of the drug's therapeutic index, increase of side effects[39] and a significant hampering of the effective treatment of chronic pain with opioid analgesics.[40,41]

The term NSAIDs (non-steroidal anti-inflammatory drugs) is used to refer to both, non-selective (nsNSAIDs) and cyclo-oxygenase COX-2 selective inhibitors (COXIBs). NSAIDs have a spectrum of analgesic, anti-inflammatory and antipyretic effects and are effective analgesics in a variety of acute pain states.[42] NSAIDs are a disparate group of weakly acidic, highly protein-bounding compounds having the common pharmacological property of inhibiting

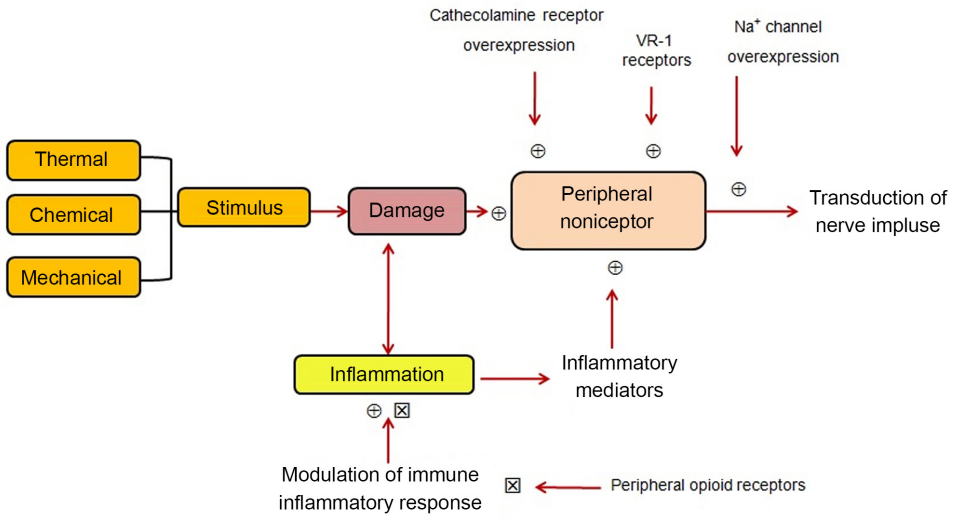

Figure 2. Events that occur during pain transmission in both the peripheral and central nervous systems.

prostaglandin biosynthesis. It was demonstrated that the acid moiety of these molecules can be extensively accumulated in inflamed tissues, where the NSAIDs exert their effects.[43,44]

Despite the diverse chemical structures of NSAIDs, the analgesic effect of these drugs is mainly due to their common property of inhibiting cyclo-oxygenases (COX) involved in the formation of prostaglandins, which are formed by the conversion of arachidonic acid.[45] There are two isoforms of COX: COX-1 (expressed in most tissues) and COX-2 (expressed in kidney, central nervous system, and cardiovascular system-endothelium and induced in response to inflammatory stimuli), both are formed from arachidonic acid (Figure 3). The two COX isoforms share 60% homology in their amino acids sequence and are both integral membrane homodimer proteins of the endoplasmic reticulum and nucleus, with roughly comparable kinetics. However, they differ in their regulatory mechanisms, cell localization, and function. A third isoform (COX-3 or COX-1b) was first described in canine as a splice variant of COX-1 gene, but its physiological role at this point remains unknown.[46]

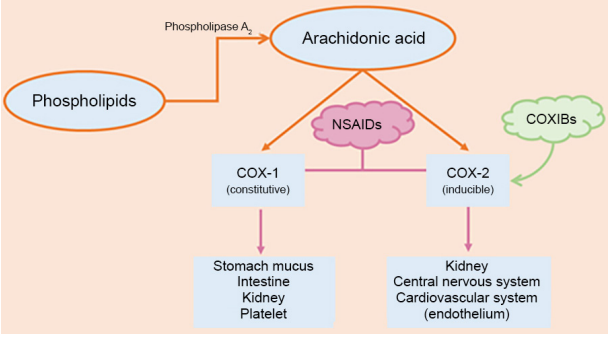

Figure 3. Cyclo-oxygenases as response to inflammatory stimuli. Where: NSAIDs: non-steroidal anti-inflammatory drugs; COX: cyclo-oxygenases; COXIBs: cyclo-oxygenase-2 inhibitors.

COX-1 isoform is expressed in most tissues, producing prostaglandins that play an important protective role in the gut by stimulating the synthesis and secretion of mucus and bicarbonate, increasing mucosal blood flow and promoting epithelial proliferation. When NSAIDs inhibit this enzyme, they create a gastric environment that is more susceptible to topical attack by endogenous and exogenous factors.[47]

The main problem in using NSAIDs are the adverse effects, especially gastrointestinal morbidities, including complications in both, upper and lower gastrointestinal tracts, prothrombotic effects and peptic ulceration.[47]

COX-2 was first identified as a key element of the acute inflammatory response because its expression is rapidly induced by various inflammogens.[48] COXIBs selectively inhibit the inducible cyclo-oxygenase enzyme COX-2 and they offer the potential for effective analgesia with fewer side effects than NSAIDs. Available COXIBs include celecoxib, etoricoxib and parecoxib.[49]

Paracetamol (acetaminophen) is used in clinical practice and is an effective analgesic and antipyretic. Because paracetamol has fewer side effects than NSAIDs, it can be used in substitution to them in some treatments.[49] One of the mechanisms of action of paracetamol appears to be linked to the serotoninergic system and it is possible that other drugs with serotoninergic effects could affect pain relief. Botting and Ayoub[50] demonstrated that analgesia and hypothermia due to paracetamol are mediated by inhibition of COX 3 in the central nervous system and lowering in PGE2 levels.

Some of the agents recently used for pain relief (gabapentin, pregabalin, lamotrigine, topiramate, tramadol and venlafaxine) are believed to inhibit central sensitization by blocking the activity of glutamate, excitatory neuropeptides, and presynaptic calcium channels, while enhancing inhibitory pathways mediated by serotonin, norepinephrine, and γ-aminobutyric acid (GABA).[49]

The serotoninergic system has gained much attention as a therapeutic target for treating migraine pain and it is implicated in other pain conditions.[51] Therapeutics targeting 5-HT receptors and 5-HT re-uptake are being examined in clinical trials for their ability to treat the pain associated with migraine[51] and fibromyalgia.[52] To date, the triptan class of medicines used to treat migraine and cluster headache, including the 5-HT1B/1D agonist sumatriptan, are the only 5-HT selective therapeutics that treat pain successfully in the clinic. Other centrally-acting drugs, such as venlafaxine and duloxetine, which act as dual norepinephrine and 5-HT reuptake inhibitors, have shown some efficacy in the treatment of various pain symptoms, including fibromyalgia.[53]

The adverse effects of NSAIDs and opioids drugs have inspired the search for safer and more effective anti-inflammatory and analgesic drugs. The current trend of research is the investigation of medicines of plant origin as a source of new chemical substances with potential therapeutic effects, because of their availability and accessibility with minimal side effects.[54,55]

Natural substances obtained from plants have played an extremely important role in the development of analgesic drugs and in the understanding of the complex mechanisms involved in pain transmission and pain relief.[55] The first commercial pure natural product introduced for therapeutic use was morphine, marketed by Merck in 1826 and the first semi-synthetic pure drug Aspirin®, based on salicin, a glycoside obtained from the bark of *Salix alba*, was introduced by Bayer in 1899.[4] This led to the isolation of early drugs such as cocaine, codeine, digitoxin, quinine and pilocarpine, and several other recent plant derived

compounds, which have undergone development and have been commercialized as drugs, which include Paclitaxel from *Taxus brevifolia*, for the treatment of lung, ovarian and breast cancers.[56]

4. Experimental Models to Evaluate the Antinociceptive Effect in Natural Products Research

An animal model is useful for research because it has specific characteristics that resemble a human disease or disorder. Several nociceptive tests can be performed in animals to evaluate the antinociceptive activity of new drugs. The nociceptive stimulus is caused by a chemical, thermal or mechanical agent.[57] In Table 1 are summarized the main models of nociception, which are validated and extensively performed in rats and mice.

4.1. Chemical methods

4.1.1. Acetic acid-induced writhings

The acetic acid-induced writhings model has been used as a screening tool for the assessment of analgesic and anti-inflammatory agents as a typical model of study of inflammatory pain.[58-60] This is a standard, simple and sensitive test for measuring central and peripheral nociception.[61] Acetic acid-induced abdominal pain is not a specific model, but because of its similarity to the signs of human visceral disorders, it has been extensively used for the screening of analgesic drugs.[57,62] This test is based in the induction of abdominal writhings, causing algesia by liberation of various endogenous substances that excite the peripheral nociceptors.[58]

It has been suggested that the intraperitoneal (i.p.) injection of the irritant agent acetic acid produces episodes of characteristic stretching (writhings) movements, and the inhibition of the number of episodes by drugs is easily quantifiable.[63] Acetic acid also releases endogenous mediators that stimulate the nociceptive neurons.[58] Mediators like histamine, serotonin, bradykinin, substance P, prostaglandins, especially PGI_2, as well as some cytokines such interleukin 1β (IL-1β), necrosis tumor factor (TNF-α) and interleukin 8 (IL-8), released into peritoneal fluid, cause an increase in vascular permeability, reduce the threshold of nociception and stimulate the nervous terminal of nociceptive fibers.[64-66] These mediators activate chemosensitive nociceptores that contribute to the development of inflammatory pain.

This is a visceral model of pain, in which the processor releases arachidonic acid via cyclo-oxygenase (COX); notably, prostaglandins biosynthesis plays an important role in the nociceptive mechanism.[67,68] The acetic acid induced nociception method is sensitive to NSAIDs such as Aspirin®, diclofenac and indomethacin, narcotics, antispasmodics, calcium channel blockers, antihistamines and other central acting drugs.[58,62,69]

4.1.2. Formalin-induced nociception

Diluted formaldehyde injected subcutaneously into the paw of rodents produces a nociceptive behavior paw licking. The formalin test is believed to represent a more valid model for clinical pain.[70] This test is a very useful method not only for assessing the antinociceptive drugs but also for helping in the elucidation of the action mechanism.

The formalin test consists in a biphasic response: a short-lasting response referred as an early phase, and a longer-lasting phase, known as the late phase. The first phase, or the neurogenic phase (0-5 min), is thought to result from direct chemical activation of nociceptive afferent fibers. The second, or tonic phase (20-25 min), is characterized

Table 1. Animal models on natural products research

Test	Stimulus		Usual parameter	Specie
Tail flick	thermal, heat	fixed temperature	withdrawal latency[a]	rat/mice
Hot plate	thermal, heat	fixed temperature (48-55 °C)	withdrawal/jump latency[a]	rat/mice
Cold	thermal, cold	fixed temperature	lifting or shaking latency[a]	rat/mice
Hargreaves	thermal	infrared source	withdrawal latency[a]	rat/mice
Von Frey	mechanical	multiple fixed pressure	withdrawal threshold[b]	rat/mice
Randall-Selitto	mechanical	multiple fixed pressure	multiple fixed pressure	rat
Acetic acid	chemical	intraperitoneal injection	writhings number	rat/mice
Formalin		intraplantar injection	licking time[a]	rat/mice
Glutamate				rat/mice
Capsaicin				rat/mice

[a]Measured in seconds; [b]measured in grams.

by an inflammatory process triggered by a combination of stimuli, including inflammation of the peripheral tissues and mechanisms of central sensitization.[70-72]

The biphasic component of formalin-induced nociception reflects different underlying mechanisms: the first phase reflects centrally mediated pain with release of substance P.[57,73] The second one depends of a combination of ongoing inputs from nociceptive afferents, due to the release of excitatory amino acids, PGE_2, nitric oxide (NO), tachykinin, kinins, among other peptides and, at least in part, of central sensitization.[74,75]

Formalin activates the primary afferent sensory neurons through a specific and direct action on the transient receptor potential cation channel, member A1 (TRPA1), which is highly expressed by a subset of the C-fiber nociceptors.[76] It is generally agreed that *N*-methyl-*D*-aspartate (NMDA) receptors contribute to the persistent chemical stimulus during the late phase of central sensitization of dorsal horn neurons.[77]

It has been shown that drugs that act mainly centrally, such as opioids and narcotics, inhibit both phases of formalin-induced pain, while drugs as Aspirin®, hydrocortisone and dexamethasone, which are primarily peripherally acting, only inhibit the late phase.[78,79] Exclusive inhibition of the formalin test's second phase is a typical characteristic of cyclo-oxygenases inhibitors.[80]

4.1.3. Capsaicin-induced nociception

Capsaicin (8-methyl-*N*-vanillyl-6-noneamide), the pungent active ingredient of hot chili peppers, produces painful sensations upon cutaneous application by activating transient receptor potential vanilloid receptor-1 (TRPV-1), located on peripheral terminals of nociceptors.[81] The intradermic injection of capsaicin is regarded as a potentially predictive model of neuropathic pain in humans, because of its qualitative, mechanistic, and pharmacological similarity to neuropathic pain states.[82-84]

The capsaicin test is widely used as a model of pain in mice,[85] rats[86] and humans.[87] The subcutaneous (s.c.) injection of capsaicin into the hind paw of mice produces a short-lasting paw-licking/biting response.[88] The acute nociceptive response (flinching, licking and biting of the hind paw) occurs immediately following an intraplantar capsaicin injection and persists for about 5 min. The activation of primary afferents nociceptors by capsaicin causes the release of nociceptive transmitters, substance P and glutamate from the dorsal spinal cord *in vivo* and *in vitro*.[89,90]

It is believed that capsaicin activates a non-selective ionotropic channel in the C-fiber of nociceptive afferents through VRTP1 receptors.[91-93] Furthermore, some studies attribute to capsaicin the release of neuropeptides, excitatory amino acids such as glutamate and aspartate, nitric oxide and pro-inflammatory mediators in the periphery and the transmission of nociceptive information to the spinal cord.[94,95]

4.1.4. Glutamate-induced nociception

Glutamate is the major excitatory amino acid neurotransmitter present in the central nervous system, where it participates in a great diversity of biological functions, such as learning, memory, neurodegenerative diseases and neuronal death.[96]

The intraplantar injection of glutamate into the mouse hind paw produces nociceptive-like behaviors of rapid onset and short duration (about 15 min).[85] Accumulating evidence now suggests that there is an excess of excitatory amino acids, mainly glutamate, following injury at the spinal cord or following certain inflammatory process, suggesting that excitatory amino acids might play a relevant role in sensory transmission.[97-99]

The nociceptive response induced by glutamate is primarily mediated by the release of neuropeptides from sensory fibers, namely neurokinins and kinins.[96] In addition, glutamate is found in sensory C-fibers where it is believed to play a role in the transmission of nociceptive mechanisms at the spinal cord.[100]

The nociceptive response caused by glutamate involves peripheral, spinal and supraspinal sites of action. It has been reported that the glutamate injection stimulates marked nociceptive reactions, that are mediated by neuropeptides (like SP) liberated from sensory fibers. Besides, the activation of glutamate receptors like α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), kainate and NMDA receptors, play an important role modulating this nociceptive response[96,101,102] by stimulating the production of a sort of intracellular second messengers, including NO.[103]

There is large evidence that substances that are capable of blocking ionotropic and metabotropic glutamate receptors exhibit pronounced antinociceptive and analgesic effects in several mammalian species, including humans.[104,105]

4.2. Thermal methods

4.2.1. Tail flick

The tail flick is one of the oldest nociceptive tests. The measured parameter is the latency, in seconds, for tail flick reflex following tail exposure to a heat stimulus. The stimulus may be applied by dipping the tail tip into a bath at a controlled temperature (55 °C) or by an infrared heat beam. The apparatus allows an automated detection of the tail flick and measuring of its latency. The tail flick is a spinal reflex, but it is subject to supraspinal influences that

can affect the reflex.[106] This test is highly sensitive to opiate drugs[57] and, according to Grumbach,[107] the effectiveness of analgesic agents in this pain model is highly correlated with relief of human pain.

4.2.2. Hot plate

The hot plate is a classic test in the field. The test consists in placing a rodent on an enclosed hot plate and measuring the latency to lick a hind paw or jump out of the enclosure.[108] The temperature is often set at 52 or 55 °C and the set up allows observing baseline latencies between 5 and 10 s for paw licking. The temperature is 10-15 °C higher than the response threshold of heat nociceptors, which reflects the time required for skin temperature to increase until detection of the nociceptive stimulus, and the delay to provoke the withdrawal response.[109]

The advantages of the hot plate test are that it is objective, quantifiable, can be administered repeatedly without causing inflammation, and assesses supraspinally-organized responses to a noxious stimulus. Although, good correspondence between drugs that produce antinociception on this test and drugs used clinically to treat pain were observed.[110]

Despite they are suitable for measuring the effects of opioid analgesics, tests based on the use of thermal stimuli, such as the hot plate and tail flick, are not sensitive to the analgesic effects of nonsteroidal anti-inflammatory agents.[57,110]

4.3. Mechanical methods

4.3.1. Von Frey

Since von Frey invented his "hairs" in the 1890s, they have been used countless times in sensory testing and there is a vast literature in that subject.[111] The von Frey is a mechanical test that involves the application of a calibrated and graduated force to a sensory field by using filaments (the hairs); the assessed force is that at the point when the von Frey hair bends. Von Frey hairs is a subjective test, once the patient under evaluation needs to report the sensation. In animal experiments, the end point is usually a more objective parameter such as the discharge of a neuron.[112]

4.3.2. Randall Selitto

In this mechanical test, the effectiveness of antinociceptive drugs is accessed by observing the response thresholds of the animal to a gradually increasing mechanical pressure on an inflamed paw.[113] This method is somewhat better suited for the detection of such thresholds than the von Frey filaments, because it avoids the manual application of the force and, thus, provides a better consistency of stimuli.[57]

5. Antinociceptive Effect of Essential Oils

Plants are used worldwide for the treatment of diseases and novel drugs continue to be developed from plants. The number of species of plants used in traditional medicine overcomes 20,000, making them a potential source for prospecting new drugs.[114]

In this context, EOs have been received much attention since they present many biological activities, like antioxidant, antibacterial, antidepressant and antinociceptive ones.[12-20,115] The EOs and the respective nociception model used to determine their antinociceptive activity that are discussed in this work are summarized on Table 2. The EOs are arranged according to the botanical family of the plant they were obtained and in an alphabetical order (Table 2, column 1).

Table 2. Models used to evaluate the antinociceptive effect of EOs

Plant essential oils	Performed test	Route of administration	Tested dose / (mg kg^{-1})	Reference
Anacardiaceae				
Schinus terebinthifolius Raddi	SNI[a] animals mechanical sensitivity cold hyperalgesia	oral	10-100	116
Annonaceae				
Duguetia lanceolata A. St.-Hil.	acetic acid formalin test (phases I and II)	intraperitoneal	1-200	117,118
Xylopia laevigata (Mart.) R. E. Fr.	acetic acid formalin test (phases I and II)	intraperitoneal	12.5-50	119
Apiaceae				
Bunium persicum (Boiss.) B. Fedtsch.	acetic acid formalin test (phases I and II)	oral	100-400[b]	120
	acetic acid opioidergic and histamine H_1 and H_2 receptors	oral	100-400[b]	121

Table 2. Models used to evaluate the antinociceptive effect of EOs (cont.)

Plant essential oils	Performed test	Route of administration	Tested dose / (mg kg^{-1})	Reference
Carum copticum (L.) Benth. & Hook. f. ex C. B. Clarke	formalin test (phases I and II)	intraperitoneal	20	122
Cuminum cyminum L.	formalin test (phases I and II) tail flick	intraperitoneal	0.0125-2[c]	123
Distichoselinum tenuifolium (Lag.) F. García Mart. & Silvestre	acetic acid hot plate formalin test (phases I and II)	oral	25-75	124
Heracleum persicum Desf. ex Fisch., C. A. Mey. & Avé-Lall.	acetic acid formalin test (phase II)	oral	50-100	125
Pimpinella anisum L.	tail flick formalin test (phases I and II)	intraperitoneal	125-250	126
Asteraceae				
Achillea aleppica DC.	4-benzoquinona	intraperitonal	200	127
Ageratum fastigiatum (Gardner) R. M. King & H. Rob.	acetic acid hot plate formalin test (phases I and II)	intraperitonal	100-200	128
Artemisia absinthium L.	acetic acid formalin test hot plate	intraperitonal	2-8	129
Artemisia dracunculus L.	acetic acid formalin test hot plate	intraperitonal	10-300	130
Vanillosmopsis arborea (Gardner) Baker	mustard model visceral nociception	intraperitonal	5-50	131
	acetic acid formalin test (phase I and II)	intraperitonal	5-50	131,132
Burseraceae				
Protium heptaphyllum (Aubl.) Marchand	formalin test (phases I and II) hot plate capsaicin tail flick	oral	50-100	133
Cyperaceae				
Cyperus esculentus L.	formalin test (phases I and II)	oral	250-500	134
Cyperus rotundus L.	formalin test (phases I and II)	oral	250-500	134
Remirea maritima Aubl.	acetic acid formalin test (phases I and II)	oral	50-200	135
Euphorbiaceae				
Croton adamantinus Müll. Arg.	acetic acid formalin test	oral	10-100	136
Croton cordiifolius Baill.	acetic acid formalin test (phases I and II) glutamate capsaicin evaluation of opioid involvement	intraperitoneal	50-100	137
Croton nepetaefolius Baill.	acetic acid hot plate formalin test (phases I and II) capsaicin	oral	30-300	138
Croton sonderianus Müll. Arg.	acetic acid capsaicin formalin test (phases I and II) opioid system potassium channels	oral	50-200	69
Lamiaceae				
Hyptis pectinata (L.) Poit.	acetic acid hot plate opioid mechanism	intraperitoneal	10-100	139,140
Lavandula angustifolia Mill.	acetic acid formalin test (phase I and II)	oral	50 and 200	141

Table 2. Models used to evaluate the antinociceptive effect of EOs (cont.)

Plant essential oils	Performed test	Route of administration	Tested dose / (mg kg^{-1})	Reference
Lavandula hybrida Balb. ex Ging.	acetic acid hot plate opioid mechanism cholinergic system	oral	100	142
Melissa officinalis L.	formalin test (phases I and II)	oral	0.01, 0.02 and 0.04	143
Mentha × *villosa* Huds.	acetic acid formalin test (phase II)	oral	100-200	144
Nepeta cataria L.	tail immersion acetic acid	intraperitoneal	0.0005 and 0.001[c]	145
Nepeta crispa Willd.	tail flick formalin test (phases I and II)	intraperitoneal	30-200	146
Nepeta pogonosperma Jamzad & Assadi	tail flick formalin test (phases I and II)	intraperitoneal	50-200	147
	acetic acid hot plate opioid system formalin test (phase I and II)	subcutaneous	50-200	148
Ocimum basilicum L.	formalin test (phase I and II) capsaicin glutamate	intraperitoneal	50-200	149
Ocimum gratissimum L.	acetic acid formalin test	oral	30-300	150
	hot plate formalin test (phase I and II)	oral	10-40	151
Ocimum micranthum Willd.	acetic acid formalin test (phase I and II)	oral	15-100	152
	acetic acid formalin test (phase II) via NO	oral	1-10	153
	PFIR (pain-induced functional impairment model) opioid and serotoninergic systems	oral	50-200	154
Rosmarinus officinalis L.	acetic acid hot plate	oral	70-500	155
	acetic acid formalin test (phases I and II) hot plate	oral	10-300	156
Satureja hortensis L.	formalin test (phases I and II) acetic acid opioid and adenosinergic system	oral	50-200	157
	acetic acid formalin test (phase II)	intraperitoneal	100-400[b]	158
Teucrium polium L.	acetic acid	intraperitoneal	9.37-150	159
	tail flick	intraperitoneal	100-200	160
Vitex agnus-castus L.	tail immersion test formalin test (phases I and II) acetic acid	subcutaneous	50-62.5	161
Vitex negundo L.	acetic acid hot plate	oral	150-250	162
Zataria multiflora Boiss.	acetic acid formalin test (phase I and II)	intraperitoneal	0.3[c]	163
Myrtaceae				
Eucalyptus camaldulensis Dehnh.	hot plate tail flick opioid system	intraperitoneal	0.3	164
Eucalyptus citriodora Hook.	acetic acid hot plate	intraperitoneal	50	165
Eucalyptus globulus Labill.	acetic acid hot plate	intraperitoneal	0.1-100	165

Table 2. Models used to evaluate the antinociceptive effect of EOs (cont.)

Plant essential oils	Performed test	Route of administration	Tested dose / (mg kg^{-1})	Reference
Eucalyptus tereticornis Sm.	acetic acid hot plate	intraperitoneal	0.1-100	165
Eugenia candolleana DC.	acetic acid formalin test (phase II)	intraperitoneal	25, 50 and 100	166
Eugenia uniflora L.	acetic acid hot plate	oral	100 and 200	21
Myrcia ovata Cambess.	acetic acid formalin test (phase II) tail flick	oral	200-300	167
Ugni myricoides (Kunth) O. Berg	carragenan-induced mechanical hypernociception complete Freund's adjuvant (CFA)	oral	5-50	168
Piperaceae				
Peperomia serpens (Sw.) Loud.	acetic acid hot plate formalin test (phases I and II)	oral	62.5-500	169
Piper aleyreanum C. DC.	formalin test opioid mechanism studies	oral	10-100	170
Poaceae				
Chrysopogon zizanioides (L.) Roberty	acetic acid formalin test (phase II) hot plate	intraperitoneal	50-100	171
Cymbopogon citratus (DC.) Stapf	hot plate acetic acid formalin test (phases I and II) opioid system	oral or intraperitoneal	5-100	172
Cymbopogon nardus (L.) Rendle	hot plate acetic acid tail flick	oral	0.5-4.0	173
Cymbopogon winterianus Jowitt	hot plate acetic acid formalin test (phases I and II)	oral	50-200	174
Ranunculaceae				
Nigella sativa L.	hot plate tail-pinch acetic acid formalin test (phase I) indirect activation of the supraspinal μ_1- and k-opioid receptor	oral	50-400	175
Rutaceae				
Choisya ternata Kunth	acetic acid hot plate	oral	3-30	176
	formalin test (phases I and II)	oral	3-30	177
Citrus bergamia Risso & Poit.	capsaicin opioid system	intraplantar	10-20	178
Citrus limon (L.) Osbeck	acetic acid opioid system	oral	50-150	179
Verbenaceae				
Lippia gracilis Schauer	acetic acid	oral	50-200	180
	acetic acid hot plate formalin test (phases I and II) via NO and cholinergic and opioid systems	oral	10-300	181
Lippia grata Schauer	formalin test (phases I and II) glutamate capsaicin	oral	6-24	182
Lippia sidoides Cham.	acetic acid hot plate	subcutaneous	100-400	183

Table 2. Models used to evaluate the antinociceptive effect of EOs (cont.)

Plant essential oils	Performed test	Route of administration	Tested dose / (mg kg^{-1})	Reference
Zingiberaceae				
Alpinia zerumbet (Pers.) B. L. Burtt & R. M. Sm.	acetic acid hot plate formalin test opioid system	oral	100-300	184
Zingiber zerumbet (L.) Roscoe ex Sm.	acetic acid capsaicin glutamate PMA (intraperitoneal) activation of *L*-arginine/NO, cGMP, protein kinase C, ATP-sensitive K^+ channel pathway	intraperitoneal and oral	50-300	185,186
	acetic acid formalin test (phase I and II) hot plate opioid system	intraperitoneal	30-300	187,188

[a]Spared nerve injury (SNI); [b]unit: μL kg^{-1}; [c]unit: mL kg^{-1}.

The Table 2 presents also the administration route and doses used in the articles discussed in this review. The structures of the major constituents of the EOs discussed in this section are presented on Figures 4-7. The compounds are arranged as monoterpenoids (Figure 4), monoterpenoids oxides (Figure 5), sesquiterpenoids (Figure 6) and sesquiterpenoids oxides (Figure 7).

EOs of *Achillea* species, knowed as yarrows (Compositae family), have been the subject of several investigations; these species are used in Turkish folk medicine. In 2006, Işçan *et al.*[127] studied the antinociceptive effect of *Achillea aleppica* DC. subsp. *aleppica* and *A. schischkinii* Sosn. aerial parts EOs in the *p*-benzoquinone-induced abdominal constriction test. The main component of both EOs was eucalyptol **1** (32.5 and 26.1%, respectively) and the EO of *A. aleppica* subsp. *aleppica* was found to contain also 6.6% of bisabolol **2** and its derivatives. The authors observed that the EO of *A. aleppica* significantly reduced the writhes induced by *p*-benzoquinone. An acute toxicity assay of the *A. aleppica* EO was realized; the animals were observed during 48 h and according to the authors, any apparent acute toxicity was observed.

Ageratum fastigiatum (Gardner) R. M. King & H. Rob is a plant well distributed in Minas Gerais State, Southestern Brazil and is popularly called "matapasto".[189,190] The EO of *A. fastigiatum* is constituted mainly by diterpenes, triterpenes[191,192] and, together with *A. conyzoides*, this plant is indicated in folk medicine as anti-inflammatory, analgesic and antimicrobial.[193,194] Del-Vechio-Vieira *et al.*[128] determined the chemical composition and performed a study about analgesic effects of the EO of *A. fastigiatum*. The major constituents of the EO are germacrene D **3**, α-humulene **4** and β-cedrene **5**. The EO inhibited the acetic acid-induced writhing and the formalin first phase and second phase.[128]

Alpinia species includes important medicinal plants that are widely distributed in tropical and sub-tropical regions and are cultivated for medicinal purposes.[195] *Alpinia zerumbet* (Pers) B. L. Burtt & R. M. Sm. (Zingiberaceae) is an aromatic plant that is widely distributed in tropical and sub-tropical regions. This plant is popularly known as "colônia" in the Northeastern of Brazil, and is used in folk medicine in the treatment of intestinal disorders and hypertension.[196] The leaves EO is rich in 4-terpineol **6** (28.1%), eucalyptol **1** (15.0%) and γ-terpinene **7** (13.7%) and it was effective in the acetic acid induced writhing test and in the hot-plate test, increasing the latency time. Besides, it was verified that the EO reduced paw licking time in both phases of the formalin test and the mechanism of action probably involves the participation of opiate receptors.[184] The authors did not report any data about the toxic effect of the EO. However, the genotoxicity of *A. zerumbet* EO was recently studied on peripheral blood leukocytes *in vitro* and *in vivo* using the alkaline single-cell gel electrophoresis test (comet assay). In the *in vitro* tests, increasing concentrations (50-500 μg mL^{-1}) of EO and methylmethanesulfonate (0.4 μmol L^{-1}) as the positive control were used. According to the results, at the higher concentration (500 μg mL^{-1}) *A. zerumbet* EO caused a significant increase in the cell DNA damage index in the *in vitro* assay.[197]

Hadi *et al.*[129] studied the chemical composition and the analgesic effect of *Artemisia absinthium* (Asteraceae family) leaves EO. The main constituents found in the EO were nerolidol **8** (49.91%), santolina triene **9** (15.58%), α-pinene **10** (6.99%) and *trans*-β-farnesene **11** (4.95%). In this study, authors used male albino mice and the acetic acid-induced writhing test, formalin and hot plate assays. The results demonstrated that the administration of EO caused an inhibition of writhings in the acetic acid

assay comparable with the reference drug (Aspirin®). The EO presented effect in the late phase of formalin test with inhibition of 91%, results similar to observed using morphine (positive control, 5 mg kg^{-1}). In the hot plate test, the EO increased the reaction time of mice after 30 min of treatment. One interesting point of the article are the data about the acute toxicity; according to the authors, this EO is safe at the effective doses, since the test of acute toxicity indicated that the EO is toxic only at higher doses.[129]

Artemisia dracunculus L. (Asteraceae family), popularly known as "tarragon", is a plant used in folk medicine for the treatment of pain and gastrointestinal disturbances.[198] The major components of the essential oil are 3,7-dimethyl-1,3,7-octatriene **12** (38.4%), α-pinene **10** (37.0%), estragole **13** (8.6%) and limonene **14** (6.3%).[199] The antinociceptive effect of leaves EO of "tarragon" was assessed in the formalin, acetic acid and hot plate tests.[130] According to the authors, "tarragon" EO demonstrated peripheral (acetic acid and formalin) and central (hot plate) antinociceptive effects. Authors also studied the involvement of the opioid system in the nociceptive response of tarragon EO, but according to them, these receptors are not involved. The acute toxicity of tarragon EO was evaluated and the LD_{50} was found to be 1250 mg kg^{-1}.

Bunium persicum (Boiss) B. Fedtsh or *Carum persicum* Boiss. is a grassy plant of Apiaceae family with the common name of "wild caraway", which grows in warm climate areas of Middle East and Central Asia.[200] In Iran, the fruits or the aerial parts of the plant have been used traditionally as anticonvulsant, antihelmintic, anti-asthma, digestant, antiflatulent, diuretic and analgesic.[201,202] In 2011, Hajhashemi *et al.*[120] described the antinociceptive and anti-inflamatory activities of *B. persicum* fruits EO using the acetic acid and formalin tests to evaluate the analgesic effect. By the gas chromatography mass spectrometry (GC-MS) analysis, the authors identified 10 compounds, with γ-terpinene **7** (46.1%), cuminaldehyde **15** (23.9%) and *p*-cymene **16** (15.9%) being the main components of the EO. The EO significantly ($p < 0.01$) reduced the acetic acid-induced writhings and the pain response of both early and late phases of the formalin test. The authors declared that the analgesic effect might be due, at least in part, to the presence of γ-terpinene **7** and *p*-cymene **16**.[120]

More recently, Zendehdel *et al.*[121] described a study on the mechanism of the antinociceptive action of *B. persicum* seeds EO in the acetic acid-induced nociception model. The authors observed that the EO inhibited the writhing in mice in a dose dependent manner and this effect was attenuated by a pre-treatment with naloxone, chloropheniramine and cimetidine. These results suggest that *B. persicum* EO-induced analgesia could be mediated via opioidergic and histamine H_1 and H_2 receptors and once again, the antinociceptive activity was attributed to the presence of *p*-cymene **16**, γ-terpinene **7** and terpenoid oxides in the EO.[121]

Hejazian[122] explored the antinociceptive activity of *Carum copticum* Benth. fruits EO. *C. copticum* is a plant of Apiaceae family and the aqueous extracts from its seeds are used in household remedies and also as a spice in food in India.[202] The main constituents of the *C. copticum* seeds EO are *p*-cymene **16** (37.3%) and thymoquinone **17** (13.7%).[122] The author used the formalin test to access the antinociceptive activity of the EO. He observed that the EO had no effect in the phase I and a significant effect in the phase II of the test, which was the same as 1 mg kg^{-1} of morphine sulphate. The presence of thymol **18** in the EO is, according the author, the possible responsible by the antinociceptive activity. Opioid receptors are not involved in the mechanism of antinociception, once naloxon, an opioid antagonist, could not reverse the analgesic effect observed in the formalin test.[122]

Radulovic *et al.*[176] investigate the composition, antinociceptive and anti-inflammatory effects of the *Choisya ternata* leaves EO and three of their components, methyl, propyl and isopropyl *N*-methylanthranilate **19**. *C. ternata*, popularly known as "Mexican orange", has highly fragrant flowers and is a popular horticultural shrub. The infusion of leaves of *C. ternata* is used in Mexico as an antispasmodic and possess "simulative properties".[203] The major components of the leaves EO are sabinene **20** (ca. 30%), 4-terpineol **6** (10%), myrcene **21** (7.8-8.3%), β-phellandrene **22** (5.4-6.6%) and γ-terpinene **7** (4.2-4.7%). Isopropyl *N*-methylanthranilate **19** and the methyl and propyl esters analogs were synthesized and evaluated, with the *C. ternata* EO, for their antinociceptive effects. The authors observed that the compound **19** and the EO produced dose-related and significant antinociception in chemical (acetic acid-induced visceral pain) and thermal (hot-plate test) models of nociception in mice.[176] The *C. ternata* EO was also evaluated in the two phases of the formalin test.[177] According to the authors, these results indicate that EO could be acting through inhibition of the formation and/or liberation of the mediators in the paw tissue or by direct blockage of the receptors.[176] Among the individual compounds, isopropyl *N*-methylanthranilate was the more active, while methyl *N*-methylanthranilate presented the lower activity; however, it was still better than acetylsalicylic acid (200 mg kg^{-1}) in the acetic acid-induced test and comparable to morphine (5 mg kg^{-1}) in the hot plate test.[176]

Chrysopogon zizanioides L. Roberty (Poaceae family), popularly known as "vetiver" and "grama-das-índias", is

used in the folk medicine of Brazil as analgesic and sedative. Lima *et al.*[171] studied the chemical composition and the antinociceptive properties of the EO of roots of *C. zizanoides* at doses of 50 and 100 mg kg^{-1}. The major compounds found in the EO were khusimol **23** (19.6%), *E*-isovalencenol **24** (13.2%), α-vetivone **25** (5.2%), vetiselinenol **26** (5.1%) and α-cadinol **27** (5.0%). The EO presented effect in the acetic acid-induced writhing test similarly to the positive control, morphine (3 mg kg^{-1}), but contrasting to morphine, the opioid antagonist naloxone did not reverse the effect of the EO. In the formalin test, the EO was effective in reducing the licking response only in the second phase (inflammatory response) and in the hot plate it did not present any effect, indicating that a peripheral antinociceptive effect is involved. No data about the toxicological profile of *C. zizanoides* EO was found on literature.

Citrus bergamia or *Citrus aurantium* ssp. *bergamia* (Rutaceae family), popularly known as "bergamot", is one of the most common and familiar plants worldwide. In 2011, Sakurada *et al.*[178] studied the antinociceptive action of the intraplantar administration of fruits of "bergamot" EO, linalool **28** and linalyl acetate **29**, which are the main components of the EO in the capsaicin model and they observed that the three tested substances reduced significantly the nociceptive response. In addition, the authors showed that the antinociceptive response of the "bergamot" EO and linalool **28** is mediated by the modulation of peripheral opioids receptors.

Citrus limon L. Osbeck (Rutaceae family) is a plant from the north and northeast of Brazil, known by the popular name of "limoeiro".[204] Infusions prepared with the aerial parts (leaves) of *C. limon* are used in folk medicine for the treatment of obesity, diabetes, blood lipid lowering, cardiovascular diseases and brain disorders.[205,206] The antinociceptive effect of the EO of aerial parts of *C. limon* was evaluated by the acetic acid-induced writhings, formalin and hot plate assays and the results indicate that the EO has peripheral and central antinociceptive effects.[179] The main components of the leaves EO are limonene **14** (52.8%), geranyl acetate **30** (9.9%) and limonene oxide **31** (7.1%). The EO reduced writhings and lickings nociceptive responses in the acetic acid and first and second phases of formalin tests. The EO increased the latency time in the hot plate test. Furthermore, the pre-treatment with naloxone caused an antagonistic effect on antinociceptive effect of EO of *C. limon*; thus, opioid receptors are involved.[146] The authors did not report any data about toxicological studies of *C. limon* EO. Toxicological informations of plants are important because many natural products exert significant redox activities, which are related to their therapeutic properties, even a possible toxic effect.[63]

Ximenes *et al.*[136] studied the chemical compositon and the antinociceptive activity of the EO of *Croton adamantinus* Müll. Arg. (Euphorbiaceae family). This plant is popularly known as "carrasco" and has been used in the semi-arid region of Northeast Brazil to treat inflammation, skin and gastric disorders.[138,207] According to the authors,[136] the main components of "carrasco" leaves EO are methyleugenol **32** (14.8%) and eucalyptol **1** (13.7%). It was observed a mild antinociceptive effect in the early phase of formalin test and an activity higher than morphine (positive control) at the second phase. In the assay of abdominal contortions induced by acetic acid, the EO was more effective than indomethacin in decreasing the number of abdominal contortions. The authors also reported the results on the lethal dose of EO; according to them, a limit test of 1000 mg kg^{-1} was performed to estimate the toxicity of the EO and did not result in any death or changes in the gross necropsy. This is a complementary and important result to the antinociceptive data, once it demonstrated that the effective doses of *C. adamanthinus* did not present acute toxic potential.[136]

The shrub *Croton cordiifolius* Baill., Euphorbiaceae family, known as "quebra-faca" is one of the about 350 species of the *Croton* genus that are found in Brazil.[208] The plant is popularly used in the northeast of Brazil to treat medical conditions, such as general inflammation, pain, and gastrointestinal disturbances.[209] In 2015, Nogueira *et al.*[137] described the chemical composition and the antinociceptive activity of *C. cordiifolius* EO in mice. Eucalyptol **1** (25.09%) and α-phellandrene **33** (15.43%) are the major constituents, according to the GC-MS analysis. The antinociceptive activity was evaluated using the acetic acid, formalin, capsaicin and glutamate tests. The authors observed that the *C. cordiifolius* EO reduced the number of writhing responses induced by acetic acid and decreased the licking times in both phases of the formalin test. The EO was also effective in the glutamate test and no effect was observed in the capsaicin test. According to the authors, the antinociceptive effect of *C. cordiifolius* EO could involve the inhibition of the glutamatergic system, once naloxone, an opioid antagonist, did not affect its antinociceptive effect in the writhing test.[137]

Croton nepetaefolius Baill. (Euphorbiaceae family), popularly called "marmeleiro vermelho", is an aromatic plant native of the Northeast of Brazil, where it is extensively used in folk medicine as a sedative, orexigen and antispasmodic agent.[210] The leaves EO was effective in acetic acid-induced writhing test; in the hot plate test, the EO significantly increased the latency.[138] Also, in the formalin test, EO reduced paw licking in both phases with the mechanisms remaining to be

elucidated. The main constituents found in this EO were eucalyptol **1** (31.5%), (*E*)-caryophyllene **34** (17.2%) and methyleugenol **32** (10.3%). According to Fontenelle *et al.*[211] the intra-peritoneal administration of different doses of *C. nepetifolius* EO induced no remarkable alterations in the behavior pattern of mice, such as: trembles, convulsions, dyspnea and ataxia. After the intraperitoneal administration, the calculated LD_{50} was 163.8 mg kg^{-1}.

The species *Croton sonderianus* Müll. Arg. (Euphorbiaceae) is a widespread shrub largely grown in northeastern parts of Brazil, popularly known as "marmeleiro preto". This plant is used as fire wood due to the high content of essential oil that may vary from 0.5 to 1.5%. Leaves and barks are used as an infusion or simply chewed as a folk medicine for the treatment of gastrointestinal disturbances, rheumatism and headache.[212] The EO of *C. sonderianus* leaves is rich in monoterpenes and sesquiterpenes, such as *cis*-calamenene **35** (10.9%), bicyclogermacrene **36** (10.2%), guaiazulene **37** (8.3%), spathulenol **38** (7.2%), (*E*)-caryophyllene **34** (6.9%), β-phellandrene **22** (6.2%), α-guaiene **39** (6.6%), eucalyptol **1** (4.2%) and others. When the EO was given orally, it produced significant inhibitions on chemical nociception induced by acetic acid, formalin and capsaicin injections in mice. The antinociception probably involves glibenclamide ATP-sensitive K^+ channels, according to Santos *et al.*[69] Doses employed in this study were considered non-toxic once the EO at doses up to 3.0 g kg^{-1} did not cause any behavioral impairment or overt toxicity in mice (unpublished observations).

The fruits of *Cuminum cyminum* Linn., a wild grassy plant of Umbelliferae family, is used in Iranian folk medicine to treat diarrhea, toothache and epilepsy.[213] The major constituents of *C. cyminum* EO are γ-terpinene **7** (29.1%), *p*-cymene **16** (25.2%), β-pinene **40** (19.9%) and cuminaldehyde **15** (18.7%).[214] Sayyah *et al.*[123] studied the effect of the *C. cyminum* EO in two models of nociception, formalin and tail flick tests. The pretreatment with the EO significantly reduced the formalin-induced nociception for 1 h; the effect being more pronounced in the late phase, while no effect was observed on tail flick response. The LD_{50} for the *C. cyminum* EO used in the study was determined as 0.59 (0.52-0.68) mL kg^{-1}.[123]

Cymbopogon citratus (DC.) Stapf (Poaceae) is an herb known worldwide as lemongrass and the EO of its leaves is source of citral **41** (ranging from 47-86% in weight). Viana *et al.*[172] described the antinociceptive activity of leaves EO of *C. citratus*, West Indian type, which increased the reaction time in the hot plate test. At lower doses the EO inhibited the abdominal contraction. On the other hand, in the formalin test, the administration via i.p. was more effective on the inhibition of the licking time at the second phase than the oral administration at the same doses. Viana's work did not present data about the toxicological profile of

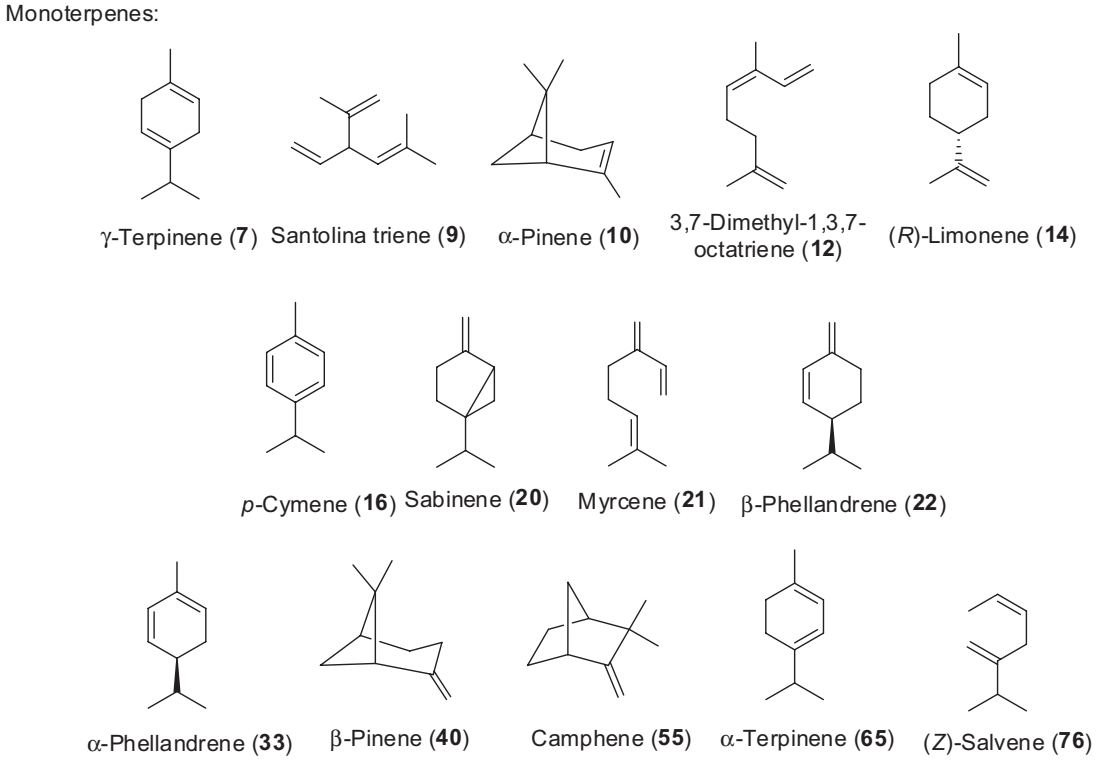

Figure 4. Structures of major constituents of EOs-monoterpenes.

Monoterpenes oxides:

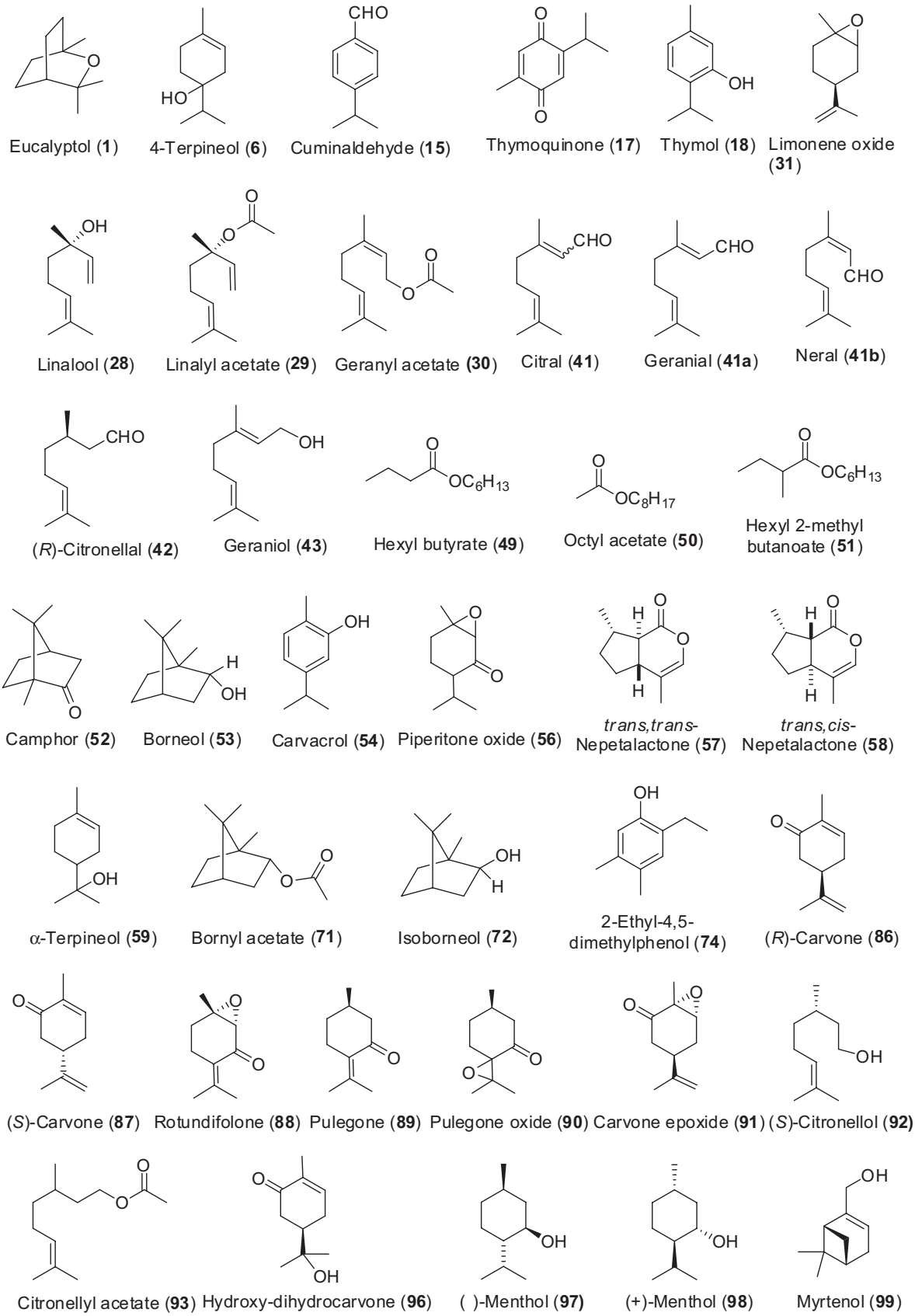

Figure 5. Structures of major constituents of EOs-monoterpenes oxides.

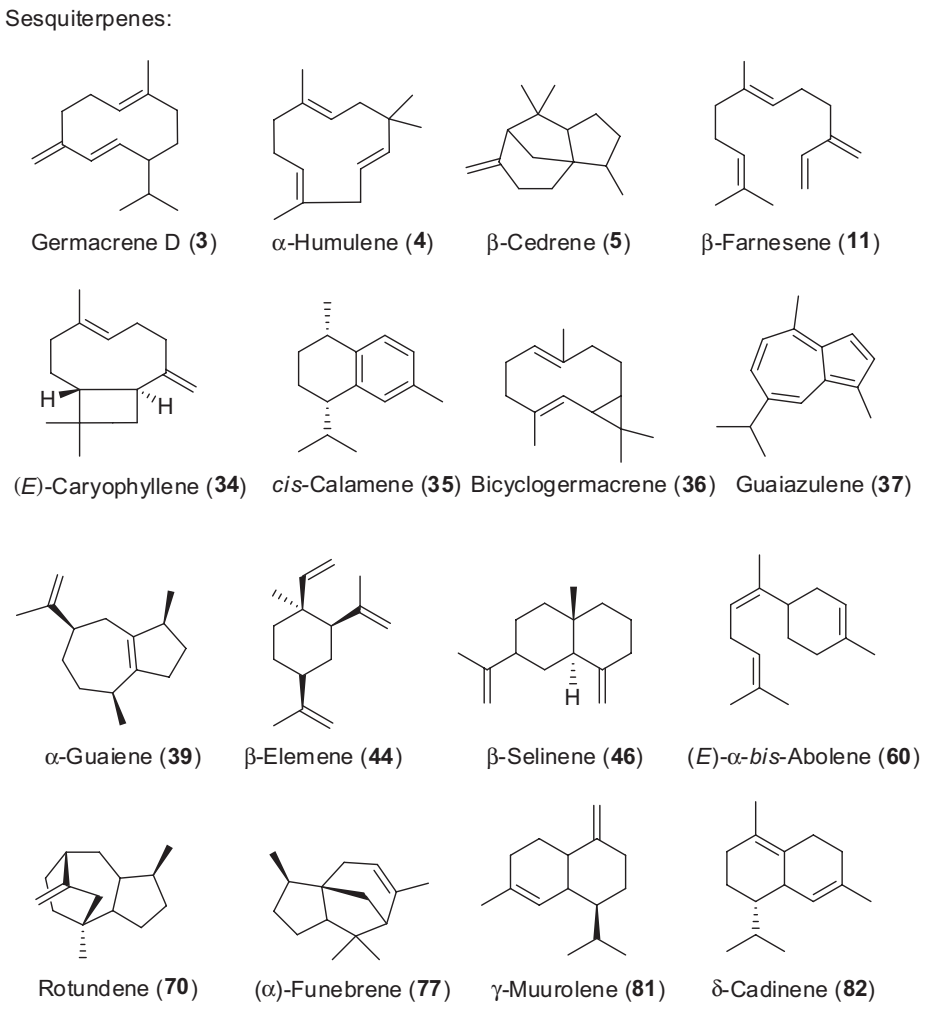

Figure 6. Structures of major constituents of EOs-sesquiterpenes.

lemongrass EO; however, according to Fandohan *et al.*[215] it did not show any acute (1 day) and sub-acute (14 days) toxicity at doses of 5-1500 mg kg^{-1} body weight, but at higher doses, 2000 and 3000 mg kg^{-1}, abnormalities were observed. The reported LD_{50} was > 3500 mg kg^{-1} body weight.

Cymbopogon nardus (L.) Rendle, is a widespread plant used in culinary, perfumery and in popular medicine in the treatment of rheumatism, fever, menstrual and digestive problems.[216] The *C. nardus* EO is commercially used as a mosquito repellent, and several pharmacological properties have been attributed to the EO and its major constituent, (*R*)-citronellal **37**, including antifungal,[217] antibacterial[218] and anti-cancer activities.[219] Abena *et al.*[173] described in 2007 a comparative study between the chemical composition and the antinociceptive activity of *C. nardus* EOs of plants cultived in Congo and Benin. The major constituents in both EOs are citronellal **42** (37.5 and 41.3%) and geraniol **43** (29.4 and 23.4%) respectively, among other more than 20 identified compounds. The three antinociceptive tests used (acetic acid, hot plate and tail flick) show that the two EOs are actives. The effect in the acetic acid-induced test was similar for both EOs. However, the EO from Benin was more effective in the hot plate test, while the Congolese EO was more active in the tail flick model.[173]

Cymbopogon winterianus Jowitt is an aromatic grass cultivated in India and Brazil that is traditionally used as an insect repellent.[220] The main components of *C. winterianus* leaf EO are geraniol **43** (36%) and citronellal **42** (42.7%) and besides a repellent, it has antimycotic and acaricidal activities.[221] The infusion of the leaf and unguent have been used in northeastern Brazil for the treatment of pain and anxiety.[174] Leite *et al.*[174] studied the antinociceptive activity of *C. winterianus* leaf EO in the acetic acid-induced writhing, formalin (phases I and II) and in the hot plate models. The authors observed that the EO reduced the number of writhings in the acetic acid and paw licking times in the first (0-5 min) and second (15-30 min) phases of the formalin tests, respectively. No effect was observed, however, in the hot-plate test at all the tested doses.[174]

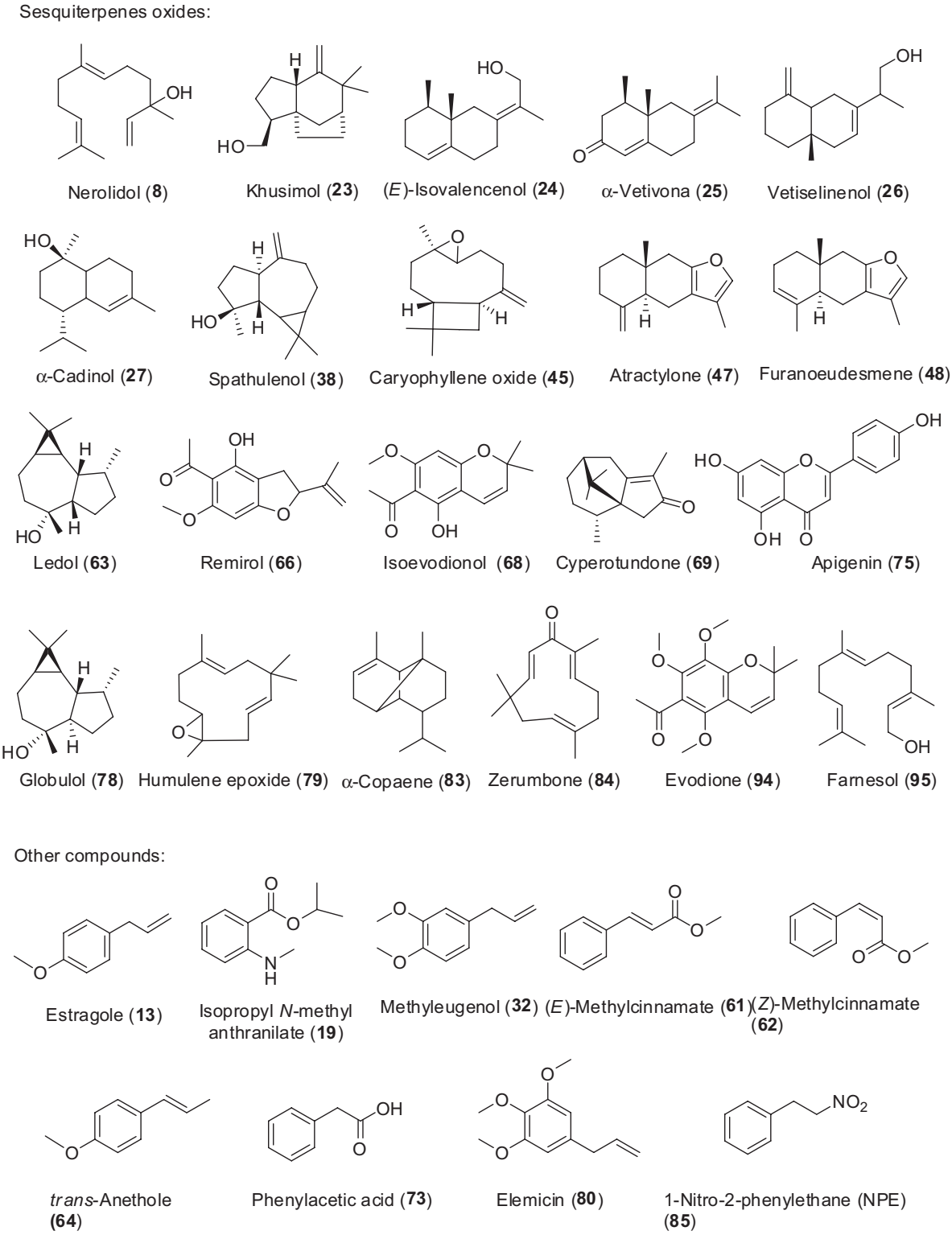

Figure 7. Structures of major constituents of EOs-sesquiterpenes oxides and other compounds.

Cyperus esculentus L. and *C. rotundus* L., are sedges of the family of Cyperaceae, which grow naturally in tropical, subtropical and temperate region and are widely distributed in the Mediterranean area. *C. esculentus* and *C. rotundus* are used for the treatment of spasms stomach disorder and as an anti-inflammatory in traditional medicine of India, China and Japan.[222] Biradar *et al.*[134] evaluated the antinociceptive effect of *C. esculentus* and *C. rotundus* EOs in the formalin test and verified that they are equaly active in both phases; however, a slightly superior effect was

observed in the second, inflammatory phase of the formalin test. Triterpenoids, flavonoids, proteins and saponins were described as the major active constituents; however, there was no information about the main volatile compounds of the EOs. A study of the acute toxicity was performed using albine rats and no mortality was observed at the dose of 5000 mg kg^{-1} after 24 h.[134]

Distichoselinum tenuifolium (Lag.) F. García Mart. & Silvestre is a plant widely used in traditional medicine in Portugal for the treatment of contact dermatitis and skin infections.[223] Goés *et al.*[124] studied the chemical composition and the antinociceptive effect of *D. tenuifolium* ripe umbels EO in rats using the acetic acid, hot plate and formalin nociception tests. The authors found myrcene **21** (85.0%) as the major constituent of the EO. The treatment with *D. tenuifolium* EO decreased the writhing induced by acetic acid. The EO administration reduced the licking time at both first and second phases of the formalin test and it was more effective then indomethacin, used as the control.[124]

Duguetia lanceolata A. St.-Hil (Annonaceae) popularly known as "pindaíba", "beribá" or "pinhão", is a perennial species distributed in several regions of Brazil.[224] In folk medicine, this plant has been used as an anti-inflammatory, cicatrizing and antimicrobial agent.[224] The EO of barks of *D. lanceolata* is rich in β-elemene **44**, caryophyllene oxide **45** and β-selinene **46** and it has shown antinociceptive effect in rat and the mechanism probably involves central and peripheral actions. Sousa *et al.*[117] described a significant reducing in the number of writhing and the lick of the paw (in the first and second phases). Recent studies of the same group[118] demonstrated the toxic effect of *D. lanceolata* EO in *Artemia salina* Leach (Brine Shrimp Lethality Bioassay), presenting a lethal concentration (LC_{50}) of 49.0 μg mL^{-1}.

Silva *et al.*[165] studied the antinociceptive and anti-inflamatory effects of the EO of three different *Eucalyptus* species: *E. citriodora* Hook, *E. globulus* and *E. tereticornis*. *Eucalyptus* are traditionally used as analgesic, anti-inflammatory and antipyretic remedies for the symptoms of respiratory infections, such as cold, flu, and sinus congestion.[225] Besides, the *Eucalyptus* EOs are also widely used in cosmetics, food and pharmaceutical industries.[226] *E. citriodora* EO has citronellal **42** as the major component (up to 60%), whereas *E. globulus* and *E. tereticornis* EOs contain 60-90% of the monoterpenoid eucalyptol **1**. The authors observed that the EOs decreased the number of acetic acid-induced writhes in mice (43-73%) compared to the animals that received vehicle only. The effect was dose-dependent for the *E. tereticornis* EO only and the *E. citriodora* EO was the most effective at the higher dose. Similarly, all the EOs were effective in the hot plate test, significantly extending the reaction time to after 30 min of treatment (i.p.), as compared to the corresponding control groups.[165]

Eugenia candolleana DC. (Myrtaceae) is commonly known as "murta", a rare *Eugenia* from the Northwestern Brazilian rainforests, bearing a small, dark-purple ripening fruit with a mildly sweet and firm pulp.[166] The infusion of the fresh leaves has been used in folk medicine for the treatment of pain and fever. The leaves EO of *E. candolleana* reduced the number of writhes significantly in a writhing test as well as the number of paw licks during the second phase of formalin test after i.p. injection. No information about the chemical composition of the *E. candolleana* used in the study was found, except that monoterpenoids and sesquiterpenoids are predominant. According the authors, the antinociceptive activity of the EO probably is mediated via a peripheral pathway.[166]

Eugenia uniflora L. (Myrtaceae) is known as "Brazilian cherry tree" (or "pitangueira"). Their leaves are used in infusions or decoctions in popular medicine to treat inflammations, against rheumatic pains and fever, as hypoglycemiant, diuretic and to avoid stomach problems.[227] The antinocicpetive effect of the leaves EO and their isolated terpenoids (a mixture of atractylone **47** and 3-furanoeudesmene **48** in a 2:1 ratio) were evaluated by Amorim *et al.*[21] The EO and their main constituents given orally, 1 h before the noxious stimulus in mice, significantly inhibited the acetic acid-induced abdominal constrictions and increased the latency time in the hot plate test. Victoria *et al.*[228] studied the acute toxicity of *E. uniflora* EO in mice and data demonstrated that the LD_{50} is higher than 200 mg kg^{-1}, since at this concentration any signal of toxicity was observed.

Fruits of *Heracleum persicum* Desf. (Apiaceae) are widely used as spices and the young stems are also used for making pickles. In Iranian folk medicine, fruits of *H. persicum* are used as a carminative and pain killer herbal drug.[229] The main constituents of *H. persicum* fruits EO are hexyl butyrate **49** (56.5%), octyl acetate **50** (16.5%) and hexyl 2-methylbutanoate **51** (5.2%) and it was evaluated for their antinociceptive action by the acetic acid-induced writhings and formalin pain models.[125] The authors observed that the oral administration of the EO reduced the number of writhings induced by acetic acid while by intra-peritoneal injection the EO was not effective. The EO also did not reduce the licking response induced by the intraplantar injection of formalin in any of used concentrations. Manzoomi *et al.*[230] studied the possible toxic effect of *H. persicum* EO and found a LC_{50} value of 337.58 μL L^{-1}.

The gender *Hyptis* (Lamiaceae family) consists of approximately 400 species distributed from the South

of the United States to Argentina[231] and exhibits a major morphological diversity in the Brazilian Cerrado.[232] *Hyptis pectinata* L. Poit is an aromatic shrub largely grown in the northeastern parts of Brazil and its leaves EO is rich in (*E*)-caryophyllene **34** (40.9%) and caryophyllene oxide **45** (38.0%). Arrigoni-Blank *et al.*[139] studied the chemical composition and antinociceptive activity of leaves EO of six genotypes of *H. pectinata*. The authors observed that all genotypes had variation in their chemical composition and all of them presented antinociceptive effect in two models using mice (hot plate and acetic acid-induced writhing). According to the authors, the antinociceptive action involves the participation of opioid receptors. In other study, Raymundo *et al.*[140] demonstrated that the antinociceptive effects of the *H. pectinata* are mediated by opioid and cholinergic receptors in mice. The EO also increased baseline measurements and the area under the curve in measurements on the hot plate model and was effective on second phase of formalin test. The acute toxicity of this EO was studied in male and female mice, by the oral administration of a single dose of 500 mg kg^{-1} of *H. pectinata* EO and, according to the presented data, any signal of toxicity was observed after 14 days.[140]

The antinociceptive effect of the EO of leaves of *Laurus nobilis* L. (Lauraceae), an evergreen and widely distributed plant in the Mediterranean area and Europe, was evaluated.[233] Folk remedies in different countries use this plant to treat numerous diseases. In Iranian traditional medicine, the leaves have been used topically for relieving rheumatic pains.[234] The main components of leaf EO of *L. nobilis* are eucalyptol **1** (44.1%), eugenol **32** (15.16%) and sabinene **20** (6.2%).[235] The pre-treatment of mice with the EO induced an increase in the tail flick latency and significantly reduced the nociception in the second phase of formalin test. According to the authors, the EO up to a dose of 0.3 mg kg^{-1} presented no lethality. However, above this dose some deaths were observed.[233]

Lavandula angustifolia Mill. (Lamiaceae), commonly known in Iran as "Ostokhoddous", is a widely distributed aromatic herb.[236] This plant is well known among people as a powerful aromatic and medicinal herb and it is used in traditional and folk medicines of different parts of world for the treatment of several gastrointestinal, nervous and rheumatic disorders.[237,238] Mice pre-treated with leaves EO of *L. angustifolia* by oral route presented reduced writhes. The same doses were effective in the first phase of formalin test and all of them were effective in the second phase of the test. The EO of *L. angustifolia* is rich in eucalyptol **1**, camphor **52** and borneol **53**.[239] Evandri *et al.*[141] studied the possible mutagenic effect of *L. angustifolia* leaves EO in the bacterial mutagenicity test (main test) using the plate incorporation method. The results demonstrated that EO did not increase the number of revertants in two *Salmonella* strains (*S. typhimurium* strain TA98 and *S. typhimurium* strain TA100) and in the *E. coli* WP2 uvrA strain.[141] Studies about the mutagenic effects of EOs are very important considering the increasing use and their frequent presence in products for personal care and medicines.

EO of *Lavandula hybrida* E. Rev. ex Briq. leaves had linalool **28** and linalyl acetate **29** as major constituents and, when orally administered or inhaled for 60 min, it reduced the acetic acid-writhing response; in the hot plate test, the involvement of opioid as well as cholinergic pathways was identified.[142] On the other hand, no analgesic results were obtained from inhalation of linalool and linalyl acetate in the hot plate test. Only linalool (by oral route) was effective in the acetic acid test. The authors also studied the acute gastrointestinal ulcerogenicity of an oral treatment (100 mg kg^{-1}) with EO and the results demonstrated that any damage on gastric mucosa was observed.[142]

Lippia gracilis Schauer (Verbenaceae) is known in Brazil as "alecrim-da-chapada" and its EO is highlighted because it presents high contents of monoterpenes, with carvacrol **54** (up 50%), *p*-cymene **16** (ca. 11%) and γ-terpinene **7** (8%) being the main components.[240] Several communities in Northeastern Brazil use *L. gracilis* to treat cough, bronchitis, nasal congestion, and headache.[241] The EO is known to possess antimicrobial activity and is used externally to treat cutaneous diseases, burns, wounds and ulcers.[242] Mendes *et al.*[180] analyzed the antinociceptive effect of the EO of *L. gracilis* leaves. The antinociceptive effect was evaluated by the acetic acid-induced writhing test, and the *L. gracilis* EO was effective at the tested doses. In addition, Guilhon *et al.*[181] studied the antinociceptive action as well as the mechanisms involved in this effect. The authors used chemical and thermal methods to determine the antinociceptive effect, like acetic-acid, formalin and hot plate tests. Increasing doses of EO decreased significantly the writhing numbers in the acetic acid assay. The peripheral antinociceptive effect was confirmed by the formalin test, with the EO presenting effect only in the second phase (10-100 mg kg^{-1}), demonstrating the possible anti-inflammatory effect of the EO. The central effect was measured in the hot plate assay and the *L. gracilis* EO increased significantly the latency in mice at the same doses. Additionally, the mechanism of antinociceptive effect was assessed by the involvement of opioid, cholinergic and nitric oxide (NO) systems, all related to the central antinociceptive effect (hot plate assay), and cholinergic and nitric oxide (NO) systems, which are related with peripheral antinociception (acetic acid and formalin).[181] The acute toxicity of EO was studied

by the authors using different oral doses (2, 3 and 4 g kg^{-1}) in a group of male and female mice and no signs of intoxication, including convulsion, death, or gastric ulcer, were observed even after 5 days of a single dose. Lethality was not observed at the highest dose of EO, indicating that it was nearly nontoxic in mice up to this dose and that it was not possible to determine the LD_{50}.

Another species of the genus *Lippia*, *L. grata* Schauer is an endemic bush of northeastern Brazil. The leaf EO of *L. grata* presented antispasmodic activitiy, which was attributed to the presence of carvacrol **54** and thymol **18**.[243] In 2014, Siqueira-Lima *et al.*[182] described the antinociceptive effect of β-CD complex of *L. grata* leaf EO in orofacial nociception in mice. It was observed that oral treatment with β-CD/EO reduced the nociception in both phases of the formalin test and also protected against nociception induced by capsaicin and glutamate. In contrast to previously reported, camphene **55** (11.3%), camphor **52** (27.2%), (*E*)-caryophyllene **34** (11.6%), bicyclogermacrene **36** (9.4%) and borneol **53** (6.0%) were the main components found in the EO used in this study. The authors observed a high stability of the β-CD/EO complex (up to 200 °C) and the antinociceptive activity was attributed to the terpenoids camphor, borneol and β-caryophyllene, which contributed to activation of the motor cortex, NRP and PAG (cerebral areas involved in pain modulation).[182]

Marçal *et al.*[183] examinated the chemical composition and the antinociceptive effect of the *Lippia sidoides* Cham. (Verbenaceae) EO on mice. *L. sidoides* is an aromatic shrub, used in Brazilian folk medicine to treat inflammation, pain and bacterial infections.[244] The major constituents found in the EO were *p*-cymene **16** (26.8%), thymol **18** (21.9%) and myrcene **21** (12.8%) and a dose-dependent antinociceptive effect was observed in the acetic acid-induced writhing test. The *L. sidoides* EO increased the latency time in the hot plate test, but no effect was observed in the presence of naloxone (3 mg kg^{-1}, i.p.), indicating that the opioidergic system is involved in the antinociceptive effect.[183]

Melissa officinalis is a widespread plant used in perfumes, cosmetics, tea and food products and possess sedative, spasmolytic and antibacterial properties.[245,246] The major components of the *M. officinalis* leaf EO are citronellal **42** (39%) and citral **41** (33%).[143] In a very interesting work, Hasanein and Riahi[143] studied the antinociceptive effect of *M. officinalis* EO in an experimental model of diabetic hyperalgesia. The authors used healthy (control) and diabetic rats in the formalin test, and they observed that the hyperalgesia was completely reversed after a cronical oral treatment of the diabetic rats with *M. officinalis* EO. On the other hand, the EO caused less intensive nociceptive effect in the control rats during both phases of the formalin test. These findings indicate for a promise treatment with *M. officinalis* EO for painful diabetic neuropathy.[143]

Many *Mentha* species are used worldwide as choleretic, spasmolytic and analgesic agents.[247] In the Northeast of Brazil, *Mentha* × *villosa* Huds. (Lamiaceae), an aromatic herb, is widely used in folk medicine as a stomachic and anxiolytic agent.[196] The chemical composition analysis of the EO of *M.* × *villosa* revealed the piperitone oxide **56** as being the major constituent. Sousa *et al.*[144] studied the antinociceptive effect of the leaves EO of *M.* × *villosa* and of piperitone oxide and they observed that both reduced the writhing response on the acetic acid test and in the second phase of formalin induced pain. Besides, other important finding is that the opioid system is not involved in the antinociceptive effect of the EO and of piperitone oxide. In the thermal models of induce nociception, tail immersion test and hot plate, the EO and pure compound **56** were not significantly effective. At similar doses, 80 and 100 mg kg^{-1}, the leaves EO of *M.* × *villosa* had no toxic effects when administered to rats for 30 days.[144]

Myrcia ovata Cambess. is popularly known as "laranjinha do mato" and their leaves are frequently used as an infusion in folk medicine to treat gastric diseases and diarrhea.[248] Dos Santos *et al.*[167] determined the chemical compostion and the antinociceptive activity of the *M. ovata* EO in the acetic-acid induced writhing, formalin (phases I and II) and tail flick tests. The GC-MS analysis revealed the monoterpene geranial **41a** (52.6%) and its isomer neral **41b** (37.14%), i.e., citral **41,** as the major components of the EO. The authors observed that the *M. ovata* EO orally administered inhibited writhing induced by acetic acid by 29 and 51%, respectively. The EO was effective in both phases of the formalin test, with a more pronounced activity in the second one. At doses of 200 and 300 mg kg^{-1} the inhibition was similar to that of morphine at 5.01 mg kg^{-1}. A maximal effect on the tail flick test of 34 and 91% was observed at doses of 200 and 300 mg kg^{-1}, respectively. The antinociceptive effect was reduced by pretreatment with naloxone, suggesting that the antinociceptive activity might involve the opioid system. The EO did not induce motor impairment and no toxic effect was observed after oral administration (LD_{50} > 3000 mg kg^{-1}).[167]

Nepeta L. (Lamiaceae family) is a genus formed by perennial or annual herbs distributed in Europe, Asia, North Africa and in Near East and has around 300 species, 75 of which are found in Iran.[249] Antispasmodic, diuretic, expectorant, antiseptic and antiasthmatic are among the activities assigned to *Nepeta* species. *N. cataria* is one of the representative of this genus that has been used for a long time in teas, dyes or infusions and in the North

American folk medicine.[250] Ricci *et al.*[145] determined the chemical profile and explored the potential of the *N. cataria* L. var. citriodora (Becker) Balb. (Lamiaceae) EO as an antinociceptive agent in the acetic acid-induced nociception and in the tail immersion tests in mice. The major constituents of the *N. cataria* EO are *trans,trans*-nepetalactone **57** (50.4%) and *trans,cis*-nepetalactone **58** (21.7%). The EO at the dose of 0.0005 mL kg^{-1} (i.p.) reduced significantly the mice writhing responses in the acetic acid-induced model and was slightly less active than morphine (20 mg kg^{-1}) in the tail immersion test. The authors observed that the EO effects started before than the morphine ones, i.e., 15 min after the treatment, and remained up to 45 min after its administration.[145]

Nepeta crispa Willd. (Lamiaceae family) is an aromatic and medicinal plant endemic to Iran and its aerial parts are used in the Iranian folk medicine as a sedative, carminative and as a restorative tonic for nervous and respiratory disorders.[251] The major components of the *N. crispa* leaves and flowers are eucalyptol **1** (71.0%), β-pinene **40** (5.0%) and α-terpineol **59** (4.1%).[252] Ali *et al.*[146] evaluated the effect of *N. crispa* EO in the tail flick and formalin nociception models. In the first phase of formalin test, it was observed reduction of jerking counts, licking and flexing duration in all doses, whereas in the second phase the EO was effective only at doses of 100 and 200 mg kg^{-1}.[146]

One of the more recently identified species of *Nepeta* genus in Iran was *N. pogonosperma* Jamzad *et* Assadi, reported in 1984.[249] Ali *et al.*[147] studied the chemical composition of the *N. pogonosperma* EO and evaluated its antinociceptive effect (i.p.) in the tail flick and in the formalin tests. Similarly to other *Nepeta* plants, the *N. pogonosperma* EO is mainly constituted by eucalyptol **1** (31.2%) and *trans,cis*-nepetalactone **58** (14.5%), followed by α-terpineol **59** (5.4%) and (*E*)-α-bisabolene **60** (5.4%), among other terpenoids in minor amounts.[147] Authors observed that the EO presents antinociception at doses of 100 and 200 mg kg^{-1} in the tail flick test and in both phases of the formalin test at all doses.

Nigella sativa L. (Ranunculaceae) seeds have been used for thousands of years as a spice and food preservative, as well as a protective and curative remedy for numerous disorders. Abdel-Fattah *et al.*[175] studied the antinociceptive effect of the EO of seeds of *N. sativa* and its major component, thymoquinone **17**. Authors used four experimental models of induced pain and observed that the oral administration of *N. sativa* EO significantly increased the latency of nociceptive responses in the hot-plate and tail-pinch tests. The writhing behavior caused by i.p. injection of 0.6% acetic acid was attenuated in a dose-dependent manner. *N. sativa* EO also significantly suppressed the nociceptive response in the early phase, but did not reduce the response in the late phase of the formalin test. Regarding the antinociceptive effect of thymoquinone, the systemic administration by different routes: p.o. (5 and 10 mg kg^{-1}), i.p. (4 and 6 mg kg^{-1}) and intracerebroventricular, i.c.v., (2 and 4 μg mL^{-1}) dose-dependently attenuated the nociceptive response in the early and late phases of the formalin test. The s.c. and i.c.v. injection of naloxone significantly antagonized the effect of systemic thymoquinone (i.p.) on the early phase response. In contrast, s.c. and i.c.v. naloxone failed in reversing the thymoquinone-induced antinociception in the late phase. Studies demonstrated that the oral administration of the seed EO at doses up to 10 mL kg^{-1} in rats and mice did not cause any mortality or overt toxicity during the observation period of 48 h.[253] This was recently confirmed when it was demonstrated that oral administration of the EO of *N. sativa* at a dose of 10 mL kg^{-1}, for up to 12 weeks did not cause any mortality or significant alterations of the key hepatic enzymes in rats.[254] However, acute administration of high doses (2 g kg^{-1} or more) caused hypoactivity and difficulty in respiration.[255]

Ocimum (Lamiaceae) is a genus that comprises more than 150 species, which are distributed from tropical to subtropical regions.[256] *Ocimum* plants are rich in essential oils which contain mainly myrcene **21**, eugenol **32**, and (*E*)-caryophyllene **34**.[257] These substances have a proven influence on the central nervous system. Several species of *Ocimum* have been reported with regard to their antinociceptive properties, such as *O. micranthum* Willd*, O. basilicum* L.*, O.* L. and *O. sanctum* L.

O. basilicum L., popularly known as "basil", is an aromatic herb used in Brazil to treat illnesses such as respiratory and rheumatic problems, vomiting, and pain.[258] The leaves EO of *O. basilicum* reduced significantly the number of writhings on the acetic acid assay and the number of lickings of both phases of the formalin assay.[148] Besides, it increased the time for mice response to the thermal stimulus at 50 mg kg^{-1} in different times of exposure. Moreover, this study revealed the modulation of opioid mechanism on the antinociceptive response of this EO on the hot plate test. The authors also demonstrated the lack of toxicity or mortality at doses of 250 mg kg^{-1}. The lethal dose for 50% of animals (LD_{50}) was of 532 mg kg^{-1}, which could be associated to the high content of linalool in the EO.[148]

In other study, Venâncio *et al.*[149] also analyzed the antinociceptive response of leaves EO of *O. basilicum* on the acetic acid, formalin, capsaicin, glutamate tests and in the orofacial pain. In the EO used by the authors, linalool **28** was the major component (76%), followed by geraniol **43** (11%). The results indicated an action of the EO on phases I

and II of the formalin assay and in the glutamate and capsaicin tests. In the same work, the authors compared the activity of the EO with that of pure (−)-linalool and very close results were obtained in both cases.[149]

Another species of *Ocimum* plant with antinociceptive effect is *O. gratissimum* L., known as "alfavaca" and widely used in the culinary as a condiment. In 2003, Rabelo *et al.*[150] analyzed the chemical profile and the antinociceptive action of the EO of the leaves of *O. gratissimum* on the acetic acid-induced writhings and in the formalin assays. The major constituents found in the EO were eugenol **32** (52.1%), eucalyptol **1** (29.2%) and β-selinene **46** (5.6%). The authors observed that the EO produced a dose-dependent inhibition of acetic acid-induced writhing, comparable to indomethacin (an analgesic drug) and of the second phase of formalin-induced pain. A significant reduction on the first phase of formalin test was observed only at doses of 300 mg kg^{-1}.[150] The acute toxicity of *O. gratissimum* was studied in three month-old Wistar albino rats at doses of 5-3500 mg kg^{-1}, during 14 days. According to the results, rats which received 5-500 mg kg^{-1} of *O. gratissimum* EO also showed normal general behavior on day 1. At 1000 mg kg^{-1}, animals became torpid just after gavage, but this lasted no more than 30 min. In contrast, rats that received 1500 mg kg^{-1} stayed torpid all the day 1. Those that received doses above 2000 mg kg^{-1} died all less than 24 h after the EO administration. The LD_{50} in rats was 1750 mg kg^{-1}.

More recently, a study performed using *O. gratissimum* EO and two of its main constituents, myrcene **21** and eugenol **32** (40 mg kg^{-1}), revealed peripheral and central antinociceptive effects at the formalin (two phases) and hot plate tests, respectively.[151] To extend the studies, the authors analyzed the participation of the opioid system in the antinociceptive effect of the EO (20-40 mg kg^{-1}) and the isolated constituents in the hot plate test. Results showed that the pre-treatment of mice with naloxone, a non-selective opioid antagonist, have blocked the antinociceptive effect of EO, myrcene and eugenol, suggesting that modulation of opioid receptors is involved in the antinociceptive action. The authors also studied the acute toxicity of the EO in mice and observed few signs of toxicity, such as ptosis and reductions in defecation and ambulation, particularly at the highest dose (300 mg kg^{-1}).[151]

O. micranthum Willd is an herb native of the lowlands of Central and South America and West Indian. It is used locally to flavour beverages and soups, and for the treatment of fever, stomach disturbances and dysentery. A decoction of the plant is also used for nervous disorders, earache, colic and convulsion in children as well as for painful menstruation.[259] The antinociceptive effect of the leaves EO of *O. micranthum* Willd was evaluated by the acetic acid and formalin tests.[152] The authors also analyzed the influence of the opioids and nitric oxide systems on the antinociceptive response. Results demonstrated that the EO of leaves of *O. micranthum* Willd has activity in the acetic acid-induced writhing involving the opioid mechanism and in both phases of formalin test with participation of the opioid and nitric oxide systems. In a more recent work, Pinho *et al.*[153] studied the antinociceptive effect of *O. micranthum* leaves EO, (*E*)-caryophyllene **34**, (*E*)-methyl cinnamate **61** and (*Z*)-methyl cinnamate **62** (the major constituents of the EO) by the acetic acid, formalin and hot plate tests. The EO was effective on reducing the nociceptive response in the acetic acid and in the second phase of the formalin assay, indicating a peripheral action. (*Z*)-Methyl cinnamate **62** reduced the licking response on the first and second phases of the formalin assay, while the (*E*)-isomer **61** was effective only in reducing the nociceptive response in the second phase, while (*E*)-caryophyllene **34** did not present effect in the three tests used in this study.[228]

Peperomia serpens (Sw.) Loud. (Piperaceae) is largely used in popular medicine to treat inflammation and pain. *P. serpens* is an epiphyte herbaceous liana, with petiolate, cordate and succulent leaves, known as "carrapatinho" or "carapitinha"; it grows wild on different host trees in the Amazon rainforest. The decoction of its leaves is recommended due to their anti-inflammatory and analgesic properties, particularly against flu, asthma, cough, earache and irritation provoked by ant bites.[260] Pinheiro *et al.*[169] evaluated the chemical composition and the antinociceptive effect of the EO of the whole plant. (*E*)-Nerolidol **8** (38.0%), ledol **63** (27.1%) and α-humulene **4** (11.5%) were found in major amounts in the EO that was effective in reducing significantly writhings induced by acetic acid and in the two phases of formalin test (188.8 mg kg^{-1}). However, the EO did not increase the response latency of noxious behavior, presenting peripheral instead of central effects. Furthermore, it was observed that the antinociceptive effect of *P. serpens* EO did not involve the modulation of opioid receptors. Studies on the acute toxicity demonstrated that neither mortality nor sign of toxicity were detected during the behavioral observations, indicating no toxicity of this EO.[169]

Pimpinella anisum L., knowed as anise, is a member of Apiaceae family, which is widespread in tropical regions of the world. Aniseed, its extracts and EO are used as a food spice in many countries and in traditional medicine as a carminative, diuretic, expectorant, antiseptic and antispasmodic.[261] Jamshidzadeh *et al.*[126] evaluated the chemical profile of *P. anisum* seeds EO and its antinociceptive effect in the tail flick and formalin tests. The authors identified 15 compounds in the EO and *trans*-

anethole **64** (87.6%) was the major constituent and the responsible for most of its properties. The EO enhanced the tail flick reaction time in rats compared to the control group (DMSO) in 30, 60, 120 min after the injection. When 500 mg kg^{-1} of EO was administered, the antinociceptive effect was superior to that of paracetamol (100 mg kg^{-1}) at times of 60 and 120 min. The *P. anisum* EO was effective in both early and late phases of the formalin test at doses of 250 and 500 mg kg^{-1}. The effect was comparable to that of paracetamol at the dose of 500 mg kg^{-1} in phase I and at doses of 250 and 500 mg kg^{-1} in the phase II.[126]

The genus *Piper* is one of the five members of the Piperaceae family and it is present in almost all regions of Latin America. A large number of species of *Piper* are known by the pharmacological and insecticidal properties of their EOs.[262] This plant has been used as immunomodulator, analgesic and antidepressant in folk medicine. Lima *et al.*[170] studied the chemical profile and the antinociceptive effect of the aerial parts EO of *Piper aleyreanum* C. DC., popularly known in Brazil as "pimenta longa" and "pimenta de cobra". The main constituents of the *P. aleyreanum* EO described in the Lima's study were caryophyllene oxide **45** (11.5%), β-pinene **40** (9.0%), spathulenol **38** (6.7%), camphene **55** (5.2%) and β-elemene **44** (4.7%). The EO presented antinociceptive effect in both phases of the formalin model. However, this EO presents a more pronounced effect in the second phase of this pain model, evidencing the anti-inflammatory potential of this plant. The antinociceptive mechanism was also studied and it was observed that the opioid system is not involved in the effect of the EO of *P. aleyreanum*. The possible toxic effects of *P. aleyreanum* EO has not been studied yet; this lack of information can compromise results of antinociceptive effect, since pharmacological and toxicological data need to be complementary.[170]

Rao *et al.*[133] studied the chemical profile and the antinociceptive effect of the *Protium heptaphyllum* resin EO. The gum and oleoresins of *P. heptaphyllum* (Burseraceae family) are used in folk medicine as anti-inflamatory, analgesic, expectorant and wound-healing.[263] The major components of the *P. heptaphyllum* EO are monoterpenes eucalyptol **1** (58.7%), α-terpinene **65** (13.7%) and α-phellandrene **33** (10.4%). The antinociceptive effects of the EO were evaluated using four different models in mice: formalin-induced nociception, capsaicin-induced paw licking, tail flick and hot plate tests. The *P. heptaphyllum* EO suppressed only the second phase response of formalin test, which was resistant to naloxone. In the capsaicin test, the EO produced antinociception at both tested doses, as evidenced by suppression of the hind-paw licking response. In the tail flick test, the EO significantly prolonged the response latency, whereas no effect was observed in the hot plate test at the used doses.[133] According to the authors, these findings suggest that the *P. heptaphyllum* EO is an orally effective antinociceptive agent with peripheral and spinal levels of action.

Remirea maritima is a tropical species of the Cyperaceae family, known in some regions of Brazil as "capim-da-praia", which is used in the folk medicine to treat diarrhea, kidney disease, high fever, pain and inflammations.[264] Rabelo *et al.*[135] described recently the chemical profile and a series of biological properties of *R. maritima* roots and rhizome EO, including the activity in the acetic acid and formalin nociceptive tests. The main components of the EO are remirol **66** (43.2%), cyperene **67** (13.8%), isoevodionol **68** (5.8%), cyperotundone **69** (5.7%), caryophyllene oxide **45** (4.9%) and rotundene **70** (4.6%). The EO significantly inhibits the acetic acid-induced writhings and the two phases of formalin-induced nociception in mice.[135]

Martínez *et al.*[154] studied the antinociceptive properties of the EO from aerial parts of *Rosmarinus officinalis* L. (Lamiaceae), commonly known as "alecrim". This plant is used in aromatherapy, a form of alternative and complementary medicine that uses EOs and has been commonly employed in folk medicine since ancient times to minimize painful conditions in humans.[265] The authors observed that the EO showed a dose-dependent antinociceptive effect, manifested by a significant reduction in the dysfunction in the pain-induced functional impairment model in rat (PIFIR model), mainly at high doses. This model assess the antinociceptive effect of both analgesic and non-steroidal antiinflammatory drugs. The rats receive a unilateral intra-articular knee injection of a uric acid suspension in mineral oil to produce acute inflammation, pain, and functional motor impairment. The antinociceptive activity is assessed by measuring the capacity to walk with the injured extremity. The procedure determines both the potencies of analgesic drugs and the time course of the effect.[266] Analysis by GC-MS indicated the presence of α-pinene **10** (14.1%), camphene **55** (11.5%), β-pinene **40** (12.0%), myrcene **21** (3.3%), α-phellandrene **33** (7.9%), camphor **52** (8.7%), eucalyptol **1** (8.6%), bornyl acetate **71** (6.49%), borneol **53** (4.85%) and isoborneol **72** (3.5%) in the EO.[265] The antinociceptive effects of *R. officinalis* EO were evaluated in the presence of 0.12 mg kg^{-1} WAY100635, s.c. (an antagonist of 5-HT(1A) receptors) or 1 mg kg^{-1} naloxone, i.p. (an antagonist of endogenous opioid receptors), demonstrating in both cases inhibition of the antinociceptive response. This study suggests the involvement, at least in part, of the serotoninergic system via 5-HT(1A) receptors and endogenous opioids in the antinociceptive effect of *R. officinalis* EO in the PIFIR model.

The antinociceptive activity and the chemical compostition of *R. officinalis* EO were assessed by Takaki *et al.*[155] using the acetic acid and hot plate tests.[249] The major compounds found in the EO were myrcene **21** (24.6%), eucalyptol **1** (19.8%), phenylacetic acid **73** (10.3%) and 2-ethyl-4,5-dimethylphenol **74** (6.5%). EO decreased the number of acetic acid-induced writhes in mice but it did not present antinociceptive effect in the hot plate test with no extention of the latency time compared with the control animals.[155] A similar lack of effect in the hot plate test was observed by de Faria *et al.,*[156] who studied the antinociceptive and anti-inflammatory activities of *R. officinalis* EO. In this study, the authors examined also the effect of the EO in the acetic acid- and formalin-induced nociceptive models and they observed a dose-dependent effect of the EO in the writhing test, with an ED_{50} of 260 mg kg^{-1}. The oral treatment with EO inhibited the phase I (40%) and the phase II (48%) in the formalin assay. The EO did not show toxicity in the LD_{50} assay at a dose of 2000 mg kg^{-1}.[156] The possible mutagenic effect of *R. officinalis* in *Salmonella typhimurium* TA908 strain was investigated by Zegura *et al.*[267] and no mutagenicity was observed.

Satureja hortensis L. (Lamiaceae) is one of the most important of twelve Iranian *Satureja* species cultivated in several areas of Iran. Whole dried herb has been widely used in food as a flavor component and in folk and traditional medicine as a carminative and diuretic. The antinociceptive effects of the EO of aerial parts[157] and seeds[158] of *S. hortensis* have been reported by Hajhashemi *et al.*[158] The EO of the aerial parts (leaves and flowers) are mainly constituted by carvacrol **54**, apigenin **75** and apigenin derivatives, while γ-terpinene **7** (50.5%) and thymol **18** (32.7%) were the two main constituents of the seed EO.[158] The EO of the aerial parts presented antinociceptive action in the acetic acid-induced writhings and in both phases of the formalin test, but failed in the tail flick test.[157] The seeds EO presented antinociceptive effects in the acetic acid test, while in the formalin-induced pain test it inhibits only the second phase (the inflammatory pain).[158] Both articles did not report on the possible toxic effects of the *S. hortensis* EO, an important data in the study of a new phytomedicine.

Schinus terebinthifolius fruits, bark and leaf have been used in the popular medicine as anti-inflamatory, wound healing, analgesic among others medicinal uses.[268-271] The main components of the *S. terebinthifolius* fruits EO are α-pinene **10**, sabinene **20**, (*Z*)-salvene **76**, β-pinene **40**, α-funebrene **77**, (*R*)-(+)-limonene **14**, myrcene **21** and α-phellandrene **33**.[116] Piccinelli *et al.*[116] described the antihyperalgesic effect of the *S. terebinthifolius* fruits EO and two of its main constituents, (*R*)-(+)-limonene **14** and α-phellandrene **33**, in two models of spared nerve injury (SNI) neuropathic pain in rats. It was observed that the daily oral administration of the EO and the isolated compounds (*R*)-(+)-limonene and α-phellandrene for up to 15 days, respectively, inhibited the SNI-induced mechanical hyperalgesia. The *S. terebinthifolius* EO reduced in 100% the SNI-induced increasing in sensitivity to a mechanical stimulus after 10-15 days of treatment, while using (*R*)-(+)-limonene and α-phellandrene the inhibition was of 63 and 55%, respectively.[116]

The genus *Teucrium* (Lamiaceae family) is represented for more than 340 species.[272] *Teucrium polium* L. is a wild-growing flowering plant, which is found abundantly in Southwestern Asia, Europe and North Africa. It has been used as a medicinal herb in folk medicine for over 2000 years as diuretic, diaphoretic, tonic, antipyretic and antispasmodic.[272] Abdollahi *et al.*[159] reported their observations on the antinociceptive effect of the *T. polium* aerial parts EO and observed a decreasing in the number of writhings on acetic acid test. The chemical profile and the antinociceptive activity of *T. polium* EO were evaluated by Skouti *et al.*[160] in 2012. The main components of the aerial parts EO are α-pinene **10** (27.5%) and β-pinene **40** (12.4%). The EO was effective in the tail flick test, increasing the latency time in a dose dependent manner. The authors observed that the EO caused hepatotoxicity after treatment for 21 days.[160]

Quintão *et al.*[168] analyzed the chemical composition of the EO from the leaves of *Ugni myricoides* (Kunth) O. Berg (Myrtaceae), which contains six major constituents: α-pinene **10** (52.1%), eucalyptol **1** (11.9%), α-humulene **4** (4.6%), caryophyllene oxide **45** + globulol **78** (4.5%), humulene epoxide **79** (4.2%) and (*E*)-caryophyllene **34** (2.9%). In Costa Rica, this shrub is popularly known as "arrayán" and "mirto".[273] The antinociceptive effects of *U. myricoides* EO were compared with those of indomethacin (5 or 10 mg kg^{-1}, p.o.), a drug used clinically to treat inflammation and it significantly prevents mechanical hypernociception induced by carrageenan or complete Freund's adjuvant (CFA) in mice. Repeated treatment with *U. myricoides* EO, α-pinene, or gabapentin also abolished the mechanical sensitization induced by CFA, or following the partial ligation of the sciatic nerve (PLSN). The authors advocated that the relevant effects of *U. myricoides* EO are due to the presence of α-pinene.[168]

Leite *et al.*[131] analyzed the antinociceptive effect of *Vanillosmopsis arborea* (Gardner) Baker (Compositae family) EO in a visceral model of pain. Visceral pain is the most common form of pain for which the patients often look for medical care and in this study, authors used the formalin, capsaicin and mustard oil as visceral pain inducers. The *V. arborea* leaves EO contains up to 50 and

90% of α-(−)-bisabolol **2**, which is the responsible for most of its biological activities.[274] The authors observed that the nociceptive response was significantly inhibited by the EO in the three tested models. Authors also observed that the serotoninergic, nitrergic, ATP-sensitive K^+ channels and TRPV1 receptors are not involved in the antinociceptive effect of the EO in the mustard oil test.[131]

More recently, Santos *et al.*[132] peformed a study on the chemical profile and antinociceptive activity of the *V. arborea* barks EO. Similarly to the leaves, the barks EO is predominantly α-bisabolol **2** (70%). α-Cadinol **27** (8.4%) and elemicin **80** (6.21%) were also indentified among the major compounds of the EO. The *V. arborea* EO inhibited the acetic acid-induced abdominal constrictions and was effective in both phases of the formalin test, predominantly in the second phase.

Khalilzadeh *et al.*[161] described the chemical profile of the *Vitex agnus-castus* leaves EO and evaluated its antinociceptive effect in rats. *Vitex agnus-castus* (Lamiaceae family) is a shrub known as monk pepper or chaste tree and is widely distributed in the Middle East and Mediterranean region.[275] In the folk medicine, *V. agnus-castus* is used as an anti-inflamatory, analgesic and in the treatment of menstrual problems and sexual dysfunction.[276] The authors identified 22 compounds in the EO among which α-pinene **10** (14.8%), limonene **14** (10.3%), caryophyllene **34** (6.9%), β-farnesene **11** (5.9%) and sabinene **20** (5.3%) were in higher amounts.[275] The authors used three different nociceptive models (acetic acid-induced writhing, formalin and tail immersion tests) to evaluate possible peripheral and central nociceptive effects of the *V. agnus-castus* EO. It was observed that the EO reduced the number of abdominal writhes in comparison with the control group (piroxicam, 5 mg kg^{-1}) in the acetic acid-induced test. The *V. agnus-castus* EO (s.c.) induced antinociceptive effect compared to the control group in both first and second phases of the formalin test. In the tail immersion test, the EO was effective on increasing the latency at various time points post-treatment. The pretreatment with naloxone (a non-selective opioid receptors antagonist) or atropine (1 mg kg^{-1}) prevented the nociceptive effect of the EO on both phases of the formalin test as well as tail immersion test. These findings suggest that the activation of endogenous opioidergic system and acetylcholine muscarinic receptors are involved in the antinociception induced by the *V. agnus-castus* EO. Moreover, the acute toxicity was evaluated and any mortality was observed even at a high dose (5 g kg^{-1}, p.o.) of the EO.[161]

Vitex negundo Linn plant is another *Vitex* with a vast use in popular medicine, including as an analgesic, anti-inflammatory, bronchial relaxant, anti-allergic, anti-arthritic among other applications.[277] Khokra *et al.*[162] evaluated the antinociceptive effects of *V. negundo* leaves, flowers, dry ripe and green fruit EOs in mice using the acetic acid-induced writhing and the hot plate tests. The authors observed that all the EOs inhibit the acetic acid-induced writhing response, with the leaves EO presenting the maximum inhibition (60%) while other oils resulted in 50-55% inhibition. Similarly, all the EOs were effective in the hot plate test, with the flower's EO being moderately active.[162] The major components of the EO were not determined in the present study.

Leaves and flowers of *Xylopia laevigata* are used in Northeast Brazil to treat painful disorders, heart disease and inflammatory conditions. Recently, it was described the anticancer activity of *X. laevigata* EO.[278] Queiroz *et al.*[119] determined the chemical composition of the *X. laevigata* leaf EO and investigated its antinociceptive and anti-inflammatory activities. The main components of the EO are γ-muurolene **81** (17.8%), δ-cadinene **82** (12.2%), bicyclogermacrene **36** (7.8%), and α-copaene **83** (7.2%). It was observed that the *X. laevigata* EO was effective in inhibiting the acetic acid-induced writhings and in the two phases of the formalin-induced nociception in mice.

Previous reports indicate the popular use of *Zataria multiflora* Boiss. (Lamiaceae) as an effective remedy for treating pain and gastrointestinal disorders.[150] Jaffary *et al.*[163] demonstrated the antinociceptive effect of aerial parts of *Z. multiflora* EO in the acetic acid-induced writhings and formalin test in rats. There are many reports about the antibacterial activity of *Z. multiflora* EO;[279-281] however, any information about the toxicological potential in eukaryotic cells was reported.

Zingiberaceae species are among the most prolific plants in the tropical rainforests. In folk medicine, the decoction of *Zingiber zerumbet* (L.) Roscoe ex Sm. rhizomes is normally drunk to treat indigestion, stomachache, fever and worm infestation.[187] The main compounds found in the *Z. zerumbet* rhizomes EO were zerumbone **84** (69.9%) and α-humulene **4** (12.9%).[188] The antinociceptive effect of the *Z. zerumbet* rhizome EO has been studied and it was effective in the acetic acid induced writhings, in both phases of the formalin test and in the hot plate.[186] Moreover, there is involvement of the opioid system in the peripheral (formalin) and central (hot plate) antinociception. In another work, the same authors extended the studies on the antinociceptive effect of the EO using different tests like capsaicin, glutamate and phorbol 12-myristate 13-acetate (PMA)-induced nociception.[186] The involvement of *L*-arginine/NO, cyclic guanosine monophosphate (cGMP) and ATP-sensitive K^+ channel pathway in the acetic acid-induced writhings was also evaluated. Results demonstrated

that the EO reduced the time spent licking on the capsaicin, glutamate and PMA tests. Another important additional finding of this study was the demonstration of the possible involvement of the glutamatergic system, TRPV1 receptor and *L*-arginine, nitric oxide, cGMP, PKC/ATP-sensitive K^+ channel pathways in the EO-induced antinociception in mice. The acute toxicity of *Z. zerumbet* EO was evaluated by the administration of EO i.p. at the doses of 300, 1000 and 5000 mg kg^{-1} and no mortality was observed even at the highest dose during the observation period.[186] These results indicate that it might have a reasonable safety margin concerning acute toxicity.

6. Antinociceptive Effect of Compounds Isolated from EOs

As mentioned before, in the Section 1 of this review, EOs are very complex natural mixtures of volatile compounds, which can contain a several tens or even hundreds of components at quite different concentrations.[10,11,282] They are characterized by two or three major components at fairly high concentrations (20-70%) compared to others compounds, wich are present in trace amounts, but it is not a general rule. The aromatic properties of some EOs, however, are determined by few compounds, even if present in low amount.[10]

Regarding the biological activity of EOs, it is common to speculate when their biological effects are the result of a synergism of all molecules or reflect only the activity of their main constituents.[115] Generally, the major components are found to reflect quite well the biophysical and biological features of the EOs from which they were isolated,[283] the amplitude of these effects being just dependent on their concentration when they were tested alone or included in the EO. Thus, synergistic functions of the various molecules presented in an EO, in comparison to the action of one or two of its main components, could be questionable.[115]

We will discuss in this section studies on the antinociceptive effect of EO constituents, isolated or used as a mixture. The chemical structures of these compounds are presented in Figures 4-7 and the antinociceptive models used to assess their activity is presented in the Table 3 following the same order they appears in this section (column 1).

Table 3. Compilation of antinociceptive assays using EOs major constituents

Essential oil constituent	Performed test	Route of administration	Tested dose / (mg kg^{-1})	Reference
Eucalyptol **1**	hot plate tail flick opioid system	oral	100-400	284
	hot plate tail flick	intraperitoneal	0.3	164
3-Furanoeudesmene **48**	acetic acid hot plate	oral	100-200	21
1-Nitro-2-phenylethane **85**	acetic acid formalin test (phase II) opioid system	intraperitoneal	15-50	285
Atractylone **47**	acetic acid hot plate	oral	100-200	21
(*E*)-Caryophyllene **34**	hot plate formalin opioid system neuropathic pain mechanical hypernocicception thermal hypernociception opioid and endocannabinoid systems	oral	1.5-10	286
(−)-Carvone **86**	acetic acid	intraperitoneal	250	287
	acetic acid formalin test (phases I and II) opioid system	intraperitoneal	250	288
	acetic acid	intraperitoneal	250	289
(+)-Carvone **87**	acetic acid	intraperitoneal	250	289
Carvacrol **54**	acetic acid formalin test (phases I and II) hot plate		25-100	63
Citral **41**	formalin test (phase II)	oral	100-1000	290

Table 3. Compilation of antinociceptive assays using EOs major constituents (cont.)

Essential oil constituent	Performed test	Route of administration	Tested dose / (mg kg^{-1})	Reference
Citronellal **42**	orofacial nociception: formalin test (phases and II) capsaicin glutamate	intraperitoneal	50-200	291
	acetic acid formalin test (phases I and II) hot plate	intraperitoneal	50-200	292
Citronellol **92**	acetic acid formalin test (phases I and II) hot plate	intraperitoneal	25-100	293
	formalin test (phases I and II) capsaicin glutamate	intraperitoneal	25-100	294
Citronellyl acetate **93**	acetic acid formalin test (phases I and II) capsaicin glutamate	oral	100-200	295
Evodione **94**	acetic acid tail flick	oral	50-100	296
Carvone epoxide **91**	acetic acid	intraperitoneal	250	289
	acetic acid formalin hot plate	intraperitoneal	100-300	297
Farnesol **95**	acetic acid formalin	intraperitoneal	50-200	298
Hydroxydihydrocarvone **96**	acetic acid tail immersion test hot plate formalin phases I and II opioid system	intraperitoneal	25-400	299,300
(+)-Limonene **14**	SNI[a] animals		10	116
	acetic acid formalin test (phase II) no opioid system		25 and 50	301
Limonene oxide **31**	acetic acid	intraperitoneal	250	289
	glutamate mechanisms operated by ionotropic glutamate receptors	intraperitoneal intrathecal oral	10-200 0.1-3[b] 5-100	302
Linalool **28**	neuropathic pain induced by spinal nerve ligation	subcutaneous	50-150	303
	acetic acid hot plate opioid and cholinergic systems	subcutaneous	25-100	304
	acetic acid formalin test (phases I and II) cholinergic system	subcutaneous	25-100	304
	hyperalgesia induced by carrageenan, *L*-glutamate and prostaglandin E_2	oral	50-150	305
	hot plate	subcutaneous	25-75	306
	glutamate	subcutaneous	25-75	307
(−)-Menthol **97** (+)-Menthol **98**	hot plate acetic acid opioid system	oral or intracerebroventricular	3 and 10 10[c]	308
Isopropyl *N*-methylanthranilate **19**	acetic acid hot plate	oral	0.3 and 3	176
Methyleugenol **32**	formalin test (phase II) NMDA[d] receptors	oral	3 and 10	309

Table 3. Compilation of antinociceptive assays using EOs major constituents (cont.)

Essential oil constituent	Performed test	Route of administration	Tested dose / (mg kg^{-1})	Reference
Myrtenol **99**	acetic acid formalin hot plate glutamate capsaicin	intraperitoneal	75	310
'-Phellandrene **33**	SNI[a] animals	oral	10	116
'-Pinene **10**	carrageenan (mechanic hipernociception) CFA[e] (EO[f] and '-pinene)	oral	5-25	273
'-Pinene **40**	hot plate tail flick opioid system	intraperitoneal	0.3	164
(+)-Pulegone **89**	acetic acid	intraperitoneal	250	289
	formalin test (phases I and II) hot plate	intraperitoneal	250	311
Pulegone oxide **90**	acetic acid	intraperitoneal	250	289
Rotundifolone **86**	acetic acid	intraperitoneal	250	289
Thymoquinone **17**	formalin test (phase I and II)	intracerebroventricular	1-4[g]	175

[a]Spared nerve injury (SNI); [b]unit: μg site^{-1}; [c]unit: μg mL^{-1}; [d]NMDA: *N*-methyl-*D*-aspartate; [e]CFA: complete Freund's adjuvant; [f]EO: essential oil; [g]unit: μg mouse^{-1}.

Eucalyptol (1,8-cineole) **1** is a terpene oxide, major constituent of the EOs of most *Eucalyptus* species, which is present also in many other EOs. This compound shows antinociceptive effect by inhibiting the acetic acid-induced increase in peritoneal capillary permeability activity in mice.[284] Eucalyptol significantly inhibited the paw licking response in both phases of formalin test, with a significant inhibition only at the second phase. This effect was not reversed by pretreatment with naloxone suggesting the involvement of a non-opioid mechanism.[285] According to the authors, the oral administration of eucalyptol up to 4 g kg^{-1} in mice did not induce mortality.

Aniba canellila (Kunth) Mez (Lauraceae), an aromatic plant from the Amazon region known as "casca-preciosa" is a medicinal plant used in the Amazon folk therapeutic as antispasmodic, antidiarreic, carminative, tonic agent and a stimulant of the digestive and central nervous systems.[312] The main constituent of its EO is 1-nitro-2-phenylethane (NPE, **85**) in concentrations of 39-95% m/m. This compound showed dose-dependent antinociceptive activity by i.p. administration in the acetic acid-induced writhing test. Additionally, NPE presented a significant antinociceptive effect in reducing the licking time in the second phase (inflammatory) of the formalin test. Besides, the authors observed that opioid receptors are involved in the antinociceptive action.[286] The acute toxicity of NPE was previously studied by the same research group, using male Swiss mice that receive oral doses of 500-1000 mg kg^{-1} and the LD_{50} was 712 ± 176.39 mg kg^{-1}.

Carvacrol **54** is the predominant monoterpenic phenol in many EOs of the Lamiaceae family, including the genus *Origanum*, *Satureja*, *Thymbra*, *Thymus* and *Corydothymus* species. Carvacrol **54** presents antinociceptive activity by reducing the number of writhings in the acetic acid test and reducing the time spent licking the paw in the formalin first and second phases. In the glutamate and capsaicin tests, carvacrol was effective at doses slightly lowers. Moreover, it increased the latency on the hot plate test.[63] Authors did not report any data about toxicological effects of carvacrol; however, Monzote *et al.*[287] investigated the toxic effects of carvacrol on mammalian mitochondria, and data demonstrated that it inhibits the mitochondrial electron-transferring complex I in uncoupled and coupled respiration.

(*R*)-(−)-Carvone (*p*-mentha-6,8-dien-2-one, **86**) is a monoterpene that is found as the main active component of *Mentha* plant species like *Mentha spicata* L. (Lamiaceae). This monoterpene produced slightly higher antinociceptive effect in inhibition of the writhing response than its enantiomer (*S*)-(+)-carvone **87** when administered 30 min before the acetic acid injection (0.8%, 0.1 mL 10 g^{-1}, i.p.).[313] This difference in effects indicates an influence of the chirality of these enantiomers on the pharmacological activity. According to Gonçalves *et al.*[288] (−)-carvone **86** presented antinociceptive effect by writhing reduction in the first and second phases of the formalin test, suggesting that this activity could be connected with central or peripheral mechanisms. Besides, the opioid system does not participate of the mechanism in the modulation of pain promoted by (−)-carvone. Jenner *et al.*[314] reported the acute toxicity of carvone in rats at doses of 1260-2130 mg kg^{-1} and the LD_{50} was of 1640 mg kg^{-1}.

The antinociceptive activity of both enantiomers of carvone (**86** and **87**) was evaluated by de Sousa *et al.*[289] during their studies on the determination of a relationship between the chemical structure of rotundifolone **88** and its antinociceptive activity. Rotundifolone is present in many *Mentha* species EO, such as *M.* × *villosa*, which has cardiovascular relaxant of intestinal smooth muscle and antinociceptive properties.[315] In this interesting study, the authors compared the antinociceptive effect in the acetic acid-induced test of (−) **86** and (+)-carvone **87**, rotundifolone **88**, limonene oxide **31**, (+)-pulegone **89**, pulegone oxide **90** and carvone epoxide **91**. The authors observed that all six analogs were more effective than rotundifolone in reducing the number of writhings, with (−) and (+)-carvon being the more active ones. The structure-activity analysis showed that the antinociceptive activity is influenced by the presence of the epoxide group as well as by the position of the functional group on the six-membered ring.[289]

Citral **41**, a mixture of *cis*- and *trans*-3,7-dimethyl-2,6-octadienal **41a** and **41b**, is a monoterpene that occurs naturally in herbs, plants, and citrus fruits, including *C. citratus* and *C. nardus* L. Rendle. When rats were orally treated it was observed antinociceptive effect during the second phase of the formalin test.[290] In the same study, the authors investigated the antinociceptive interaction of naproxen (anti-inflammatory drug that is used for treating painful conditions) and citral after systemic administration. Dieter *et al.*[316] evaluated the toxicity of citral in male and female F344/N rats and B6C3F1 mice. According to the authors, no animal died during a treatment of 14 days.

Citronellal **42** is a monoterpenic aldehyde typically isolated as a non-racemic mixture of their *R* and *S* enantiomers from the EO of *Eucalyptus citriodora* Hook (Myrtaceae), *Cymbopogon nardus* L. Rendle (Poaceae), *C. citratus* (DC) Stapf. (Poaceae), *C. winterianus* Jowitt (Poaceae) and Java citronella.[317] The antinociceptive effect of citronellal has shown to involve the modulation of neuropathic and inflammatory pain in tests of orofacial pain induced by formalin, capsaicin, and glutamate in mice.[291] Citronellal reduced the number of writhes in the acetic-acid induced test in a dose-dependent manner.[292] In the hot plate test, citronellal increased the latency time and this effect was blocked by naloxone. These findings indicates that citronellal has a central analgesic effect. The authors did not report data about the toxicological role of citronellal. Data of our research group, however, demonstrated that (*R*)-citronellal **42** did not present any signal of toxicity in 72 hours at doses of 200 and 400 mg kg^{-1} (p.o.) (data not published).

Citronellol **92** is a monoterpenic alcohol naturally occurring as pure enantiomers *R* and *S* in EOs of various aromatic plant species, such as *C. citratus* (DC) Stapf. (Poaceae).[317] In mice, when evaluated in the acetic acid-induced abdominal writhing test, (*S*)-citronellol **92** reduced the amount of writhes and inhibited both phases of formalin-induced licking.[293] (*S*)-Citronellol caused a significant increase in the latency response on the hot-plate test according to the authors.[293] The same group studied the effect of (*S*)-citronellol in orofacial nociceptive models induced by formalin, capsaicin and glutamate.[294] (*S*)-Citronellol was effective at all the doses in the tested models and they observed that the opioid receptors are involved. The authors attributed the antinociceptive action of compound **92** to the inhibition of peripheral mediators and to the activation of CNS regions involved in pain.

Citronellyl acetate (3,7-dimethyl-6-octen-1-yl acetate, **93**) is a monoterpene which is present mainly in *Eucalyptus citriodora* as a secondary metabolite. Besides being frequently used in perfumery industries, citronellyl acetate has a list of interesting biological activities, including antihepatoma, fungicidal, larvicidal, bactericidal and repelling/insecticidal activities. Rios *et al.*[295] evaluated the effect of cytronellyl acetate in three different models of induced nociceptivity: acetic acid, formalin and glutamate. It was observed that citronellyl acetate decreases the number of writhings (ED_{50} = 74.4 mg kg^{-1}) for up to 4 h. Two doses of **93** promoted antinociception in both early and later phases of the formalin test and in the glutamate and capsaicin ones. To verify the possible mechanism involved in the antinociception effect of citronellyl acetate, the authors performed additional tests, such as menthol, acidified saline, cynnamaldehyde, PMA and 8-Br-cAMP. They demonstrated that the K^+_{ATP} channel is involved in the antinociceptive mechanism of citronellyl acetate that could modulate TRPV1, K^+_{ATP}, and ASIC, as well as glutamate receptors.[295]

The antinociceptive activity of evodione **94**, isolated from leaves EO of *Melicope lunu-ankenda* (Gaertn.) T. G. Hartley (Rutaceae), was demonstrated by Johnson *et al.*[296] The authors observed activity in models of acetic acid-induced writhing and tail immersion assay. Evodione was effective when administrated 30 min before the chemical stimulus.

The antinociceptive effect of carvone epoxide **91** in mice was demonstred by da Rocha *et al.*[297] Compound **91** is a monoterpene found in the EO of *Carum carvi*,[318] *Kaempferia galangal*[319] and other plants.[317] In the acetic acid-induced writhings, carvone epoxide presented effect similar to those using morphine (used as a positive control). Compound **91** reduced pain in mice in the first and second phases of the formalin test. In the hot plate test, carvone epoxide altered the latency of response to thermal

stimulus during a 30 min analysis period, compared to the control group. Long-lasting antinociceptive effects (60 and 120 min) were observed only when at the higher studied dose. In the study, no data about the toxicological effect of compound **90** was presented.[297] The toxicity of carvone epoxide in mice, however, was previously studied by de Sousa *et al.*[313] and they found a LD_{50} of 923 mg kg^{-1}, with a confidence interval of 820-1037 mg kg^{-1}.

Farnesol **95** is a 15-carbon, naturally occurring sesquiterpene, that can be obtained from the EO of citronella (*C. nardus*).[320,321] Oliveira Jr. *et al.*[298] investigated the antinociceptive effect of farnesol in the acetic acid-induced writhings and formalin assays. Male Swiss mice received doses of compound **95** and morphine (the positive control). The inhibition of the nociceptive response was observed in the acetic acid test, with complete inhibitions of contortions, and in both phases of formalin test. Authors also evaluated the effect of these doses in a possible damage to striatum and hippocampus.[298] The histopathology of animals treated with 200 mg kg^{-1} revealed neuronal loss, gliosis, and typical vacuolar degeneration in the hippocampal region. According to the authors, this was observed in only 16% of treated animals and did not constitute a significant neurotoxic effect. However, more studies are necessary to evaluate possible interactions of farnesol with the central nervous system.

Compounds with analogue structure, such as hydroxydihydrocarvone (HC, **96**), show antinocipective activity in different models. HC is a synthetic intermediate obtained from (*R*)-(−)-carvone hydration. HC decreased the incidence of acetic acid-induced writhing but presented a central nervous system depressant effect.[299] More details of antinociceptive activity of HC were described by de Oliveira *et al.*[300] who observed that it was effective in the tail immersion test (TIT), which consists of a thermal stimulus. An increase in the reaction time is generally considered a parameter for evaluating central antinociceptive activity by this model. The prolonged delay in response when mice were subjected to the TIT and the increase in reaction time in the hot plate test indicate that compound **96** has a central antinociceptive effect. Evidence for the involvement of a central antinociceptive effect was confirmed by the HC dose-dependent inhibition of both phases of the formalin test.[300]

D-Limonene [*R*-(+)-isomer, **14**] is a monoterpene prevalent in EOs of various plants and some studies have demonstrated the anti-inflammatory potential of this compound.[301] The antinociceptive effect of *D*-limonene was evaluated in the acetic acid and in the formalin tests in both phases. The antinociceptive properties of compound **14** was evaluated also using chemical and thermal models of nociception in mice.[301] *D*-Limonene produced significant inhibition of the acetic-acid induced nociception and also in the second phase of formalin test (insensitive to naloxone). No significant effect was observed in the hot-plate test. It was also demonstrated that *D*-limonene (25 and 50 mg kg^{-1}) neither significantly enhanced the pentobarbital-sleeping time nor impaired the motor performance in rotarod test, indicating that the observed antinociception is unlikely to be due to sedation or motor abnormality. Authors related the antinociceptive action of *D*-limonene with peripheral analgesia, not with the stimulation of opioids receptors.[301]

(−)-Linalool **28** is a natural occurring monoterpene commonly found as a major volatile component of the EOs of several aromatic plant species, including *O. basilicum, Origanum vulgare* and *Aeolanthus suaveolens*. The antinociceptive action of linalool has been reported in several models of inflammatory and neuropathic pains, making it one of the most studied EO constituents. According to Peana *et al.*[304] (−)-linalool caused a significant reduction of the acid-induced writhing and in the hot plate test. The authors also observed that the activation of opioidergic and cholinergic systems is involved in the antinociceptive effect of (−)-linalool.[304] In other study, to further characterize the antinociceptive profile of compound **28**, the same group[322] found that the compound was effective in the hot plate test and also caused a significant antinociceptive effect on both phases of formalin test. The involvement of cholinergic, local anesthetic activity and its ability to block NMDA and others pathways was evidenced. Additional experimental evidences were collected by Batista *et al.*[302] that performed assays using the glutamate-induced test. The authors verified that the pronounced antinociception against glutamate-induced nociception by linalool in mice involves ionotropic glutamate receptors, namely AMPA, NMDA and kainate.[302]

Peana *et al.*[305] studied the effect of the systemic administration of (−)-linalool **28** by abdominal subcutaneous injection in Wistar rats. The authors observed that compound **28** inhibits the development of acute hyperalgesia induced by carrageenan (200 mg kg^{-1}, injected paw). In addition, the treatment with (−)-linalool reduced the hyperalgesia induced by *L*-glutamate and prostaglandin E_2.

Additional studies performed by the same group showed that (−)-linalool is effective on reducing pain responses by pathways mediated by the activity of adenosine A_1 and A_{2A} receptors in the hot plate test.[306]

Batista *et al.*[307] reported that (−)-linalool has antinociceptive activity against glutamate induced pain in mice, possibly due to mechanisms operated by ionotropic glutamate receptors (AMPA, NMDA and kainate) in i.p., oral and intrathecal treatments. In other model, the

mechanical allodynia, developed and maintained over time following spinal nerve ligation, the number of neuropathic animals was reduced when linalool was administered for seven consecutive days.[303]

Batista *et al.*[307] showed that (−)-linalool displays significant antinociceptive effects in models of chronic pain in mice, specifically in reduction of mechanical hypersensitivity induced by the neuropathic pain (PSNL) and in the mechanical and cold hypersensitivity caused by a chronic inflammatory model (CFA). Authors administered linalool chronically twice a day for 10 days. The ability to inhibit nociception by proinflammatory cytokines and to modulate the NMDA glutamatergic receptor may be responsible for the activity of linalool in these models.

Menthol (**97** and **98**) is a natural compound present in several EOs from different species of plants, such as *Mentha piperita* and *M. arvensis* and is largely used in the pharmaceutical, cosmetics and food chemistry industries. In 2002, Galeotti *et al.*[308] studied the antinociceptive effect of the two optical isomers of menthol: (−)-menthol **97** and (+)-menthol **98**. The results demonstrated peripheral and central effects in mice in the assays of acetic acid and hot plate for the (−)-menthol, while its enantiomer (+)-menthol did not present any effect. Moreover, the study revealed that the antinociceptive effect of (−)-menthol involves the modulation of opioid system.

Methyleugenol (1-allyl-3,4-dimethoxybenzene, **32**) is an alkenylbenzene compound found in several EOs (basil, clove, lemongrass and others). According data of Yano *et al.*[309] methyleugenol significantly inhibited the duration of the second phase of formalin test and also inhibited pain-related behaviors induced by intrathecal injection of *N*-methyl-*D*-aspartic acid (NMDA). The antinociceptive mechanism can be due to the inhibition of NMDA receptor-mediated hyperalgesia via $GABA_A$ receptors.

Silva *et al.*[310] evaluated the antinociceptive effect of myrtenol **99**, a monoterpenic alcohol found in EOs of some aromatic plants, such as *Tanacetum vulgare*[323] and *Aralia cachemirica*.[324] The antinociceptive effect was investigated in male Swiss mice using acetic acid-induced writhings, hot plate, formalin, glutamate and capsaicin tests. In this study, morphine (5 mg kg^{-1}, i.p.) and dizocilpine (MK-801, 0.03 mg kg^{-1}, i.p.) were used as the positive controls. Myrtenol reduced 69.6% of writhing responses in the acetic acid assay, 97.6% of the licking time in the second phase of formalin test, 44.9% of licking time in the glutamate test and inhibited 36.9% of the response in capsaicin assay.[310] According to these results, myrtenol presented a potential as an antinociceptive drug; however, this work did not report data about its toxicological role. The LD_{50} of myrtenol was determined by Bhatia *et al.*[325] and values of 2.45 g kg^{-1} (for males) and 0.63 g kg^{-1} (for females) were found.

The effect of (*E*)-caryophyllene **34** on acute and chronic pains was studied by Paula-Freire *et al.*[286] (*E*)-Caryophyllene is a bicyclical sesquiterpene and is one of the major active principles from *Cannabis sativa*,[326] *Ocimum gratissimum*[327] and *Cordia verbenaceae*.[328] Compound **34** was administered in male C57BL/6J mice. Morphine (5 mg kg^{-1}, i.p.) was used as positive control for the acute assays and pregabalin (20 mg kg^{-1}) for the chronic ones. According the authors, (*E*)-caryophyllene showed marked oral antinociceptive properties in both acute and chronic models of pain. The study of the mechanism of action revealed the involvement of opioid and endocannabinoid pathways. This work did not show any data about the toxicological profile of (*E*)-caryophyllene.

β-Pinene **40** and eucalyptol **1** are the major components of the EO of *Eucalyptus camaldulensis* Dehnh. The antinociceptive action of compounds **40** and **1** was evaluated using the tail flick and hot plate tests.[164] Both compounds presented antinociceptive activity in the tail flick and hot plate tests. Moreover, the antinociceptive effect of eucalyptol was almost equivalent to that of morphine and the effect of β-pinene was reversed by the pre-administration of naloxone, indicating the possible participation of opioid receptors on the antinociceptive response.

The major component of the EO from plants of the Labiatae family is pulegone **89**, a monoterpene with two enantiomeric forms. (*R*)-(+)-Pulegone is the major constituent (73.4 %) of *Mentha pulegium* flowers EO.[329] The antinociceptive properties of (*R*)-(+)-pulegone **89** was studied by de Sousa *et al.*[311] using the formalin and the hot plate tests. It was observed that (*R*)-(+)-pulegone inhibits in a dose-dependent manner both phases of the formalin test, similarly to morphine and the effect was not blocked by naloxone. A positive effect of (*R*)-(+)-pulegone was also observed in the hot plate test, with an increase in the reaction time latency.[329]

7. Conclusions

This review attempts to shed light on the therapeutic potential of EOs and some of their isolated volatile constituents in the prevention or therapy of pain. As can be seen by the analysis of more than 300 articles, EOs and their constituents show antinociceptive effects in different models and their action mechanism is quite variable. There are, however, a limited number of commercially available analgesic drugs based on or made from EOs and terpenoids. The new techniques to improve the effectiveness of terpenoids as a therapetutic agent, such as the complexation

with β-CD, which allows the controlled liberation of the active molecule, can contribute to increase the number of natural compounds-based drugs in the market. The chemical modification of EOs and their constituents, aiming to improve the water-solubility or to reduce their volatility are also alternatives to be considered. The authors hope that this review attracts the attention of researchers who are seeking for new, natural occurring drugs to consider EOs and their constituents in a near future for additional clinical evaluations and possible applications.

Acknowledgements

The authors are grateful to CAPES, CNPq and FAPERGS for financial support.

Eder J. Lenardão *was born in 1968 in Sabáudia-PR, Brazil. He received his BSc from State University of Londrina and MSc degree from Federal University of Santa Maria-RS under the guidance of Prof Claudio C. Silveira. In 1997, he earned a PhD degree in organic chemistry at University of São Paulo, under the guidance of Prof Miguel J. Dabdoub and in 2003, he worked with Prof Antonio L. Braga at UFSM as a postdoctoral fellow. His research interest lies in the area of organic and green chemistry.*

Lucielli Savegnago *is graduated in Pharmacy-Clinical Analysis from the Federal University of Santa Maria (2001), Master's in Biochemistry by the Federal University of Santa Maria (2004) and PhD in Biochemistry from Federal University of Santa Maria (2007). Her current research interests center around the study of organoselenium compounds with antioxidant, antinociceptive and antidepressant-like activities.*

Raquel G. Jacob *was born in 1964 in Rio de Janeiro-RJ, Brazil. She received her BSc (1989) and MSc degrees (1994) from Federal University of Rio de Janeiro (Brazil) under the guidance of Prof Claudio C. Neto. In 1998, she earned a PhD degree in organic chemistry at University of São Paulo, under the guidance of Prof Miguel J. Dabdoub and in 2005 she worked with Prof Antonio L. Braga at UFSM as a postdoctoral fellow. Her research interest lies in the area of structural modifications in essential oils and their constituents by using clean methods.*

Francine N. Victoria *was born in Pelotas, Brazil. She received her MSc dregree (2010) and her PhD degree in Food Science and Technology (2013), working under the guidance of Prof Eder João Lenardão, at the Federal University of Pelotas (UFPel). Currently, she is Professor at the Center of Chemical, Pharmaceutical and Food Sciences at UFPel. Her scientific interests include biological activity of natural compounds, like essential oils and fruits extracts, with emphasis in their effect on the oxidative stress.*

Débora M. Martinez *was born in Cascavel, Brazil. She received her MSc dregree from the Federal University of Pelotas-RS in 2011 and her PhD degree in Food Science and Technology (2014) working under the direction of Prof Eder João Lenardão. She is currently postdoctoral fellow with Prof Rafael Radi at the Center for Free Radical and Biomedical Research (CEINBIO), Uruguay, with a CNPq Postdoctoral Fellowship. Her current research interests center on the study of natural antioxidants analogs against nitroxidative stress conditions in model systems.*

References

1. Calixto, J. B.; Campos, M. M.; Santos, A. R. S.; *Botanical Analgesic & Antiinflamatory Drug*, *Ethnopharmacology, Vol. II - Encyclopedia of Life Support Systems (EOLSS)*; EOLSS Publishers: Oxford, 2007.
2. Martínez, M. J.; Betancourt, J.; Alonso-González, N.; Jauregui, A.; *J. Ethnopharmacol.* **1996**, *52*, 171.
3. Calixto, J. B.; Beirith, A.; Ferreira, J.; Santos, A. R. S.; Cechinel Filho, V.; Yunes, R. A.; *Phytother. Res.* **2000**, *14*, 401.
4. Butler, D.; *Nature* **2008**, *453*, 840.
5. Li, J. W. H.; Vederas, J. C.; *Science* **2009**, *325*, 161.
6. Almeida, R. N.; Navarro, D. S.; Barbosa-Filho, J. M.; *Phytomedicine* **2001**, *8*, 310.
7. Silva, M. A. G.; Aquino, N. M. R.; Moura, B. A.; de Sousa, H. L.; Lavor, E. P. H.; Vasconcelos, P. F.; Macedo, D. S.; de Sousa, D. P.; Vasconcelos, S. M. M.; de Sousa, F. C. F.; *Fitoterapia* **2009**, *80*, 506.
8. Yunes, R. A.; Cechinel Filho, V.; Ferreira, J.; Calixto, J. B.; *Stud. Nat. Prod. Chem.* **2005**, *30*, 191.

9. Farmilo, C. G.; Rhodes, H. L. J.; Hart, H. R. L.; Taylor, H.; *Bull. Narc.* **1953**, *5*, 26.
10. Franz, C.; Novak, J. In *Handbook of Essential Oils: Science, Technology, and Applications*; Baser, K. H. C.; Buchbauer, G., eds.; CRC Press: New York, 2010.
11. Harrewijn, P.; van Oosten, A. M.; Piron, P. G. M.; *Natural Terpenoids as Messengers: a Multidisciplinary Study of Their Production, Biologica1 Functions, and Practical Applications*; Kluwer Academic Publishers: Dordrecht, 2000.
12. Dobetsberger, C.; Buchbauer, D.; *Flavour Frag. J.* **2011**, *26*, 300.
13. Adorjan, B.; Buchbauer, G.; *Flavour Frag. J.* **2010**, *25*, 407.
14. Navarra, M.; Mannucci, C.; Delbò, M.; Calapai, G.; *Front. Pharmacol.* **2015**, *6*, 36.
15. Woronuk, G.; Demissie, Z.; Rheault, M.; Mahmoud, S.; *Planta Medica* **2011**, *77*, 7.
16. de Sousa, D. P.; *Molecules* **2011**, *16*, 2233.
17. Guimarães, A. G.; Quintans, J. S.; Quintans Jr., L. J.; *Phytother. Res.* **2013**, *27*, 1.
18. Gonzalez-Burgos, E.; Gomez-Serranillos, M. P.; *Curr. Med. Chem.* **2012**, *19*, 5319.
19. Huang, M.; Lu, J. J.; Huang, M. Q.; Bao, J. L.; Chen, X. P.; Wang, Y. T.; *Expert Opin. Invest. Drugs* **2012**, *21*, 1801.
20. Sá, R. C. S.; Andrade, L. N.; Oliveira R. R. B.; de Sousa, D. P.; *Molecules* **2014**, *19*, 1459.
21. Amorim, A. C. L.; Lima, C. K. F.; Hovell, A. M. C.; Miranda, A. L. P.; Rezende, C. M.; *Phytomedicine* **2009**, *16*, 923.
22. Guimarães, A. G.; Serafini, M. R.; Quintans Jr., L. J.; *Expert Opin. Ther. Pat.* **2014**, *24*, 243.
23. Marreto, R. N.; Almeida, E. E. C. V.; Alves, P. B.; Niculau, E. S.; Nunes, R. S.; Matos, C. R. S.; Araújo, A. A. S.; *Thermochim. Acta* **2008**, *475*, 53.
24. Pinho, E.; Grootveld, M.; Soares, G.; Henriques, M.; *Carbohydr. Polym.* **2014**, *101*, 121.
25. Brito, R. G.; Araújo, A. A.; Quintans, J. S.; Sluka, K. A.; Quintans Jr., L. J.; *Expert Opin. Drug Deliv.* **2015**, *12*, 1677.
26. Clifford, J.; Woolf, M. D.; *Ann. Intern. Med.* **2004**, *140*, 441.
27. Burian, M.; Geisslinger, G.; *Pharmacol. Ther.* **2005**, *107*, 139.
28. Gottschalk, A.; Smith, D. S.; *Am. Fam. Physician* **2001**, *6*, 1979.
29. Besson, J. M.; *Lancet* **1999**, *353*, 1610.
30. Collis, M. G.; Hourani, S. M. O.; *Trends Pharmacol. Sci.* **1993**, *14*, 360.
31. Millan, M. J.; *Prog. Neurobiol.* **1999**, *57*, 1.
32. Hille, B.; *Ion Channels of Excitable Membranes*, 3rd ed.; Sinauer Associates: Sunderland, 2001.
33. Wood, J. N.; Docherty, R.; *Annu. Rev. Physiol.* **1997**, *59*, 457.
34. Pang, M.; Kim, Y.; Jung, K. W.; Cho, S.; Lee, D. H.; *Drug Discovery Today* **2012**, *17*, 425.
35. Steinmeyer, J.; *Arthritis Res.* **2000**, *2*, 379.
36. Warner, E. A.; *Am. J. Med.* **2012**, *12*, 1155.
37. Haghparast, A.; Khani, A.; Lashgari, R.; Fallahian, S.; *Drug Alcohol Depen.* **2008**, *93*, 185.
38. Pourmotabbed, A.; Rostamian, B.; Manouchehri, G.; Pirzadeh-Jahromi, G.; Sahraei, H.; Ghoshooni, H.; Zardooz, H.; Kamalnegad, M.; *J. Ethnopharmacol.* **2004**, *95*, 431.
39. Pasternak, G. W.; *J. Clin. Invest.* **2007**, *117*, 3185.
40. Bie, B.; Pan, Z. Z.; *Mol. Pain* **2005**, *1*, 1.
41. Nestler, E. J.; *Trends Pharmacol. Sci.* **2004**, *25*, 210.
42. Furst, D. E.; Paulus, H. E. In *Arthritis and Allied Conditions*; McCarty, D. J.; Koopman, W. J., eds.; Lea & Febiger: Philadelphia, 1993.
43. Kirtikara, K.; Swangkul, S.; Ballou, L. R.; *Inflamm. Res.* **2001**, *50*, 327.
44. Smith, W. L.; Meade, E. A.; de Witt, D. L.; *Ann. N. Y. Acad. Sci.* **1994**, *744*, 50.
45. Garavito, R. M.; de Witt, D. L.; *Biochim. Biophys. Acta* **1999**, *1441*, 278.
46. Aïd, S.; Bosetti, F.; *Biochimie* **2011**, *93*, 46.
47. Scheiman, J. M.; *Gastroenterol. Clin. North Am.* **1996**, *25*, 279.
48. O'Banion, M. K.; *Crit. Rev. Neurobiol.* **1999**, *13*, 45.
49. Macintyre, P. E.; Scott, D. A.; Schug, S. A.; Visser, E. J.; Walker, S. M.; *APM:SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine*, *Acute Pain Management: Scientific Evidence*, 3rd ed.; ANZCA & FPM: Melbourne, 2010.
50. Botting, R.; Ayoub, S. S.; *Prostaglandins, Leukotrienes Essent. Fatty Acids* **2005**, *72*, 85.
51. Chen, L. C.; Ashcroft, D. M.; *Headache* **2008**, *48*, 236.
52. Hauser, W.; Bernardy, K.; Uceyler, N.; Sommer, C.; *JAMA, J. Am. Med. Assoc.* **2009**, *301*, 198.
53. Andrews, N.; O'Neill, M. F.; *Curr. Opin. Pharmacol.* **2011**, *11*, 39.
54. Calixto, J. B.; Scheidt, C.; Otuki, M.; Santos, A. R. S.; *Expert Opin. Emerging Drugs* **2001**, *6*, 261.
55. Calixto, J. B.; Otuki, M. F.; Santos, A. R. S.; *Planta Med.* **2003**, *69*, 973.
56. Veeresham, C.; *J. Adv. Pharm. Technol. Res.* **2012**, *3*, 200.
57. Le Bars, D.; Gozariu, M.; Cadden, S. W.; *Pharmacol. Rev.* **2001**, *53*, 597.
58. Collier, H. O.; Dinneen, L. C.; Johnson, C. A.; Schneider, C.; *Br. J. Pharmacol. Chemother.* **1968**, *32*, 295.
59. Vinegar, R.; Truax, J. F.; Selph, J. L.; Johnston, P. R. In *Handbook of Experimental Pharmacology*, *Vol. 50/II*; Vane, J. R.; Ferreira, S. H., eds.; Springer-Verlag: Berlin, 1979.
60. Koster, R.; Anderson, M.; de Beer, E. J.; *Fed. Proc.* **1959**, *18*, 412.
61. Fukawa, K.; Kawano, O.; Hibi, M.; Misaki, M.; Ohba, S.; Hatanaka, Y.; *J. Pharmacol. Methods* **1980**, *4*, 251.
62. Vogel, H. G.; Vogel, W. H.; *Drug Discovery and Evaluation*; Springer: Berlin, 1997.

63. Guimarães, A. G.; Oliveira, G. F.; Melo, M. S.; Cavalcanti, S. C. H.; Antoniolli, A. R.; Bonjardim, L. R.; Silva, F. A.; Santos, J. P. A.; Rocha, R. F.; Moreira, J. C. F.; Araújo, A. A. S.; Gelain, D. P.; Quintans Jr., L. J.; *Basic Clin. Pharmacol. Toxicol.* **2010**, *107*, 949.
64. Deraedt, R.; Jougney, S.; Delevalcee, F.; Falhout, M.; *Eur. J. Pharmacol.* **1980**, *61*, 17.
65. Ikeda, Y.; Ueno, A.; Naraba, H.; Oh-Ishi, S.; *Life Sci.* **2001**, *69*, 2911.
66. Martínez, V.; Thakur, S.; Mogil, J. S.; Taché, Y.; Mayer, E. A.; *Pain* **1999**, *81*, 163.
67. Duarte, I. D.; Nakamura, M.; Ferreira, S. H.; *Braz. J. Med. Biol. Res.* **1988**, *21*, 341.
68. Franzotti, E. M.; Santos, C. V. F.; Rodrigues, H. M. S. L.; Mourão, R. H. V.; Andrade, M. R.; Antoniolli, A. R.; *J. Ethnopharmacol.* **2000**, *72*, 273.
69. Santos, F. A.; Jeferson, F. A.; Santos, C. C.; Silva, E. R.; Rao, V. S. N.; *Life Sci.* **2005**, *77*, 2953.
70. Hunskaar, S.; Hole, K.; *Pain* **1987**, *30*, 103.
71. Coderre, T. J.; Melzack, R.; *J. Neurosci.* **1992**, *12*, 3665.
72. Abbadie, C.; Taylor, B. K.; Peterson, M. A.; Basbaum, A. I.; *Pain* **1997**, *69*, 101.
73. Raboisson, P.; Dallel, R.; *Neurosci. Biobehav. Rev.* **2004**, *28*, 219.
74. Capuano, A.; de Corato, A.; Treglia, M.; Tringali, G.; Russo, C. D.; Navarra, P.; *Eur. J. Pharmacol.* **2009**, *605*, 57.
75. Okuse, K.; *Int. J. Biochem. Cell Biol.* **2007**, *39*, 490.
76. McNamara, C. R.; Mandel-Brehm, J.; Bautista, D. M.; Siemens, J.; Deranian, K. L.; Zhao, M.; Hayward, N. J.; Chong, J. A.; Julius, D.; Moran, M. M.; Fanger, C. M.; *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 13525.
77. Hunter, J. C.; Singh, L.; *Neurosci. Lett.* **1994**, *174*, 217.
78. Chen, Y. F.; Tsai, H. Y.; Wu, T. S.; *Planta Med.* **1995**, *61*, 2.
79. Elisabetsky, E.; Amador, T. A.; Albuquerque, R. R.; Nunes, D. S.; Carvalho, A. C. T.; *J. Ethnopharmacol.* **1995**, *48*, 77.
80. Rosland, J. H.; Tjolsen, A.; Maehle, B.; Hole, D. K.; *Pain* **1990**, *42*, 235.
81. Caterina, M. J.; Leffler, A.; Malmberg, A. B.; Martin, W. J.; Trafton, J.; Petersen-Zeitz, K. R.; Koltzenburg, M.; Basbaum, A. I.; Julius, D.; *Science* **2000**, *288*, 306.
82. Gottrup, H.; Juhl, G.; Kristensen, A. D.; Lai, R.; Chizh, B. A.; Brown, J.; Bach, F. W.; Jensen, T. S.; *Anesthesiology* **2004**, *101*, 1400.
83. Torebjork, H. E.; Lundberg, L. E.; la Motte, R. H.; *J. Physiol.* **1992**, *448*, 765.
84. Woolf, C. J.; *Pain* **2011**, *152*, S2.
85. Sakurada, T.; Katsumata, K.; Tan-No, K.; Sakurada, S.; Kisara, K.; *Neuropharmacology* **1992**, *31*, 1279.
86. Pelissier, T.; Pajot, J.; Dallel, R.; *Pain* **2002**, *96*, 81.
87. Hughes, A.; Macleod, A.; Growcott, J.; Thomas, I.; *Pain* **2002**, *99*, 323.
88. Sakurada, T.; Yogo, H.; Katsumata, K.; Tan-No, K.; Sakurada, S.; Kisara, K.; *Brain Res.* **1994**, *646*, 319.
89. Gamse, R.; Molnar, A.; Lembeck, F.; *Life Sci.* **1979**, *25*, 629.
90. Sorkin, L. S.; McAdoo, D. J.; *Brain Res.* **1993**, *607*, 89.
91. Calixto, J. B.; Kassuya, C. A.; Ferreira, A. E.; *Pharmacol. Ther.* **2005**, *106*, 179.
92. di Marzo, V.; Blumberg, P. M.; Szallasi, A.; *Curr. Opin. Neurobiol.* **2002**, *12*, 372.
93. Szallasi, A.; Cortright, D. N.; Blum, C. A.; Eid, S. R.; *Nat. Rev. Drug Discovery* **2007**, *6*, 357.
94. Sakurada, T.; Matsumura, T.; Moriyama, T.; Sakurada, C.; Ueno, S.; Sakurada, S.; *Pharmacol. Biochem. Behav.* **2003**, *75*, 115.
95. Santos, A. R. S.; Calixto, J. B.; *Neuropeptides* **1997**, *31*, 381.
96. Beirith, A.; Santos, A. R. S.; Calixto, J. B.; *Brain Res.* **2002**, *924*, 219.
97. Jackson, D. L.; Graff, C. B.; Richardson, J. D.; Hargreaves, K. M.; *Eur. J. Pharmacol.* **1995**, *284*, 321.
98. Zhou, S.; Bonasera, L.; Carlton, S. M.; *NeuroReport* **1996**, *7*, 895.
99. McNearney, T.; Speegle, D.; Lawand, N. B.; Lisse, J.; Westlund, K. N.; *J. Rheumatol.* **2000**, *27*, 739.
100. Hudspith, M. J.; *Br. J. Anaesth.* **1997**, *78*, 731.
101. Neugebauer, V.; *Expert Rev. Neurother.* **2001**, *1*, 207.
102. Neugebauer, V.; *Trends Neurosci.* **2001**, *24*, 550.
103. Carlton, S. M.; Zhou, S.; Coggeshall, R. E.; *Brain Res.* **1998**, *790*, 160.
104. Chizh, B. A.; *Amino Acids* **2002**, *23*, 169.
105. Lufty, K.; Cai, S. X.; Woodward, R. M.; Weber, E.; *Pain* **1997**, *70*, 31.
106. Yaksh, T. L.; Rudy, T. A.; *Pain* **1978**, *4*, 299.
107. Grumbach, L. In *The Prediction of Analgesic Activity in Man by Animal Testing*; Knighton, R. S.; Dumke, P. R., eds.; Pain Little Brown and Co.: Boston, 1966.
108. Bannon, A. W. In *Current Protocols in Pharmacology*; John Wiley & Sons: New Jersey, 2001, ch. 5.7.1-11.
109. Yeomans, D. C.; Proudfit, H. K.; *Pain* **1996**, *68*, 141.
110. Taber, R. I. In *Advances in Biochemical Psychopharmacology*; Braude, M. C.; Harris, L. S.; May, E. L.; Smith, J. P.; Villareal, J. E., eds.; Raven Press: New York, 1974.
111. Pearce, J. M. S.; *J. Neurol., Neurosurg. Psychiatry* **2006**, *77*, 1317.
112. Lambert, G. A.; Mallos, G.; Zagami, A. S.; *J. Neurosci. Methods* **2009**, *177*, 420.
113. Randall, L. O.; Selitto, J. J.; *Arch. Int. Pharmacodyn. Ther.* **1957**, *111*, 409.
114. Vaidya, A. B.; Antarkar, V. D. S.; *J. Assoc. Physicians India* **1994**, *42*, 221.
115. Bakkali, F.; Averbeck, S.; Averbeck, D.; Idaomar, M.; *Food Chem. Toxicol.* **2008**, *46*, 446.

116. Piccinelli, A. C.; Santos, J. A.; Konkiewitz, E. C.; Oesterreich, S. A.; Formagio, A. S. N.; Croda, J.; Ziff, E. B.; Kassuya, C. A. L.; *Nutr. Neurosci.* **2015**, *18*, 217.
117. Sousa, O. V.; Soares Jr., D. T.; Del-Vechio, G.; Mattosinhos, R. G.; Gattass, C. R.; Kaplan, M. A. C.; *Rev. Bras. Farmacogn.* **2004**, *14*, 11.
118. Sousa, O. V.; Del-Vechio-Vieira, G.; Alves, M. S.; Araújo, A. A. L.; Pinto, M. A. O.; Amaral, M. P. H.; Rodarte, M. P.; Kaplan, M. A. C.; *Molecules* **2012**, *17*, 11056.
119. Queiroz, J. C. C.; Antoniolli, A. R.; Quintans Jr., L. J.; Brito, R. G.; Barreto, R. S. S.; Costa, E. V.; da Silva, T. B.; Prata, A. P. N.; de Lucca Jr., W.; Almeida, J. R. G. S.; Lima, J. T.; Quintans, J. S. S.; *Sci. World J.* **2014**, *2014*, 816450.
120. Hajhashemi, V.; Sajjadi, S. E.; Zomorodkia, M.; *Pharm. Biol.* **2011**, *49*, 146.
121. Zendehdel, M.; Torabi, Z.; Hassanpour, S.; *Vet. Med.-Czech.* **2015**, *60*, 63.
122. Hejazian, S. H.; *World J. Med. Sci.* **2006**, *2*, 95.
123. Sayyah, M.; Peirovi, A.; Kamalinejad, M.; *Iran. Biomed. J.* **2002**, *6*, 141.
124. Goés, L. D. M.; Carvalho, H. O.; Duarte, J. L.; Salgueiro, L. R.; Cavaleiro, C.; Perazzo, F. F.; Carvalho, J. C. T.; *Afr. J. Pharm. Pharmacol.* **2015**, *9*, 460.
125. Hajhashemi, V.; Sajjadi, S. E.; Heshmati, M.; *J. Ethnopharmacol.* **2009**, *124*, 475.
126. Jamshidzadeh, A.; Hamedi, A.; Altalqi, A.; Najibi, A.; *Int. J. Pharm. Res. Scholars* **2014**, *3*, 228.
127. Isçan, G.; Kirimer, N.; Kürkçüoglu, M.; Arabaci, T.; Küpeli, E.; Baser, K. H.; *J. Agric. Food Chem.* **2006**, *54*, 170.
128. Del-Vechio-Vieira, G.; de Sousa, O. V.; Miranda, M. A.; Senna-Valle, L.; Kaplan, M. A. C.; *Braz. Arch. Biol. Technol.* **2009**, *52*, 1115.
129. Hadi, A.; Hossein, N.; Shirin, P.; Najmeh, N.; Abolfazl, M.; *Int. J. Pharm. Sci. Rev. Res.* **2014**, *24*, 237.
130. Maham, M.; Moslemzadeh, H.; Jalilzadeh-Amin, G.; *Pharm. Biol.* **2014**, *52*, 208.
131. Leite, G. O.; Leite, L. H. I.; Sampaio, R. S.; Araruna, M. K. A.; Rodrigues, F. F. G.; Menezes, I. R. A.; Costa, J. G. M.; Campos, A. R.; *Biomed. Prev. Nutr.* **2011**, *1*, 216.
132. Santos, N. A.; Viana, G. B.; Cunha, W.; Campos, A. R.; da Costa, J. M.; *Int. J. Green Pharm.* **2015**, *9*, 138.
133. Rao, V. S.; Maia, J. L.; Oliveira, F. A.; Lemos, T. L. G.; Chaves, M. H.; Santos, F. A.; *Nat. Prod. Commun.* **2007**, *2*, 1199.
134. Biradar, S.; Kangralkar, V. A.; Mandavkar, Y.; Thakur, M.; Chougule, N.; *Int. J. Pharm. Pharm. Sci.* **2010**, *2*, 112.
135. Rabelo, A. S.; Serafini, M. R.; Rabelo, T. K.; de Melo, M. G.; Prado, D. S.; Gelain, D. P.; Moreira, J. C.; Bezerra, M. S.; da Silva, T. B.; Costa, E. V.; Nogueira, P. C. L.; Moraes, V. R. S.; Prata, A. P. N.; Quintans Jr., L. J.; Araújo, A. A.; *BMC Complementary Altern. Med.* **2014**, *14*, 514.
136. Ximenes, R. M.; Nogueira, L. M.; Cassundé, N. M. R.; Jorge, R. J. B.; Santos, S. M.; Magalhães, L. P. M.; Silva, M. R.; Viana, G. S. B.; Araújo, R. M.; de Sena, K. X. F. R.; Albuquerque, J. F. C.; Martins, R. D.; *J. Nat. Med.* **2013**, *67*, 758.
137. Nogueira, L. M.; da Silva, M. R.; dos Santos, S. M.; de Albuquerque, J. F. C.; Ferraz, I. C.; de Albuquerque, T. T.; Mota, C. R. F. C.; Araújo, R. M.; Viana, G. S. B.; Martins, R. D.; Havt, A.; Ximenes, R. M.; *J. Evidence-Based Complementary Altern. Med.* **2015**, article ID 620865.
138. Abdon, A. P. V.; Leal-Cardoso, J. H.; Coelho-de-Souza, A. N.; Morais, S. M.; Santos, C. F.; *Braz. J. Med. Biol. Res.* **2002**, *35*, 1215.
139. Arrigoni-Blank, M. F.; Antoniolli, A. R.; Caetano, L. C.; Campos, D. A.; Blank, A. F.; Alves, P. B.; *Phytomedicine* **2008**, *15*, 334.
140. Raymundo, L. J. R. P.; Guilhon, C. C.; Alviano, D. S.; Matheus, M. E.; Antoniolli, A. R.; Cavalcanti, S. C. H.; Alves, P. B.; Alviano, C. S.; Fernandes, P. D.; *J. Ethnopharmacol.* **2011**, *134*, 725.
141. Evandri, M. G.; Battinelli, L.; Daniele, C.; Mastrangelo, S.; Bolle, P.; Mazzanti, G.; *Food Chem. Toxicol.* **2005**, *43*, 1381.
142. Barocelli, E.; Calcina, F.; Chiavarini, M.; Impicciatore, M.; Bruni, R.; Biachi, A.; Ballabeni, V.; *Life Sci.* **2004**, *76*, 213.
143. Hasanein, P.; Riahi, H.; *Med. Princ. Pract.* **2015**, *24*, 47.
144. Sousa, P. J. C.; Linard, C. G. B. M.; Batista, D. A.; Oliveira, A. C.; Coelho-de-Souza, A. N.; Leal-Cardoso, J. H.; *Braz. J. Med. Biol. Res.* **2009**, *42*, 655.
145. Ricci, E. L.; Toyama, D. O.; Lago, J. H. G.; Romoff, P.; Kirsten, T. B.; Reis-Silva, T. M.; Bernardi, M. M.; *J. Health Sci. Inst.* **2010**, *28*, 289.
146. Ali, T.; Javan, M.; Sonboli, A.; Semnanian, S.; *Nat. Prod. Res.* **2012**, *26*, 1529.
147. Ali, T.; Javan, M.; Sonboli, A.; Semnanian, S.; *Daru, J. Pharm. Sci.* **2012**, *20*, 1.
148. Araújo, B. S.; Venâncio, A. M.; Onofre, A. S. C.; Lira, A. F.; Alves, P. B.; Blank, A. F.; Antoniolli, A. R.; Marchioro, M.; Estevam, C. S.; *Planta Med.* **2011**, *77*, 825.
149. Venâncio, A. M.; Marchioro, M.; Estavam, C. S.; Melo, M. S.; Santana, M. T.; Onofre, A. S. C.; Guimarães, A. G.; Oliveira, M. G. B.; Alves, P. B.; Pimentel, H. C.; Quintans Jr., L. J.; *Braz. J. Pharmacog.* **2011**, *21*, 1043.
150. Rabelo, M.; Souza, E. P.; Soares, P. M. G.; Miranda, A. V.; Matos, F. J. A.; Criddle, D. N.; *Braz. J. Med. Biol. Res.* **2003**, *36*, 521.
151. Paula-Freire, L. I.; Andersen, M. L.; Molska, A. G. R.; Köhn, D. O.; Carlini, E. L. A.; *Phytother. Res.* **2013**, *27*, 1220.
152. Lino, C. S.; Gomes, P. B.; Lucetti, D. L.; Diógenes, J. P. L.; Sousa, F. C. F.; Silva, M. G. V.; Viana, G. S. V.; *Phytother. Res.* **2005**, *19*, 708.

153. Pinho, J. P. M.; Silva, A. S. B.; Pinheiro, B. G.; Sombra, I.; Bayma, J. C.; Lahlou, S.; Sousa, J. C.; Magalhães, P. J. C.; *Planta Med.* **2012**, *78*, 681.
154. Martínez, A. L.; González-Trujano, M. E.; Pellicer, F.; López-Muñoz, F. J.; Navarrete, A.; *Planta Med.* **2009**, *75*, 508.
155. Takaki, I.; Bersani-Amado, L. E.; Vendruscolo, A.; Sartoretto, S. M.; Diniz, S. P.; Bersani-Amado, C. A.; Cuman, R. K. N.; *J. Med. Food* **2008**, *11*, 741.
156. de Faria, L. R. D.; Lima, C. S.; Perazzo, F. F.; Carvalho, J. C. T.; *Int. J. Pharm. Sci. Rev. Res.* **2011**, *7*, 1.
157. Hajhashemi, V.; Ghannadi, A.; Pezeshkian, S. K.; *J. Ethnopharmacol.* **2002**, *82*, 83.
158. Hajhashemi, V.; Zolfaghari, B.; Yousefi, A.; *Med. Princ. Pract.* **2012**, *21*, 178.
159. Abdollahi, M.; Karimpour, H.; Monsef-Esfehani, H. R.; *Pharmacol. Res.* **2003**, *48*, 31.
160. Skouti, E.; Kattah, A.; Alachkar, A.; Hedda, J. B.; Vincieri, F.; *Int. J. Pharm. Pharm. Sci.* **2012**, *4*, 193.
161. Khalilzadeh, E.; Saiah, G. F.; Hasannejad, H.; Ghaderi, A.; Ghaderi, S.; Hamidian, G.; Mahmoudi, R.; Eshgi, D.; Zangisheh, M.; *Avicenna J. Phytomed.* **2015**, *5*, 218.
162. Khokra, S. L.; Jain, S.; Kaushik, P.; Kaushik, D.; *J. Biol. Act. Prod. Nat.* **2012**, *2*, 239.
163. Jaffary, F.; Ghannadi, A.; Siahpoush, A.; *Fitoterapia* **2004**, *75*, 217.
164. Liapi, C.; Anifandis, G.; Chinou, I.; Kourounakis, A. P.; Theodosopoulos, S.; Galanopoulou, P.; *Planta Med.* **2007**, *73*, 1247.
165. Silva, J.; Abebe, W.; Sousa, S. M.; Duarte, V. G.; Machado, M. I. L.; Matos, F. J. A.; *J. Ethnopharmacol.* **2003**, *89*, 277.
166. Guimarães, A. G.; Melo, M. S.; Bonfim, R. R.; Passos, L. O.; Machado, S. M. F.; Ribeiro, A. S.; Sobral, M.; Thomazzi, S. M.; Quintans Jr., L. J.; *Rev. Bras. Farmacogn.* **2009**, *19*, 883.
167. dos Santos, G. C. M.; Gomes, G. A.; Gonçalves, G. M.; de Sousa, L. M.; Santiago, G. M. P.; de Carvalho, M. G.; Marinho, B. G.; *Planta Med.* **2014**, *80*, 1588.
168. Quintão, N. L.; da Silva, G. F.; Antonialli, C. S.; Rocha, L. W.; Cechinel Filho, V.; Cicció, J. F.; *Planta Med.* **2010**, *76*, 1411.
169. Pinheiro, B. G.; Silva, A. S. B.; Souza, G. E. P.; Figueiredo, J. G.; Cunha, F. Q.; Lahlou, S.; Silva, J. K. R.; Maia, J. G. S.; Sousa, P. J. C.; *J. Ethnopharmacol.* **2011**, *138*, 479.
170. Lima, D. K.; Ballico, L. J.; Lapa, F. R.; Gonçalves, H. P.; de Souza, L. M.; Iacomini, M.; Werner, M. F.; Baggio, C. H.; Pereira, I. T.; da Silva, L. M.; Facundo, V. A.; Santos, A. R.; *J. Ethnopharmacol.* **2012**, *142*, 274.
171. Lima, G. M.; Melo, M. S.; Serafini, M. R.; Cavalcanti, S. C. H.; Gelain, D. P.; Santos, J. P. A.; Blank, A. F.; Alves, P. B.; Oliveira Neta, P. M.; Lima, J. T.; Rocha, R. F.; Moreira, J. C. F.; Araújo, A. A. S.; *Braz. J. Pharmacog.* **2012**, *22*, 443.
172. Viana, G. S. B.; Vale, T. G.; Pinho, R. S. N.; Matos, F. J. A.; *J. Ethnopharmacol.* **2000**, *70*, 323.
173. Abena, A. A.; Gbenou, J. D.; Yayi, E.; Moudachiroub, M.; Ongokac, R. P.; Ouamba, J. M.; Silou, T.; *Afr. J. Tradit., Complementary Altern. Med.* **2007**, *4*, 267.
174. Leite, B. L. S.; Bonfim, R. R.; Antoniolli, A. R.; Thomazzi, S. M.; Araújo, A. A. S.; Blank, A. F.; Estevam, C. S.; Cambui, E. V. F.; Bonjardim, L. R.; Albuquerque Jr., L. R. C.; Quintans Jr., L. J.; *Pharm. Biol.* **2010**, *48*, 1164.
175. Abdel-Fattah, A. M.; Matsumoto, K.; Watanabe, H.; *Eur. J. Pharmacol.* **2000**, *400*, 89.
176. Radulovic, N. S.; Miltojevic, A. B.; McDermott, M.; Waldren, S.; Parnell, A.; Pinheiro, M. M. G.; Fernandes, P. D.; Menezes, F. S.; *J. Ethnopharmacol*. **2011**, *135*, 610.
177. Pinheiro, M. M. G.; Miltojevic, A. B.; Radulovic, N. S.; Abdul-Wahab, I. R.; Boylan, F.; Fernandes, P. D.; *PLoS One* **2015**, *10*, e0121063.
178. Sakurada, S.; Sakurada, T.; Mizoguchi, H.; Kuwahta, H.; Katsuyama, S.; Komatsu, T.; Morrone, L. A.; Corasaniti, M. T.; Bagetta, G.; *Pharmacol. Biochem. Behav.* **2011**, *97*, 436.
179. Campêlo, L. M. L.; Almeida, A. A. C.; Freitas, R. L. M.; Cerqueira, G. S.; Sousa, G. F.; Saldanha, G. B.; Feitosa, C. M.; Freitas, R. M.; *J. Biomed. Biotechnol.* **2011**, article ID 678673.
180. Mendes, S. S.; Bomfim, R. R.; Jesus, H. C. T.; Alves, P. B.; Blank, A. F.; Estevam, C. S.; Antoniolli, A. R.; Thomazzi, S. M.; *J. Ethnopharmacol.* **2010**, *129*, 391.
181. Guilhon, C. C.; Raymundo, L. J. R. P.; Alviano, D. S.; Blank, A. F.; Arrigoni-Blank, M. F.; Matheus, M. E.; Cavalcanti, S. C. H.; Alviano, C. S.; Fernandes, P. D.; *J. Ethnopharmacol.* **2011**, *135*, 406.
182. Siqueira-Lima, P. S.; Araújo, A. A. S.; Lucchese, A. M.; Quintans, J. S. S.; Menezes, P. P.; Alves, P. B.; de Lucca Jr., W.; Santos, M. R. V.; Bonjardim, L. R.; Quintans Jr., L. J.; *Basic Clin. Pharmacol. Toxicol.* **2014**, *114*, 188.
183. Marçal, R. M.; Ptak, D. M.; Krempser, R. R.; Krempser, M. R.; Cardoso, G. C.; Santos, R. B.; Blank, A. F.; Alves, P. B.; *Planta Med.* **2006**, *72*, 291.
184. Pinho, F. V. S. A.; Coelho-de-Souza, A. N.; Morais, S. M.; Santos, C. F.; Leal-Cardoso, J. H.; *Phytomedicine* **2005**, *12*, 482.
185. Sulaiman, M. R.; Mohamad, T. A. S. T.; Mossadeq, W. S. M.; Moin, S.; Yusof, M.; Mokhtar, A. F.; Zakaria, Z. A.; Israf, D. A.; Lajis, N.; *Planta Med.* **2010**, *76*, 107.
186. Khalid, M. H.; Akhtar, M. N.; Mohamad, A. S.; Perimal, E. K.; Akira, A.; Israf, D. A.; Lajis, N. Sulaiman, M. R.; *J. Ethnopharmacol.* **2011**, *137*, 345.
187. Tang, W.; Eisenbrand, G.; *Chinese Drugs of Plant Origin. Chemistry, Pharmacology and Use in Traditional and Modern Medicine*; Springer-Verlag: Kaiserlautern, 1992.
188. Vendruscolo, A.; Takaki, I.; Bersani-Amado, L. E.; Dantas, J. A.; Bersani-Amado, C. A.; Cuman, R. K. N.; *Indian J. Pharmacol.* **2006**, *38*, 58.
189. Almeida, A. M.; Prado, P. I.; Lewinsohn, T. M.; *Plant Ecol.* **2004**, *174*, 163.

190. Guimarães, A. J. M.; Araújo, G. M.; Corrêa, G. F.; *Acta Bot. Bras.* **2002**, *16*, 317.
191. Bohlmann, F.; Ahmed, M.; King, R. M.; Robinson, H.; *Phytochemistry* **1981**, *20*, 1434.
192. Bohlmann, F.; Ludwig, G.-W.; Jakupovic, J.; King, R. M.; Robinson, H. A.; *Phytochemistry* **1983**, *22*, 983.
193. Lorenzi, H.; Matos, F. J. A.; *Plantas Medicinais no Brasil*; Instituto Plantarum: Nova Odessa, 2002.
194. Carvalho, J. C. T.; *Fitoterápicos Antiinflamatórios: Aspectos Químicos, Farmacológicos e Aplicações Terapêuticas*; Tecmedd Editora: São Paulo, 2004.
195. Arambewela, L. S. R.; Arawwawala, L. D. A. M.; Ratnasooriya, W. D.; *J. Ethnopharmacol.* **2004**, *95*, 311.
196. Leal-Cardoso, J. H.; Fonteles, M. C.; *An. Acad. Bras. Ciênc.* **1999**, *71*, 207.
197. Cavalcanti, B. C.; Ferreira, J. R.; Cabral, I. O.; Magalhães, H. I.; de Oliveira, C. C.; Rodrigues, F. A.; Rocha, D. D.; Barros, F. W.; da Silva, C. R.; Júnior, H. V.; Canuto, K. M.; Silveira, E. R.; Pessoa, C.; Moraes, M. O.; *Food Chem. Toxicol.* **2012**, *50*, 4051.
198. Balza, F.; Towers, G. H. N.; *Phytochemistry* **1984**, *23*, 2333.
199. Zhang, Y.; Zhang, J.; Yao, J.; Yang, Y. L.; Wang, L.; Dong, L. N.; *China J. Chin. Mater. Med.* **2005**, *30*, 594.
200. Sofi, P. A.; Zeerak, N. A.; Singh, P.; *Turk. J. Biol.* **2009**, *33*, 249.
201. Salehi, P.; Mohammadi, F.; Asghari, B.; *Chem. Nat. Compd.* **2008**, *44*, 111.
202. Devasankaraiah, G.; Hanin, I.; Haranath, P. S. R. K.; Ramanamurthy, P. S. V.; *Br. J. Pharmacog.* **1974**, *52*, 613.
203. Creche, J.; Tremouillaux-Guiller, J.; Groeger, D.; Chenieux, J. C.; Rideau, M. In *Biotechnology in Agriculture and Forestry 24 (Medicinal and Aromatic Plants V)*; Bajaj, Y. P. S., ed.; Springer: Berlin, 1993.
204. Benavente-García, O.; Castillo, J.; Marin, F. R.; Ortuno, A.; del Río, J. A.; *J. Agric. Food Chem.* **1997**, *45*, 4505.
205. Miyake, Y.; Yamamoto, K.; Morimitsu, Y.; Osawa, T.; *J. Agric. Food Chem.* **1997**, *45*, 4619.
206. Monforte, M.; Trovato, A.; Kirjarainen, S. A.; Forestieri, M.; Galati, E. M.; lo Curto, R. B.; *Farmaco* **1995**, *9*, 595.
207. Salantino, A.; Salantino, M. L. F.; Negri, G.; *J. Braz. Chem. Soc.* **2007**, *18*, 11.
208. Berry, P. E.; Hipp, A. L.; Wurdack, K. J.; van Ee, B.; Riina, R.; *Am. J. Bot.* **2005**, *92*, 1520.
209. Cartaxo, S. L.; Souza, M. M. A.; de Albuquerque, U. P.; *J. Ethnopharmacol.* **2010**, *131*, 326.
210. Craveiro, A. A.; Fernandes, A. G.; Andrade, C. H. S.; Matos, F. J. A.; Alencar, J. W.; *Ciênc. Cult.* **1977**, *29*, 445.
211. Fontenelle, R. O. S.; Moraisa, S. M.; Brito, E. H. S.; Brilhante, R. S. N.; Cordeiro, R. A.; Nascimento, N. R. F.; Kerntopf, M. R.; Sidrimc, J. J. C.; Rocha, M. F. G.; *J. Appl. Microbiol.* **2008**, *104*, 1383.
212. Matos, F. J. A.; *Plantas da Medicina Popular do Nordeste: Propriedades Atribuídas e Confirmadas*; EUFC: Fortaleza, 1999.
213. Saini, N.; Singh, G. K.; Nagori, B. P.; *Int. J. Res. Ayurveda Pharm.* **2014**, *5*, 74.
214. Borges, P.; Pino, J.; *Nahrung* **1993**, *37*, 123.
215. Fandohan, P.; Gnonlonfin, B.; Laleye, A.; Gbenou, J. D.; Darboux, R.; Moudachirou, M.; *Food Chem. Toxicol.* **2008**, *46*, 2493.
216. Barceloux, D. G.; *Citronella Oil [Cymbopogon nardus (L.) Rendle], in Medical Toxicology of Natural Substances: Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals*; John Wiley & Sons: Hoboken, 2008.
217. Nakahara, K.; Alzoreky, N. S.; Yoshihashi, T.; Nguyen, H. T. T.; Trakoontivakorn, G.; *JARQ* **2003**, *37*, 249.
218. Victoria, F. N.; Radatz, C. S.; Sachini, M.; Jacob, R. G.; Alves, D.; Savegnago, L.; Perin, G.; Motta, A. S.; da Silva, W. P.; Lenardão, E. J.; *Food Control* **2012**, *23*, 95.
219. Stone, S. C.; Vasconcellos, F. A.; Lenardão, E. J.; do Amaral, R. C.; Jacob, R. G.; Leite, F. P. L.; *Int. J. Appl. Res. Nat. Prod.* **2013**, *6*, 11.
220. Tawatsin, A.; Wratten, S. D.; Scott, R. R.; Thavara, U.; Techadamrongsin, Y.; *J. Vector Ecol.* **2001**, *26*, 76.
221. Cassel, E.; Vargas, R. M. F.; *J. Mex. Chem. Soc*. **2006**, *50*, 126.
222. Kilani, S.; Ben Ammar, R.; Bouhlel, I.; Abdelwahed, A.; Hayder, N.; Mahmoud, A.; Ghedira, K.; Chekir-Ghedira, L.; *Environ. Toxicol. Pharmacol.* **2005**, *20*, 478.
223. Morillas-Sánchez, L.; Fernández-López, C.; *Blancoana* **2006**, *22*, 65.
224. Leboeuf, M.; Cave, A.; Bhaumik, P. K.; Mukherjee, B.; Mukherjee, R.; *Phytochemistry* **1982**, *21*, 2783.
225. Parker, J. N.; Parker, P. M.; *Eucalyptus: A Medical Dictionary, Bibliography, and Annotated Research Guide to Internet References*; ICON Health Publications: San Diego, 2004.
226. Coppen, J. J. W.; *Eucalyptus the Genus Eucalyptus*; Taylor & Francis: London, 2002.
227. Auricchio, M. T.; Bacchi, E. M.; *Rev. Inst. Adolfo Lutz* **2003**, *62*, 55.
228. Victoria, F. N.; Lenardão, E. J.; Savegnago, L.; Perin, G.; Guimarães, R. J.; Alves, D.; da Silva, W. P.; da Motta, A. S.; Nascente, P. S.; *Food Chem. Toxicol.* **2012**, *50*, 2668.
229. Asgarpanah, J.; Mehrabani, G. D.; Ahmadi, M.; Ranjbar, R.; Ardebily, M. S.; *J. Med. Plants Res.* **2012**, *6*, 1813.
230. Manzoomi, N.; Ganbalani, G. N.; Dastjerdi, H. R.; Fathi, S. A. A.; *Mun. Ent. Zool.* **2010**, *5*, 118.
231. Bordignon, S. A. L.; *Napaea* **1992**, *8*, 1.
232. Fiaschi, P.; Pirani, J. R.; *Rev. Bras. Bot.* **2008**, *31*, 633.
233. Sayyah, M.; Saroukhani, G.; Peirovi, A.; Kamalinejad, M.; *Phytother. Res.* **2003**, *17*, 733.

234. Zargari, A.; *Medicinal Plants*, *Vol. 4*; Tehran University Publications: Tehran, 1990.
235. Riaz, M.; Ashraf, C. M.; Chaudhary, F. M.; *Pak. J. Sci. Ind. Res.* **1989**, *32*, 33.
236. Omidbaigi, R.; *Production and Processing of Medicinal Plants*, *Vol. 3*; Astane Ghods Publications: Mashhad, 2000.
237. Duke, J. A.; *CRC Handbook of Medicinal Herbs*; CRC Press: Boca Raton, 1989.
238. Leung, A. Y.; Foster, S.; *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics*; Wiley: New York, 1996.
239. Hajhashemi, V.; Ghannadi, A.; Sharif, B.; *J. Ethnopharmacol.* **2003**, *89*, 67.
240. Neto, R. M.; Matos, F. J. A.; Andrade, V. S.; de Melo, M. C. N.; Carvalho, C. B. M.; Guimarães, S. B.; Pessoa, O. D. L.; Silva, S. L.; Silva, S. F. R.; Vasconcelos, P. R. L.; *Rev. Bras. Farmacogn.* **2010**, *20*, 261.
241. Albuquerque, F. S.; Peso-Aguiar, M. C.; Assunção-Albuquerque, M. J.; *Braz. J. Biol.* **2008**, *68*, 837.
242. Pascual, M. E.; Slowing, K.; Carretero, E.; Sánchez-Mata, D.; Villar, A.; *J. Ethnopharmacol.* **2001**, *76*, 201.
243. Viana, G. S. B.; Matos, F. F.; Araújo, W. L.; Matos, F. J. A.; Craveiro, A. A.; *Q. J. Crude Drug Res.* **1981**, *19*, 1.
244. Aguiar, M. L. B. A.; Matos, F. J. A.; Moura, V. R. A.; *Ciênc. Cult.* **1984**, *36*, S547.
245. Canadanovic-Brunet, J.; Cetkovic, G.; Djilas, S.; Tumbas, V.; Bogdanovic, G.; Mandic, A.; Markov, S.; Cvetkovic, D.; Canadanovic, V.; *J. Med. Food* **2008**, *11*, 133.
246. Moradkhani, H.; Sargsyan, E.; Bibak, H.; Naseri, B.; Sadat-Hosseini, M.; Fayazi-Barjin, A.; Meftahizade, H.; *J. Med. Plants Res.* **2010**, *4*, 2753.
247. McKay, D. L.; Blumberg, J. B.; *Phytother. Res.* **2006**, *20,* 619.
248. Andrade, G. S.; Guimarães, A. G.; Santana, M. T.; Siqueira, R. S.; Passos, L. O.; Machado, S. M. F.; Ribeiro, A. S.; Sobral, M.; Almeida, J. R. G. S.; Quintans Jr., L. J.; *Rev. Bras. Farmacogn.* **2012**, *21*, 181.
249. Jamzad, Z.; Ingrouille, M.; Simmonds, M.; *Taxon.* **2003**, *52*, 92.
250. Lynn, C.; Smitherman, M. D.; James, J.; Mathur, A.; *Pediatrics* **2005**, *115*, 297.
251. Sonboli, A.; Salehi, P.; Yousefzadi, M.; *Z. Naturforsch.* **2004**, *59c*, 653.
252. Mojaba, F.; Nickavara, B.; Tehrani, H. H.; *Iran. J. Pharm. Sci.* **2009**, *5*, 43.
253. Khanna, T.; Zaidi, F. A.; Dandiya, P. C.; *Fitoterapia* **1993**, *5*, 407.
254. Zaoui, A.; Cherrah, Y.; Mahassine, N.; Alaoui, K.; Amarouch, H.; Hassar, M.; *Phytomedicine* **2002**, *9*, 69.
255. Badary, O. A.; Al-Shabanah, O. A.; Nagi, M. N.; Al-Bekairi, A. M.; Almazar, M. M. A.; *Drug Dev. Res.* **1998**, *44*, 56.
256. Telci, I.; Bayram, E.; Yilmaz, G.; Avci, B.; *Biochem. Syst. Ecol.* **2006**, *34*, 489.
257. Trevisan, M. T. S.; Silva, M. G. V.; Pfundstein, B.; Spiegelhalder, B.; Owen, R. W.; *J. Agric. Food Chem.* **2006**, *54*, 4378.
258. Boskabady, M. H.; Kiani, S.; Haghiri, B.; *Daru, J. Pharm. Sci.* **2005**, *13*, 28.
259. Braga, R.; *Plantas do Nordeste, Especialmente do Ceará*, *Coleção Mossoroense, XLIII*, 3ª ed.; Editora Universidade Federal do Rio Grande do Norte: Mossoró, 1992.
260. Grenand, P.; Moretti, C.; Jacquemin, H.; *Farmacopées Traditionnelles en Guyane*; Orstom Edition: Paris, 1987.
261. Gülçın, I.; Oktay, M.; Kireçci, E.; Küfrevioglu, O. I.; *Food Chem.* **2003**, *83*, 371.
262. Amaral, F. M. M.; Ribeiro, M. N. S.; Barbosa-Filho, J. M.; Reis, A. S.; Nascimento, F. R. F.; Macedo, R. O.; *Rev. Bras. Farmacog.* **2006**, *16*, 696.
263. Siani, A. C.; Ramos, M. F. S.; de Lima, M. O.; Santos, R.; Ferreira, F. E.; Soares, E. C.; Susunaga, G. S.; Guimarães, A. C.; Zoghbi, M. G. B.; Henriques, M. G. M. O.; *J. Ethnopharmacol.* **1999**, *66*, 57.
264. Allan, R. D.; Correl, R. L.; Wells, R. J.; *Tetrahedron Lett.* **1969**, *10*, 4669.
265. Kim, M. J.; Nam, E. S.; Paik, S. I.; *J. Korean Acad. Nurs.* **2005**, *35*, 186.
266. López-Muñoz, F. J.; Salazar, L. A.; Castañeda-Hernández, G.; Villarreal, J. E.; *Drug Dev. Res.* **1993**, *28*, 169.
267. Zegura, B.; Dobnik, B.; Niderl, M. N.; Filipi, M.; *Environ. Toxicol. Pharmacol.* **2011**, *32*, 296.
268. dos Santos, O. J.; Barros-Filho, A. K.; Malafaia, O.; Ribas-Filho, J. M.; Santos, R. H.; Santos, R. A.; *ABCD: Arq. Bras. Cir. Dig.* **2012**, *25*, 140.
269. Coutinho, I. H. I. L. S.; Torres, O. J. M.; Matias, J. E. F.; Coelho, J. C. U.; Stahlke Jr., H. J.; Agulham, M. A.; Bachle, E.; Camargo, P. A. M.; Pimentel, S. K.; de Freitas, A. C. T.; *Acta Cir. Bras.* **2006**, *21*, 49.
270. Cavalher-Machado, S. C.; Rosas, E. C.; Brito, F. A.; Heringe, A. P.; de Oliveira, R. R.; Kaplan, M. A.; Figueiredo, M. R.; Henriques, M. G. M. O.; *Int. Immunopharmacol.* **2008**, *8*, 1552.
271. Formagio, A. S. N.; Iriguchi, E. K. K.; Roveda, L. M.; Vieira, M. C.; Cardoso, C. A. L.; Zarate, N. A. H.; Tabaldi, L. A.; Kassuya, C. A. L.; *Lat. Am. J. Pharm.* **2011**, *30*, 1555.
272. Galati, E. M.; Mondello, M. R.; D'Aquino, A.; Miceli, N.; Sanogo, R.; Tzakou, O.; Monforte, M. T.; *J. Ethnopharmacol.* **2000**, *72*, 337.
273. Rosário, A. S.; Secco, R. S.; da Silva, J. B. F.; *Acta Amaz.* **2004**, *34*, 139.
274. Kamatou, G. P. P.; Viljoen, A. M.; *J. Am. Oil Chem. Soc.* **2010**, *87*, 1.
275. Stojkovic, D.; Sokovic, M.; Glamoclija, J.; Dzamic, A.; Ciric, A.; Ristic, M.; Grubisic, D.; *Food Chem.* **2011**, *128*, 1017.
276. Nasri, S.; Ebrahimi, S.; *J. Babol Univ. Med. Sci.* **2006**, *7*, 49.

277. Ravishankar, B.; Bhaskaran, R.; Sasikala, C. K.; *Bull. Med. Ethano. Biol. Res.* **1985**, *6*, 72.
278. Quintans, J. S. S.; Soares, B. M.; Ferraz, R. P. C.; Oliveira, A. C. A.; da Silva, T. B.; Menezes, L. R. A.; Sampaio, M. F. C.; Prata, A. P. N.; Moraes, M. O.; Pessoa, C.; Antoniolli, A. R.; Costa, E. V.; Bezerra, D. P.; *Planta Med.* **2013**, *79*, 123.
279. Basti, A. A.; Misaghi, A.; Khaschabi, B.; *LWT - Food Sci. Technol.* **2007**, *40*, 973.
280. Misaghi, A.; Basti, A. A.; *Food Control* **2007**, *18*, 1043.
281. Moosavy, M.; Basti, A. A.; Misaghia, A.; Salehi, T. Z.; Abbasifar, R.; Mousavid, H. A. E.; Alipoura, M.; Razavie, N. E.; Gandomia, H.; Nooria, N.; *Food Res. Int.* **2008**, *41*, 1050.
282. Li, Y.; Fabiano-Tixier, A. S.; Chema, F.; *Essential Oils as Reagents in Green Chemistry*; Springer: London, 2014.
283. Ipek, E.; Zeytinoglu, H.; Okay, S.; Tuylu, B. A.; Kurkcuoglu, M.; Baser, K. H. C.; *Food Chem.* **2005**, *93*, 551.
284. Santos, F. A.; Rao, V. S.; *Phytother. Res.* **2000**, *14*, 240.
285. de Lima, A. B.; Santana, M. B.; Cardoso, A. S.; da Silva, J. K. R.; Maia, J. G. S.; Sousa, P. J. C. C.; *Phytomedicine* **2009**, *16*, 555.
286. Paula-Freire, L. I. G.; Andersen, M. L.; Gama, V. S.; Molska, G. R.; Carlini, E. L. A.; *Phytomedicine* **2014**, *21*, 356.
287. Monzote, L.; Stamberg, W.; Staniek, K.; Gille, L.; *Toxicol. Appl. Pharmacol.* **2009**, *240*, 337.
288. Gonçalves, J. C.; Oliveira, F. S.; Benedito, R. B.; de Sousa, D. P.; de Almeida, R. N.; de Araújo, D. A.; *Biol. Pharm. Bull.* **2008**, *31*, 1017.
289. de Sousa, D. P.; Júnior, E. V. M.; Oliveira, F. S.; de Almeida, R. N.; Nunes, X. P.; Barbosa-Filho, J. M.; *Z. Naturforsch.* **2007**, *62c*, 39.
290. Ortiz, M. I.; Montiel, M. L. R.; García, M. P. G.; Monter, H. A. P.; Hernandez, G. C.; Cortés, R. C.; *Arch. Pharm. Sci. Res.* **2010**, *33*, 1691.
291. Quintans Jr., L. J.; Melo, M. S.; de Sousa, D. P.; Araújo, A. A. S.; Onofre, A. C. S.; Gelain, D. P.; Gonçalves, J. C. R.; Araújo, D. A. M.; Almeida, J. R. G. S.; Bonjardim, L. R.; *J. Orofac. Pain* **2010**, *24*, 305.
292. Melo, M. S.; Sena, L. C. S.; Barreto, F. J. N.; Bonjardim, L. R.; Almeida, J. R. G. S.; Lima, J. T.; de Sousa, D. P.; Quintans Jr., L. J.; *Pharm. Biol.* **2010**, *48*, 411.
293. Brito, R. G.; Guimarães, A. G.; Quintans, J. S. S.; Santos, M. R. V.; de Sousa, D. P.; Passos Jr., D. B.; Lucca Jr., W.; Brito, F. A.; Barreto, E. O.; Oliveira, A. P.; Quintans Jr., L. J.; *J. Nat. Med.* **2012**, *66*, 637.
294. Brito, R. G.; Santos, P. L.; Prado, D. S.; Santana, M. T.; Araújo, A. A. S.; Bonjardim, L. R.; Santos, M. R. V.; de Lucca Jr., W.; Oliveira, A. P.; Quintans Jr., L. J.; *Basic Clin. Pharmacol. Toxicol.* **2013**, *112*, 215.
295. Rios, E. R. V.; Rocha, N. F. M.; Carvalho, A. M. R.; Vasconcelos, L. F.; Dias, M. L.; de Sousa, D. P.; de Sousa, F. C. F.; Fonteles, M. M. F.; *Chem.-Biol. Interact.* **2013**, *203*, 573.
296. Johnson, A.; Kumar, R. A.; Rasheed, S. A.; Chandrika, S.; Chandrasekhar, A.; Baby, S.; Subramoniam, A.; *J. Ethnopharmacol.* **2010**, *130*, 267.
297. da Rocha, M. L.; Oliveira, L. E. G.; Santos, C. C. M. P.; Sousa, D. P.; Almeida, R. P.; Araújo, D. A. M.; *J. Nat. Med.* **2013**, *67*, 743.
298. Oliveira Jr., W. M.; Benedito, R. B.; Pereira, W. B.; Torres, P. A.; Ramos, C. A. F.; Costa, J. P.; Tomé, A. R.; de Sousa, D. P.; Freitas, R. M.; Diniz, M. F. F. M.; Almeida, R. N.; *Fundam. Clin. Pharmacol.* **2013**, *27*, 419.
299. de Sousa, D. P.; Oliveira, F. S.; Almeida, R. N.; *Biol. Pharm. Bull.* **2006**, *29*, 811.
300. de Oliveira, F. S.; de Sousa, D. P.; de Almeida, R. N.; *Biol. Pharm. Bull.* **2008**, *31*, 588.
301. Amaral, J. F.; Silva, M. I.; Neto, M. R.; Neto, P. F.; Moura, B. A.; de Melo, C. T.; de Araújo, F. L.; de Sousa, D. P.; de Vasconcelos, P. F.; de Vasconcelos, S. M.; de Sousa, F. C.; *Biol. Pharm. Bull.* **2007**, *30*, 1217.
302. Batista, P. A.; Werner, M. F. P.; Oliveira, E. C.; Burgos, L.; Pereira, P.; Brum, L. F. S.; dos Santos, A. R. S.; *Neurosci. Lett.* **2008**, *440*, 299.
303. Berliocchi, L.; Russo, R.; Levato, A.; Fratto, V.; Bagetta, G.; Sakurada, S.; Sakurada, T.; Mercuri, N. B.; Corasaniti, M. T.; *Int. Rev. Neurobiol.* **2009**, *85*, 221.
304. Peana, A. T.; D'Aquila, P. S.; Chessa, M. L.; Moretti, M. D. L.; Serra, G.; Pippia, P.; *Eur. J. Pharmacol.* **2003**, *460*, 37.
305. Peana, A. T.; Montis, M. G.; Sechi, S.; Sircana, G.; D'Aquila, P. S.; Pippia, P.; *Eur. J. Pharmacol.* **2004**, *497*, 279.
306. Peana, A. T.; Rubattu, P.; Piga, G. G.; Fumagalli, S.; Boatto, G.; Pippia, P.; Montis, M. G.; *Life Sci.* **2006**, *78*, 2471.
307. Batista, P. A.; Werner, M. F. P.; Oliveira, E. C.; Burgos, L.; Pareira, P.; Brum, L. F. S.; Story, G. M.; Santos, A. R. S.; *J. Pain* **2010**, *11*, 1222.
308. Galeotti, N.; Mannelli, L. C.; Mazzanti, G.; Bartolini, A.; Ghelardini, C.; *Neurosci. Lett.* **2002**, *322*, 145.
309. Yano, S.; Suzuki, Y.; Yukurihara, M.; Kase, Y.; Takeda, S.; Watanabe, S.; Aburada, M.; Miyamoto, K.; *Eur. J. Pharmacol.* **2006**, *553*, 99.
310. Silva, R. O.; Salvadori, M. S.; Sousa, F. B. M.; Santos, M. S.; Carvalho, N. S.; Sousa, D. P.; Gomes, P. S.; Oliveira, F. A.; Barbosa, A. L. R.; Freitas, R. M.; de Almeida, R. N.; Medeiros, J. R.; *Flavour Fragrance J.* **2014**, *29*, 184.
311. de Sousa, D. P.; Nóbrega, F. F. F.; de Lima, M. R. V.; de Almeida, R. N.; *Z. Naturforsch.* **2011**, *66c*, 353.
312. Estrella, E.; *Plantas Medicinales Amazonicas: Realidad y Perspectivas*; GEF/PNUD: Lima, 1995.
313. de Sousa, D. P.; Nóbrega, F. F. F.; Claudino, F. S.; de Almeida, R. N.; Leite, J. R.; Mattei, R.; *Braz. J. Pharmacog.* **2007**, *17*, 170.
314. Jenner, P. M.; Hagan, E. C.; Taylor, J. M.; Cook, E. L.; Fitzhugh, O. G.; *Food Cosmet. Toxicol.* **1964**, *2*, 327.

315. Raya, M. D. P.; Utrilla, M. P.; Navarro, M. C.; Jimenez, J.; *Phytother. Res.* **1990**, *4*, 232.
316. Dieter, M. P.; Goehl, T. J.; Jameson, C. W.; Elwell, M. R.; Hildebrandt, P. K.; Yuan, J. H.; *Food Chem. Toxicol.* **1993**, *31*, 463.
317. Pybus, D.; Sell, C.; *The Chemistry of Fragrances*; The Royal Society of Chemistry: Cambridge, 1999.
318. Iacobellis, N. S.; lo Cantore, P.; Capasso, F.; Senatore, F.; *J. Agric. Food Chem.* **2005**, *53*, 57.
319. Jirovetz, L.; Buchbauer, G.; Shafi, P. M.; Abraham, G. T.; *Acta Pharm. Turc.* **2001**, *43*, 107.
320. Khan, R.; Sultana, S.; *Chem.-Biol. Interact.* **2011**, *192*, 193.
321. Zhao, J.; Nan, P.; Zhong, Y.; *Z. Naturforsch.* **2004**, *59c*, 153.
322. Peana, A. T.; de Montis, M. G.; Nieddu, E.; Spano, M. T.; D'Aquila, P. S.; Pippia, P.; *Eur. J. Pharmacol.* **2004**, *485*, 165.
323. Verma, R. S.; Padali, R. C.; Yadav, A.; Chauhan, A.; *Rec. Nat. Prod.* **2010**, *4*, 163.
324. Bell, S. G.; Chen, X.; Sowden, R. J.; Xu, F.; Williams, J. N.; Wong, L.; Rao, Z.; *J. Am. Chem. Soc.* **2003**, *125*, 705.
325. Bhatia, S. P.; McGinty, D.; Letizia, C. S.; Api, A. M.; *Food Chem. Toxicol.* **2008**, *46*, S237.
326. Malingré, T.; Hendriks, H.; Batterman, S.; Bos, R.; Visser, J.; *Planta Med.* **1975**, *28*, 56.
327. Silva, M. G. V.; Craveiro, A. A.; Matos, F. J. A.; Machado, M. I. L.; Alencar, J. W.; *Fitoterapia* **1999**, *70*, 32.
328. Carvalho Jr., P. M.; Rodrigues, R. F. O.; Sawaya, A. C. H. F.; Marques, M. O. M.; Shimizu, M. T.; *J. Ethnopharmacol.* **2004**, *95*, 297.
329. Lorenzo, D.; Paz, D.; Dellacassa, E.; Davies, P.; Vila, R.; Cañigueral, S.; *Braz. Arch. Biol. Technol.* **2002**, *45*, 519.

Submitted: June 30, 2015
Published online: November 25, 2015

FAPERGS/CAPES has sponsored the publication of this article.