Abstract

Recently, numerous side effects of synthetic drugs have lead to using medicinal plants as a reliable source of new therapy. Pain is a health problem with a high impact on life quality and a huge economic implication, becoming one of the most important enemies in modern medicine. The medicinal use of plants as analgesic or antinociceptive drugs in traditional therapy is estimated to be about 80% of the world population. The Lamiaceae family, one of the most important herbal families, incorporates a wide variety of plants with biological and medical applications. In this study, the analgesic activity, possible active compounds of Lamiaceae genus, and also the possible mechanism of actions of these plants are presented. The data highlighted in this review paper provide valuable scientific information for the specifics of Lamiaceae plants in pain modulation that might be used for isolation of potentially active compounds from some of these medicinal plants in future and formulation of commercial therapeutic agents.

1. Introduction

Pain comes in many forms: acute, chronic, visceral, inflammatory, or neuropathic [1, 2]. It is not simply a result of tissue damage but also reflects the influence of many psychological variables such as attention, anxiety, stress [3], suggestion, or previous experiences and may have a significant genetic contribution [4]. Pain accompanies most pathologies present in current medical practice, and 25% percent of Americans, for example, experience pain on a daily basis. Having the numbers on its side, pain became a global public health problem and a leading cause of disability all over the world [5].

As life expectancy is rising and chronic pathologies along with it, the prevalence of accompanying pain is expected to increase yearly in prevalence in elderly patients, where the treatment is also more sensitive [6, 7]. Considering the above, new therapeutic agents, efficacy, less side effects, and lower costs and leading to an improved quality of life [8–11] should become one of the primary objectives in modern medical research, together with constant monitoring [12] of the previous mentioned aspects.

The medicinal use of plants as analgesic drugs in folk medicine is an ancient tradition, far older than the current sciences of medicine in developing countries [13, 14]. According to estimations, up to 70,000 plant species are used ethnomedicinally worldwide. Effects of herbal extracts have been studied by different pain tests including writhing test, light tail flick test, tail immersion test, hot-plate test, and formalin test [15]. The exploration for new analgesic combinations from the enormous arrays of medicinal plant resources is growing. This
information holds guarantees for the finding of new therapeutic agents capable of inhibiting, decreasing, or relieving pain. The Lamiaceae family characterize a vast natural supply of appreciated compounds that might achieve primary importance for the expansion of novel survey of the effectiveness of plant-based remedies used in the folk medicine has given great reflections because they are cheap and side effects.

According to the World Health Organization (WHO), about 80% of the world population still relies mainly on plant-based one lowering at the same time the impact of self-medication side effects [6]. The data in biomedical literature presenting plants capabilities are very similar to the array of publications depicting the modulatory effects certain ones have over pain perception.

The Lamiaceae family, one of the most important herbal families, incorporates a wide variety of plants with biological and medicinal uses due to the innumerable biological and medicinal uses and properties. The most known members of this family are a variety of aromatic spices like thyme, mint, oregano, basil, sage, savory, rosemary, sweet lemon balm, and some others with more limited use [31].

Our main objective was to perform a review of this literature for the specific implications of Lamiaceae family plants in pain modulation, aid the constant search for new potential agents of natural origin with analgesic effects.

2. Materials and Methods

The search strategy employed in this review includes internationally accepted databases, namely, ScienceDirect, Scopus, Web of Science, and PubMed, using specific keywords of both whole plant products and plant extracts, pain, and analgesic and antinociceptive effects. For a combination of keywords was used [pain; analgesic; antinociceptive; plant extract] + [Betonica officinalis; Glechoma hederacea; Lavandula; Leonurus cardiaca; Lamium; Melissa officinalis; Mentha; Marrubium vulgare; Origanum; Ocimum; Rosmarinus officinalis; Salvia hortensis; Stachys lavandulifolia; Scutellaria lateriflora; Sideritis; Teucrium; Thymus; Ziziphora tenuior] + [Lamiaceae; botanical genus] in case studies, in vivo and in vitro relevant studies, and comparative studies were included in this search strategy. Additionally, potential relevant reviews were explored and included in the reference list. The literature search was confined to the period between December 2017. Several articles before 2000 were also included in order to point out the universal interest in natural products applicability in therapy. The dynamic character of the field is reflected in the number of recent publications. For example, a keyword search strategy employed in this review includes internationally accepted databases, namely, ScienceDirect, Scopus, Web of Science, and PubMed, using specific keywords of both whole plant products and plant extracts, pain, and analgesic and antinociceptive effects. For a combination of keywords was used [pain; analgesic; antinociceptive; plant extract] + [Betonica officinalis; Glechoma hederacea; Lavandula; Leonurus cardiaca; Lamium; Melissa officinalis; Mentha; Marrubium vulgare; Origanum; Ocimum; Rosmarinus officinalis; Salvia hortensis; Stachys lavandulifolia; Scutellaria lateriflora; Sideritis; Teucrium; Thymus; Ziziphora tenuior] + [Lamiaceae; botanical genus] in case studies, in vivo and in vitro relevant studies, and comparative studies were included in this search strategy. Additionally, potential relevant reviews were explored and included in the reference list. The literature search was confined to the period between December 2017. Several articles before 2000 were also included in order to point out the universal interest in natural products applicability in therapy. The dynamic character of the field is reflected in the number of recent publications. For example, a search with the keywords "Lamiaceae family and pain" in ScienceDirect yields 152 titles in 2015, 111 in 2016, and 129 in 2017, and 23 papers will be published in the first months of the next year (Figure 1).

3. Species of the Lamiaceae Family with Potential Analgesic/Antinociceptive Effects

3.1. Rosmarinus Genus

Rosmarinus in the Lamiaceae family is a genus of woody, perennial herbs with fragrant evergreen needle-like leaves that are native to the Mediterranean Basin.

3.1.1. Rosmarinus officinalis

Rosmarinus officinalis L., commonly called rosemary, is a Mediterranean shrubbery herb and widely spread in European, American, and Asian countries. It is a common spice used worldwide for culinary, medicinal, and commercial uses, including the fragrance and food industry. The leaves of rosemary (fresh or dries) are used for their characteristic aroma in cooking or consumed in small amounts as herbal tea, while rosemary extracts are regularly used for their natural antioxidant active proprieties to improve the shelf life of perishable foods. Recently, rosemary (E392) have been approved as a safe and effective natural antioxidant for food preservation by the European Union [33].

Phytochemical studies have revealed that leaves contain 0.5% to 2.5% volatile oil. The major components of rosemary oil include hydrocarbons (alpha and beta-pinene), camphene, limonene, camphor (10% to 20%), borneol, cineole, linalool, and verbenol. Rosemary's widespread variety of volatile and aromatic components. Flavonoids in the plant consist of diosmetin, diosmin, genkwanin, luteolin, hispidulin, and apigenin [34–41]. Additionally, terpenoid components from rosemary consist of the triterpenes oleaneolic and ursolic acid and the triterpene carnosol. Phenols in rosemary comprise caffeic, chlorogenic, labiatic, neochlorogenic, and rosmarinic acids. Rosemary covers hydroxycinnamic and salicylates [42–48].

Modern pharmacological studies have indicated that rosemary and its constituents, especially caffeic acid derivatives such as rosmarinic acid, have various traditional uses in ethnomedicine including analgesic, anti-inflammatory, anticarcinogenic, and antiviral properties [44–54], protection against UV and gamma radiation, and amelioration of oxidative stress.

The powdered leaves are used as an effective natural flea and tick repellent. Activity against certain bacteria including Staphylococcus albus, Vibrio choleae, Escherichia coli, and Corynebacterium has been observed. One study found that rosemary oil is effective against “meat spoiling” Gram-negative (Pseudomonas) and Gram-positive (Lactobacillus) bacteria [49].

Even though rosemary oil is used safely as a food flavoring spice and whole leaves are used as a potherb for seasoning, ingestion of rosemary oil can be associated with toxicity characterized by characterized by stomach and intestinal irritation and kidney damage. While rosemary oil is irritating to rabbit skin, leaf extracts are regularly used for their natural antioxidant active proprieties to improve the shelf life of perishable foods. Recently, rosemary extracts have been approved as a safe and effective natural antioxidant for food preservation by the European Union [33].

Figure 1: Number of publications according to ScienceDirect.
Bioactive compounds such as flavonoids, diterpenes, phenols, and triterpenes from plant sources have been traditionally used in conventional solid-liquid extraction. Nevertheless, this extraction technique presents several disadvantages, mainly because it is a labor-consuming process that requires a high consumption of solvents, and in some cases provides low recovery. For that reason, improving extraction methods are arising, which introduce some form of additional energy in order to facilitate the transfer of the sample to solvent in a faster process [54]. Thus, microwave-assisted extraction [56] and/or ultrasound-assisted ethanol, acetone, and water extraction represent alternatives to the conventional method, improving the speed and efficiency of the extraction process and reducing the consumption of solvents [57].

Previous studies have revealed that the rosemary extract may have analgesic and anti-inflammatory effects [58–62]. Therefore, one study found that the ethanolic extract of rosemary inhibited acetic acid-induced pain in mice with an ED50 of 108.84 mg/kg [23]. Furthermore, it inhibited the time mice spent licking and shaking induced by formalin injections. Nevertheless, the extract did not display any anti-inflammatory activity as evaluated by uric acid-induced hind limb edema in rats [23]. In an experiment conducted by Emami et al. [34], the effect of the extract and its major constituent, carnosol, on plasma corticosterone levels and activity of the enzymes cyclooxygenase types 1 and 2 (COX2) reduced pain in phase 2 of the formalin test, which was not inhibited by naloxone and/or memantine. In addition, pretreatment of animals with *R. officinalis* extract and/or carnosol reduced the formalin-induced inflammation. Moreover, the extract and carnosol inhibited plasma corticosterone levels compared with the control group. Interestingly, both the extract and carnosol inhibited COX1 and COX2. Going one step further, one can conclude that *R. officinalis* extract and carnosol suppress pain and inflammation induced by formalin in mice, which may be due to inhibition of the activity of COX1 and COX2 enzymes.

### 3.2. Marrubium Genus

*Marrubium* is a genus of flowering plants that are included in the Lamiaceae family and are found in the temperate regions of Europe, Africa, and Asia as far east as the Xinjiang region, and some species are also naturalized as far as North and South America. *Marrubium* species have reduced usage in western medicine [76], being listed as an endangered plant. Although the use in traditional medicine has been extensive in the abovementioned places, the possibility to use it as a new and useful analgesic agent [48] has conditioned the successful analgesic effect in mice [57]. Furthermore, the extract and carnosol reduced the formalin-induced inflammation. Moreover, the extract and carnosol inhibited plasma corticosterone levels compared with the control group. Interestingly, both the extract and carnosol inhibited COX1 and COX2. Going one step further, one can conclude that *R. officinalis* extract and carnosol suppress pain and inflammation induced by formalin in mice, which may be due to inhibition of the activity of COX1 and COX2 enzymes.

### 3.2.1. Marrubium vulgare

*Marrubium vulgare* L., commonly named as “marimba” or “marroio” in Brazil and white horehound in Europe, is regularly used as medicine to cure a diversity of maladies [63, 64].

Phytochemical investigations on different parts of *M. vulgare* have reported the presence of alkaloids, lactones, steroids, tannins, phenylpropanoid esters, diterpenoids [65], and flavonoids [64], together with their derivatives. Marrubiin, a furano labdane diterpenoid, was found to be the major chemotaxonomic marker isolated from leaves of the plant and exhibits potent antinociceptive properties and vasodilation [66–68].

Marrubiin, the main active ingredient of *M. vulgare*, seems to be generated as an artifact from premarrubiin during the extraction of the plant. High temperatures are involved in extraction or concentration [69].

The leaves and stems are known to have antiseptic, antispasmodic, antidiabetic, diuretic, strongly expectorant, and tonic roles [65]. Intensive modern research and clinical trials have confirmed several capabilities traditionally described to *M. vulgare*, such as antimicrobial [70], anti-inflammatory [71], anti-oesedematogenic [72]. Furthermore, extracts have shown some effects on type II diabetes [73] and, recently, on neurological disorders [74, 75]. One study found that marrubiin has antinociceptive effects. The antinociceptive properties were observed using different routes of administration (systemic and oral), and sustained over a long period of time.

The great potencies observed in the writhing test and formalin-induced pain test propose that marrubiin acts by some peripheral mechanisms. In the hot-plate test, marrubiin did not increase the latency period of pain induced by the thermal stimuli. Reducing the lactone ring of marrubiin has conditioned the successful analgesic effect influencing writhes in mice. Marrubiin exhibited a high analgesic effect that has been long established in other experimental models of pain, suggesting that the formation of marrubiinic acid and two esterified derivatives has conditioned the successful analgesic effect influencing writhes in mice. Marrubiin acid exhibited a high analgesic effect that has been long established in other experimental models of pain, suggesting that the formation of marrubiinic acid and two esterified derivatives has conditioned the successful analgesic effect influencing writhes in mice. Marrubiin does not prove any cytotoxicity against 66 cancer cell lines according to the NIH PubMed website [Marrubiin-Compound Summary (CID 73401)]. *In vivo* experimental studies have documented an LD50 of 39.4 mg/kg body weight [68], and recent data have highlighted a safety limit up to 100 mg/kg body weight when injected into mice [71].

### 3.3. Sideritis Genus

*Sideritis* genus counts more than 150 species of plants that are situated primarily in the Mediterranean area and also in Atlantic regions of Africa, and even Norway, with apparent differences in composition between the same species corresponding to the georegion [76]. The species have been used as flavoring agents, widely as ingredients for tea preparation or with medicinal purposes [69]. Some areas being listed as an endangered plant. Although the use in traditional medicine has been extensive in the abovementioned places, species have reduced usage in western medicine [78], because medical literature are offering data mostly on the *S. scardica*, *lotsy*, and some species.

#### 3.3.1. Sideritis scardica

*S. scardica* Gris. is also known as “Greek tea” or “mountain tea.” The components of *S. scardica* have been studied through various methods in presence as well as medical role in both animal and human studies.

By using chromatographic separations (HPLC) and mass spectrometry, one study found six different flavonoid aglycones: luteolin, apigenin, hypolaetin, 4′-O-methylhypolaetin, isocutellarein, and 4′-O-methylisocutellarein [79], and also other components like sterols, and the presence of alkaloids, lactones, steroids, tannins, phenylpropanoid esters, diterpenoids [65], and flavonoids [64], together with their derivatives. Marrubiin, a furano labdane diterpenoid, was found to be the major chemotaxonomic marker isolated from leaves of the plant and exhibits potent antinociceptive properties and vasodilation [66–68].
Gas chromatography with mass spectrometry (GC-MS) analysis demonstrated that the composition of *S. scardica* oil samples, however, varies between regions. In the oil from Macedonia, for example, α-cadinol is predominant as compared to the Bulgarian version of the same plant which contains mostly diterpene compounds and octadecanol. Interestingly, none contained menthol, nerol, or geraniol, which are common in the *S. stricta* oil from Yugoslavia [81].

An analysis of urine samples from humans who received oral administration of *S. scardica* showed that the flavonoid metabolites were excreted in the urine and that hypoxia in isocrotonaline had the highest number of metabolites (methylhypolaetin and methylglucuronides) together with apigenin [85].

The pharmacological activity of *S. scardica* is attributed to the high content of flavonoid and phenolic compounds. Studies have demonstrated that plants from the *Sideritis* genus have antioxidant, anti-inflammatory, diuretic, antibacterial, analgesic, and antifungal effects [86]. In *in vivo* models, *S. scardica* showed a capacity to inhibit human serotonin transporter (hSERT) greater than in rat models [77]. According to the same report, *S. scardica* extract orally has been associated with psychostimulant and antidepressive effects, as well as a substitute for adaptogens and thus useful for other pathologies correlated with depressive or altered mental status like increased cardiovascular risks [87–89].

The antibacterial activity seems to be influenced by the method of obtaining the extract: carbon dioxide extraction being more efficient than hydrodistillation and is attributed partially to diterpenes and fatty acids and their derivates and also to other momentarily unknown elements that might be involved [90] but with a certain degree of effect on different types of pathogens.

The antioxidant activity was widely demonstrated, probably due to the content of catechins but not limited to this and has multiple uses and implications in pain treatment proving a possible valuable agent in limiting the use of analgesics, anti-inflammatory, and anti-psychotic agents [6, 91].

*In vivo* models demonstrated the anti-inflammatory effects of *S. scardica* over a model of carrageenan-induced rat paw edema and gastroprotective activity over ethanol-induced acute stress ulcer in rats and also a promising cytotoxic activity [92], attributing to phenylpropanoid constituents (apigenin and luteolin) that can induce cell-cycle arrest and cellular apoptosis *in vitro* [93]. *In vivo* models demonstrated a capacity of *S. scardica* over Aβ-induced memory impairments in transgenic and nontransgenic mice and proved a possible positive effect on Alzheimer's disease, fully rescuing neuronal loss in transgenic mice, thus being flagged as a possible treatment for improving memory in adults and in dementia patients [78].

The usage of *S. scardica* in traditional and modern medicine has demonstrated various degrees of effectiveness with promising but currently not fully addressed results in a long series of pathologies from prevention of anemia, anxiety disorders, major depression, cardiovascular disease, hyperactivity disorder, mental impairment, or neurodegenerative diseases [77] to rheumatic problems [94], inflammatory pain, gastrointestinal, and pulmonary pathologies (common cold, lung emphysema, bronchitis, and asthma) [85], and also an effective cytotoxic activity [9] in cancer chemotherapy. Anti-inflammatory and edema-reducing capabilities should be considered as the basis for further studies of *S. scardica* implication in pain management.

### 3.3.2. *Sideritis lotsyi*

*S. lotsyi* Pit. contains tetracyclic diterpenes (ent-kaur-16-ene and epicandicandiol 7β-monoacetate-18-palmitate), rhoiptelenol, ent-trachylobane, amyrin, trachinodiol, a rare diterpene 16β,18-dihydroxy-ent-atisane, and 5-hydroxy-3,7,4′-trimethoxyflavone, but the content is different between *S. lotsyi* and *S. lotsyi* var. *mascaensis* [96]. *S. lotsyi* var. *mascaensis* extracts were studied in a comprehensive analysis for the antimicrobial activity, toxicity, and anti-inflammatory and analgesic proprieties.

A dose of 2 g/kg body weight *S. lotsyi* extracts administered orally in mice did not show any toxic effects; however, a dose of ethanol extract administered orally has shown analgesic proprieties on the visceral pain produced during the writhing test, and the fraction demonstrated antinociceptive effect. The same extracts manifested anti-inflammatory effect on the early, histamin-mediated, phase of paw edema and proved a preventive capability over pain [87]. Similarly to *S. lotsyi*, the acetone extract of *S. stricta* var. *mascaensis* demonstrated antimicrobial activity as compared to gentamicin [99], and no extensive data with the implications of *S. stricta* over pain are published.

### 3.3.3. *Sideritis stricta*

*S. stricta* Benth. is listed as an endangered plant and is being used as an aromatic and medicinal plant containing essential oils, flavonoids, iridoids, terpenoids, and glycosides [76]. The presence of phenolic antioxidants (catechins) correlating to the biological activity of Greek mountain tea was also established [80].

Gas chromatography with mass spectrometry (GC-MS) analysis demonstrated that the composition of *S. scardica* oil samples, however, varies between regions. In the oil from Macedonia, for example, α-cadinol is predominant as compared to the Bulgarian version of the same plant which contains mostly diterpene compounds and octadecanol. Interestingly, none contained menthol, nerol, or geraniol, which are common in the *S. stricta* oil from Yugoslavia [81].

For an overview of the *Sideritis* species in the Balkan area, mountain tea was analyzed by mass spectrometry coupled to high-performance liquid chromatography with diode-array detection. The analysis found that it contains 90% phenylethanol glycosides and flavonoid acetyls [97]. Turkish *S. scardica* oil has β-pine in abundance as compared to the Greek version which contains α-pine in a similar proportion. Both plants are mainly rich in monoterpene hydrocarbons unlike the ones from Macedonia and Bulgaria, which are poor in these compounds [80].

#### 3.4. *Thymus Genus*

*Thymus* species contain both anti-inflammatory and antinociceptive capabilities when combined. Similarly to *S. lotsyi*, the acetone extract of *S. stricta* var. *mascaensis* demonstrated antimicrobial activity as compared to gentamicin [99], and no extensive data with the implications of *S. stricta* over pain are published.
The *Thymus* genus, part of the Lamiaceae family, consists of over 350 species of aromatic plants with evergreen leaves. Geographically, these plants extend to Asia, North Africa, and Europe. Although more than one species is cultivated for culinary (cheese and liqueur production) and ornamental use, the most extensively studied in literature is *Thymus vulgaris*. Used for thousands of years in traditional medicine, *Thymus* species in medicine is wide, from antimicrobial and anti-inflammatory to possible treatment for dementia or oncology through apigenin [101].

### 3.4.1. *Thymus vulgaris*

GC-MS and GC-FID analyses revealed that the main active components in one type of *Thymus vulgaris* L. essential oil are thymol (26.4%), thujanol (42.2% cis-sabinene hydrate and 7.3% trans-sabinene hydrate), and linalool (72.5%) [102], and others also contain carvacrol. The chemotypes of thyme are determined based on oil compositions. Geographical provenience and weather influence and composition [103], which was demonstrated by a study comparing essential oils from two regions of France (linalool chemotype with 76.2% linalool and thymol chemotype with 47.1% thymol) and two regions of Serbia (geraniol chemotype with 59.8% geraniol and sabinene hydrate chemotype with 30.8% cis-sabinene hydrate) [104].

The terpenoids associated with *T. vulgaris* anesthetic capabilities are thymol (2-isopropyl-5-methylphenol) and eugenol (2-methoxyphenol) [105]; moreover, thymol inhibits synthesis of vitamin K and is implicated in the inhibition of platelet aggregation, resulting in potential anticoagulant activity [107].

In animals, hydroalcoholic extracts of propolis *T. vulgaris* showed promising results in the treatment of dermal leishmaniasis or *Tetun tetranychus* [108, 109]. *T. vulgaris* also has a spasmylic, antimicrobial, anti-inflammatory, immunomodulatory, and antioxidant capability, being attributed to the thymol contained in the volatile thyme oil [110]. Confirming the effect of *T. vulgaris* on respiratory pathologies, spasmylic effects underlined in *ex vivo* studies [111], a study also has indicated its promising potential for the treatment of pathologies in animal models without any toxic potential.

By inhibiting, *in vivo*, TNF-α, lipopolysaccharide inflammatory induced cell influx, IL-6, protein concentration in bronchoalveolar NF-kB activation in the lung, thymol could be a promising therapeutical agent for acute lung injury [112].

The inhibitory role over the nitric oxide (NO) by limiting iNOS mRNA expression plays a major role in the anti-inflammatory profile of *T. vulgaris* extracts [113]. Also, because of the antioxidant capabilities and being an inhibitor of acetylcholinesterase, *T. vulgaris* could act as a therapeutic agent for neurodegenerative disorders like dementia or Alzheimer's disease [114].

*In vitro* activity of *T. vulgaris* oil confirmed a high antibacterial activity over Gram-positive and also Gram-negative bacteria, though smaller on the latter [102].

In traditional medicine and in clinical practice, *T. vulgaris* is used, and *T. vulgaris* shows promising results on inflammatory skin pathologies, scabies, herpes, wounds, alopecia, dental plaque [116], ringworm, and headaches [106]. Moreover, *T. vulgaris* showed a promising effect on *Culex pipiens*, the vector for lymphatic filariasis [117], demonstrating an increased importance in many fields.

Probably in part due to the anti-inflammatory and antioxidant capabilities, *Thymus* extracts demonstrated analgesic, anti-inflammatory activity in mice models of pain. Therefore, the authors concluded that the extracts of *Thymus* may be used against pain and inflammation [118], correlating with other similar findings that position *T. vulgaris* as a modulator agent over acute and chronic inflammation in clinical practice, comparative effects of *T. vulgaris* and ibuprofen on pain severity associated with primary dysmenorrhea were found [119].

#### 3.4.2. *Thymus pulegioides*

*Thymus pulegioides* L. belongs to the genus *Thymus*, and together with three other species, it has a different phenolic content than *T. vulgaris*. It grows on the European continent, and it is used as an antiseptic in local regions of Portugal [122].

In phytochemical analysis, *Thymus pulegioides* was found to have a high flavonoid content, tannins, and hydroxycinnamic acids. Thyme oil, in one analysis, was characterized by the presence of high amounts of thymol and carvacrol [122]. The dose-dependent scavenging and the chelating activity of *T. pulegioides* are moderate to high, with an increased acetylcholinesterase inhibition [114]. A study in *T. pulegioides* among the first medicinal plants in traditional medicine and the second most relevant in respiratory pathologies usage [123].

It has an important antioxidant role [124], but as an anti-inflammatory agent, it elicits cell-type-dependent response [125]. Another consideration that increases the medicinal importance of *T. pulegioides* is that it has demonstrated considerable antifungal capacities [122], how these are required to quantify its effect in pain modulation.

#### 3.5. *Satureja* Genus

*Satureja* genus consists of aromatic plants of the Lamiaceae family that are related to rosemary and thyme. It is native to the North, southern and southeastern European regions, and the Middle East and Central Asian parts of the globe. A few species found on the continent were formerly included in *Satureja* genus but were thereafter moved to other genera.

#### 3.5.1. *Satureja hortensis*

*Satureja hortensis* L., also known as summer savory (culinary herbs), is an annual aromatic plant with origin in the Mediterranean distribution in the Mediterranean Sea region, Black Sea, Central and Southern Europe, Asia Minor, and Siberia, but nowadays cultivated worldwide [126]. The floral parts and leaves of the plant are used as aromatic spice. It is also used in medicinal purposes as decoction and compresses.

The main constituents of the plant were carvacrol, γ-terpinene, p-cymene, α-terpinene, and myrcene. The only notable sesquiterpenoid is bisabolene [126].
Regarding the biological activity, extracts from *S. hortensis* are covering a large spectrum of pathological conditions [127–132]. They include anti-inflammatory activity, antitussive activity, insecticidal activity, fumigant toxicity, insect repellent activity, antinociceptive and anesthetic activity, antiadhesive activity, genotoxic activity, anti-inflammatory activity, effects on immune system, effects on productive performance, activity, anti diarrheal activity, relaxant effect (antispasmodial activity), antigenotoxic activity, antihepatoxemia activity, contact activity, persistence, effect on virulence and healthiness of cestodes, molluscidal activity, larvicidal activity, antihepatoxemia activity, antifertility activity, effect on adhesions, aggression and secretion, effect on rhinosinusitis, amyloid beta protein aggregation inhibitory activity, and matrix metalloproteinase inhibitory activity.

Concerning the analgesic activity, *S. hortensis* extracts (hydroalcoholic extract, polyphenolic fraction, and essential oil of the aerial parts of the herb) were evaluated by use of tail flick, formalin, and acetic acid-induced writhing tests in mice. Results showed that, in the light of the literature data, neither the essential oil nor the extracts could exert any significant effect. The hydroalcoholic extract (2000 mg/kg, p.o.) and the essential oil (500–2000 mg/kg, p.o.) showed significant activity, but neither the extract nor the essential oil could significantly reduce the number of writhings in mice writhing responses caused by acetic acid. In the formalin test, hydroalcoholic extract (500–2000 mg/kg, i.p.) showed significant activity, and pretreatment with BIS (1 mg/kg, i.p.) or caffeine (20 mg/kg, i.p.) failed to reverse this antinociceptive activity. Authors suggested that antinociceptive effect may be due to the involvement of opioid and adenosine receptors in the antinociception mediation [133].

### 3.6. Stachys Genus

*Stachys* genus is one of the largest genera in the flowering plant family of Lamiaceae. Estimates of the number of species in the genus range between 300 and about 450.

#### 3.6.1. *Stachys lavandulifolia*

*Stachys lavandulifolia* Vahl., a type of *Stachys*, also known as mountain tea (Chay-e-Kouhi) has been distributed in a variety of climatic regions, including diverse areas of Europe, Asia, Africa, and Australia. The plant is known as Chay-e-Kouhi in Persian, whereas in English it is known as mountain tea. Also, its common names include heal-all, self-heal, woundwort, betony, lamb's ears, and hedge nettle [134].

Based on recent studies on this herb, 79 compounds were identified, representing 98.2% of the essential oil, in which the major compounds are germacrene-D (13.2%), β-phellandrene (12.7%), β-pinene (10.2%), myrcene (9.4%), α-pinene (8.4%), and Z-β-ocimene (5.8%). In addition, spathulenol (35.0%) and Caryophyllene oxide (25.6%) were the main components of the oil [135]. Another study revealed the presence of thujone (0.3%–32.3%), Δ-cadinene (11.6%) and 1,4-methano-1H-indene (10.1%) [136].

The aqueous extract obtained from the aerial parts of *St. lavandulifolia* is used in antipyretic, anti-inflammatory, spasmyloytic, sedative, and hypnotic treatment [137]. Also, this plant has antibacterial, antioxidant, anxiolytic, analgesic, and wound-healing effects. Decoctions or infusions are applied as tonics to treat skin or taken internally for stomach disorders [138].

Some other biological activities of *S. lavandulifolia* were signaled, and the main of those being possibility of abortion depending on the dosage in pregnant animals, useful in controlling premenstrual syndrome (PMS) and primary dysmenorrhea symptoms, helps in strengthing the heart muscle preventing gastric ulcers caused by alcohol consumption, and useful in treating *Leishmania major*. Being useful to treat fatigue and vomiting associated with primary dysmenorrhea, it could be a potentially effective treatment for dysmenorrhea, particularly as an antipyretic and spasmyloytic effect. As an undesired effect, it gives rise to failure in fetus survival and, consequently, abortion when taken for too long. Insomnia is approved. It is also known for its antidepressive and appetite-stimulating effects [139,140].

For the evaluation of the analgesic effect, hydroalcoholic, polyphenolic, and boiled extracts of the aerial parts from *S. lavandulifolia* and their analgesic effects were studied in mice using formalin, acetic acid-induced writhing, and light tail flick tests. Results showed that the tested extracts were able to reduce the abdominal constrictions in acetic acid-induced writhing test. These extracts also significantly suppressed both phases of the formalin test. In the light tail flick test, none of the extracts showed analgesic activity [141].

In another study regarding antinociceptive effects of *S. lavandulifolia* extracts, the implication of essential oil (EOSI) and (-)-α-bisabolol (BIS) main component, was studied in algogen-induced orofacial nociceptive behavior in mice. Authors have shown that the treatment with BIS has significantly reduced pain in different orofacial pain tests on mice, but BIS proved to be more effective, significantly reducing nociceptive behavior in all tests including both phases of the formalin test [142].

#### 3.6.2. *Stachys officinalis* (Synonym *Betonica officinalis*)

It is commonly known as wood betony, purple betony, woundwort, or Bishop's wort; it is a perennial herb found in dry grassland, open woods in most of Europe, western Asia, North and South America, Africa, and tropical regions. For centuries, *Betonica officinalis* (Synonym *Stachys officinalis*) has been distributed in a variety of climatic regions, including diverse areas of Europe, Asia, Africa, and Australia. The plant is known as Chay-e-Kouhi in Persian, whereas in English it is known as mountain tea. Also, its common names include heal-all, self-heal, woundwort, betony, lamb's ears, and hedge nettle [134].

The aqueous extract obtained from the aerial parts of *S. officinalis* contains α-pinene (22.2%), β-pinene (10.2%), β-myrcene (9.4%), myrcene (9.4%), and germacrene D (6.1%). In addition, β-ocimene (5.8%), 1,4-methano-1H-indene (10.1%), and spathulenol (35.0%) were the main components of the oil [135]. Another study revealed the presence of thujone (0.3%–32.3%), Δ-cadinene (11.6%) and 1,4-methano-1H-indene (10.1%) [136].

The aqueous extract obtained from the aerial parts of *S. officinalis* contained α-pinene (22.2%), β-pinene (10.2%), β-myrcene (9.4%), myrcene (9.4%), and germacrene D (6.1%). In addition, β-ocimene (5.8%), 1,4-methano-1H-indene (10.1%), and spathulenol (35.0%) were the main components of the oil [135]. Another study revealed the presence of thujone (0.3%–32.3%), Δ-cadinene (11.6%) and 1,4-methano-1H-indene (10.1%) [136].

The chemical composition of *Betonica officinalis* includes polyphenols such as tannins, phenolic acids, bavonoids, alkaloids trigonelline, and flavonoids. It also contains thujone (0.3%–32.3%), Δ-cadinene (11.6%) and 1,4-methano-1H-indene (10.1%).

Regarding the biological activity, extracts from *S. hortensis* are covering a large spectrum of pathological conditions [127–132]. They include anti-inflammatory activity, antitussive activity, insecticidal activity, fumigant toxicity, insect repellent activity, antinociceptive and anesthetic activity, antiadhesive activity, genotoxic activity, anti-inflammatory activity, effects on immune system, effects on productive performance, activity, anti diarrheal activity, relaxant effect (antispasmodial activity), antigenotoxic activity, antihepatoxemia activity, contact activity, persistence, effect on virulence and healthiness of cestodes, molluscidal activity, larvicidal activity, antihepatoxemia activity, antifertility activity, effect on adhesions, aggression and secretion, effect on rhinosinusitis, amyloid beta protein aggregation inhibitory activity, and matrix metalloproteinase inhibitory activity.

Concerning the analgesic activity, *S. hortensis* extracts (hydroalcoholic extract, polyphenolic fraction, and essential oil of the aerial parts of the herb) were evaluated by use of tail flick, formalin, and acetic acid-induced writhing tests in mice. Results showed that, in the light of the literature data, neither the essential oil nor the extracts could exert any significant effect. The hydroalcoholic extract (2000 mg/kg, p.o.) and the essential oil (500–2000 mg/kg, p.o.) inhibited the mice writhing responses caused by acetic acid. In the formalin test, hydroalcoholic extract (500–2000 mg/kg, i.p.) showed significant activity, and pretreatment with BIS (1 mg/kg, i.p.) or caffeine (20 mg/kg, i.p.) failed to reverse this antinociceptive activity. Authors suggested that antinociceptive effect may be due to the involvement of opioid and adenosine receptors in the antinociception mediation [133].
A hydroalcoholic extract of *Stachys in?ata* Bent., one of the *Stachys* species from Iran, induced antinociception and anti-inflammatory effects in two well-characterized inflammatory models in rats: carrageenan-induced paw edema and formalin-induced paw licking [151]. After intraperitoneal injection of the hydroalcoholic extract of the aerial parts from nonflowering stems of *S. in?ata*, 60 min before induction of inflammation, the extract was capable of attenuating both early and delayed phases of carrageenan-induced inflammation with a dose-related inhibition over the range of 50–200 mg/kg. Compared to a standard nonsteroidal anti-inflammatory drug, indomethacin, the hydroalcoholic extract of *S. in?ata* was significantly more effective than indomethacin. Moreover, all three doses of the extract significantly inhibited the pain associated with the second phase (inflammatory component) of the formalin test, but with no effect against the first phase (0–5 min).

The obtained data suggest that the anti-inflammatory activity of hydroalcoholic extract of *S. in?ata* may be related to the inhibition of cyclooxygenase products and polymorphonuclear leukocytes accumulation determined by myeloperoxidase activity. Furthermore, *in?ata* extracts (200 mg/kg) on inflammation and myeloperoxidase activity were confirmed by histological examination which considerably reduced the morphological injury and neutrophil infiltration in a carrageenan-induced model of local inflammation. The results presented in this study are taken as the basis for further investigation on the exact mode of action of individual compounds and the plant extract. Several components quantified in *Stachys* extracts demonstrated in vivo anti-inflammatory and antinociceptive activity, which is manifested by decreased paw edema and *p*-benzoquinone-induced abdominal constriction tests [100].

### 3.6.4. *Stachys byzantina*

Khanavi et al. [152] proved that acetone and methanol extracts of *S. byzantina* K. Koch, a species of *Stachys*, native to Turkey, Armenia, and Iran, play a significant role in the inhibition of pain and inflammatory processes by using two inflammatory models, namely, formalin-induced hind paw edema and R. artemisiroides-induced paw edema.

Dried and finely powdered aerial parts were extracted with acetone at room temperature for 2 weeks in order to isolate and identify the active diterpene ester (phytlyl nonadecanoate), two normal alkanes (tritriacontane and hentriacontane), one fatty acid (oleic acid), and a sterol (stigmasterol and lawsoitol). Structures were established by conventional methods of analysis and confirmed by 

Additionally, several inflammatory markers, such as NF-κB, TNF-α, IL-1β, and IL-6, were decreased in these animals when compared to the control group.

Other possible mechanisms that make ground ivy a potential candidate as coanalgesic include its effects on extracellular calcium 

### 3.7. *Glechoma Genus*

*Glechoma* genus is composed of flowering plants in the mint family first described in 1753. This genus is distributed in both northern Europe and Asia. In Asia, however, it is most predominantly seen in China, and it is closely related to *Marmoritis*.

#### 3.7.1. *Glechoma hederacea*

*Glechoma hederacea* L., more commonly known as ground ivy, is a perennial weed with creeping stem that can be found throughout Europe and the neighboring regions of Asia. The aerial parts of the plant (consumed as salad or tea) have been used in both Asian and European traditional medicine as a remedy for several digestive, pulmonary, skeletal, and inflammatory conditions [153]. Active components include several triterpenoids such as chlorogenic acid, caffeic acid, rutin, genistin, rosmarinic acid, quercetin, or genistein [153] and triterpenoids such as ursolic acid and oleandric acid [154, 155]. Additionally, studies report that *G. hederacea* leaves contain polysaturated fatty acids and a type of insecticidal lectin called Gleheda [157].

Current preclinical data indicate that *G. hederacea* has several pharmacological effects. As such, hot water extracts of ground ivy leaves exhibited anti-bacterial, anti-cancer, anti-inflammatory, and anti-platelet-stimulating activity [157, 158]. Currently, there are no studies specific to the anti-inflammatory activity of ground ivy. However, existing data point out that the plant has potent anti-inflammatory effects. An *in vitro* study revealed that incubating activated macrophages with a ground ivy decoction (3 h in boiling distilled water) led to a significant decrease in nitric oxide production. Furthermore, the authors noted that the expression of some inflammatory cytokines such as IL-12p70 and TNFα was significantly decreased [159]. Similarly, Kim et al. demonstrated that several compounds found in *G. hederacea* inhibited NF-kB production [160]. A water *G. hederacea* extract was shown to have anti-inflammatory activity in a rat model of hepatic inflammation: rats that received *G. hederacea* extract daily for four weeks were shown to have significantly lower levels of inflammatory cell infiltration/activity in liver sections. Additionally, several inflammatory markers, such as NF-κB, TNF-α, IL-1β, and IL-6, were decreased in these animals when compared to the control group.

There are no reported side effects following *G. hederacea* administration. However, one *in vitro* study showed that *G. hederacea* concentrations exceeding 100 μg/dl are cytotoxic [160], and several studies now focus on the plant's ability to kill different types of cancer cells [162]. Due to its ability to target and kill cancerous cells, those extracts should also be included in preclinical screenings against cancerous cells (e.g., insulinomas being one of the most frequently encountered types of neuroendocrine pancreatic tumors [163]).
3.8. Scutellaria Genus

Scutellaria genus includes over 350 species, many of which have been used in traditional medicine and are documented to have medicinal properties.

3.8.1. Scutellaria lateriflora

Scutellaria lateriflora L., also known as American skullcap, is a member of Scutellaria genus and is native to North America and is known for its sedative and anxiolytic effects. The plant is still widely used by herbal medicine practitioners for insomnia, nervous anxiety, depression, panic attacks, and fibromyalgia [164, 165]. Most often, it is prescribed as a tincture, although teas and tablets are also commercially available, with wide variability depending on the manufacturer and species of Scutellaria used [166]. Although rare, possible side effects of treatment include drowsiness, mild digestive upset, and vivid dreaming [165].

The first clinical study assessing skullcap’s effect on mood was performed on nineteen patients and had positive results [167]. In 2014, Brock et al. published the results of a larger randomized controlled clinical trial designed to assess the effect of a S. lateriflora extract on mood in 119 volunteers. Results indicated that global mood was significantly enhanced in individuals who received 350 mg of plant extract, without negative effects on energy and cognition [164]. Taking into account the fact that anxiety is a well-known enhancer of S. lateriflora extracts could have clinical value as co-analgesics. Additionally, ethanolic and aqueous S. lateriflora extracts have been shown to have potent antioxidant effects, reducing ROS and lipid peroxides in tissue homogenates [169], most likely due to the flavonoids it contains.

S. lateriflora contains several active compounds such as baicalin (40 mg/g in a 50% ETOH extract), baicalein (33 mg/g in a 95% EtOH mg/g in EtOH and H2O extracts), and glucose (31 mg/g in H2O extract) [170]. Other flavonoids found in S. lateriflora include oroxin A, genkwanin, hesperetin, quercetin, rutin, naringenin, chrysin, and daidzein [167]. While its anti-inflammatory effects are partly explained by its inhibitory effects on lipoxygenases—enzymes that play a key role in leukotriene and lipoxin synthesis, thus initiating the inflammatory response. Deschamps et al. found that baicalin has a significant analgesic effect in the carrageenan-induced rat paw inflammatory model [173]. Similarly, baicalein was found to significantly decrease pain-related behavior and c-fos expression in the spinal dorsal horn of animals exposed to painful stimuli [174]. A combination of baicalin and its glucuronide, baicalin, was assessed in three widely used animal pain models and was found to have analgesic effects in visceral, nociceptive, and inflammatory models, which has made it an interesting drug to be used as an analgesic.

Baicalein has also shown some efficacy in neuropathic pain: an in vivo study on spinal nerve ligation rats showed that tactile allodynia and hyperalgesia were reversed by intrathecal baicalin administration. Additionally, baicalein significantly enhanced the effect of morphine in neuropathic animals, most likely by suppressing histone deacetylase 1 expression in the spinal dorsal horn [176]. The compound was shown to be effective in cancer-induced bone pain: both intrathecal and oral baicalin administration reduced cytokine expression and inhibits signal transmission as assessed by behavioral and biochemical tests [177, 178] in an animal model.

This compound most likely exerts its analgesic effects through modulating the inflammatory process. Baicalein’s anti-inflammatory properties are partly explained by its inhibitory effects on lipoxgenases—enzymes that play a key role in leukotriene and lipoxin synthesis, thus limiting the inflammatory response. Deschamps et al. found that baicalin inhibits both human platelet 12-lipoxygenase and human lipoxgenase-1 [179]. Additionally, Hsieh et al. showed that baicalein inhibits IL-1β and TNF-α through modulation of the NK-κB pathway, while other authors found that it inhibits protein expression of inducible nitric oxide synthase [181] and COX2 gene expression [182]. Pretreatment with baicalin increased the concentration of antioxidant enzymes such as SOD, catalase, and GSH in an in vivo model of ischemic injury [183] and protected cells against lipid peroxidation [184]. However, it is very likely that, taking into account that baicalein is effective also in noninflammatory types of pain, it has other analgesic mechanisms as well. One hypothesis states that baicalein binds to the GABA-A receptor, which has a modulatory effect on pain because GABA is the main inhibitory neurotransmitter. When injected into the central nervous system, baicalein has strong sedative and anxiolytic effects due to GABA binding [185]. Also, a recent article indicated that through GABA modulation, baicalin could be used in orofacial pain modulation [186]. Another study also showed that baicalein modulates both intracellular and extracellular calcium levels [187], which may play a role in cell signaling and pain transmission.

3.9. Ocimum Genus

Ocimum genus species are amongst the best-known medicinal plants, with historical reports of their antimicrobial, immunomodulatory, anti-inflammatory, anti-ulcer, antidiabetic, hepatoprotective, chemoprotective, anti-hyperlipidemic, cardioprotective, antioxidant, radioprotective, memory enhancing, antiarthritic, antifebrile, antihypertensive, anticoagulant, antitumor, and anti-inflammatory activity [188]. As such, several members of the genus such as Ocimum sanctum, Ocimum gratissimum, or Ocimum micranthum are significant part in different traditional medicines and are currently considered as potential sources for innovative drugs.

3.9.1. Ocimum sanctum

Ocimum sanctum Linn., also known as tulsi, is an indigenous plant commonly found in India [189]. In Ayurvedic medicine, it is used as a fresh leaf extract or a decoction with hot water to alleviate muscular pain, joint pain, and severe headache [190]. It contains (−)-linalool (30–40%), α-pinene (5–20%), limonene (20–30%), 1,8-cineole (20–30%), humulene, citral, and (−)-linalool (30–40%). Minor constituents are (+)-delta-cadinene, 3-carene, 3-carene, and citral [191]. In recent years, the interest for evaluating the potential benefits of O. sanctum extracts in several conditions has increased, especially in the anticancer, antimicrobial, and neurobiology fields. A double-blind clinical trial assessed the effects of O. sanctum extract on mood in healthy volunteers and concluded that the drug has immunomodulatory effects and can be given for up to 12 weeks without any significant side effects [192]. Although less numerous, there are some studies that have assessed the effect of O. sanctum extract on mood in healthy volunteers and concluded that the drug has immunomodulatory effects and can be given for up to 12 weeks without any significant side effects [192]. Although less numerous, there are some studies that have assessed the effect of O. sanctum extract on mood in healthy volunteers and concluded that the drug has immunomodulatory effects and can be given for up to 12 weeks without any significant side effects [192]. Although less numerous, there are some studies that have assessed the effect of O. sanctum extract on mood in healthy volunteers and concluded that the drug has immunomodulatory effects and can be given for up to 12 weeks without any significant side effects [192].
on different types of pain, most often inflammatory or neuropathic.

*In vitro*, *O. sanctum* leaf extracts exhibited significant anti-inflammatory effects in LPS-stimulated monocyte cells, reducing cytokine and decreasing TNF-α secretion [193]. Different types of dried leaf extracts were also shown to be effective in reducing carrageenan and leukotriene-induced paw edema [194]. More recently, a triple-blind randomized clinical study compared an ethanolic extract of *O. sanctum* chlorhexidine mouthwash in regards to their effect on dental plaque and gingival inflammation and found that the two were equivalent: the *O. sanctum* extract was better tolerated and had no side effects [195].

Regarding its effect on other pain models, there are several studies that have demonstrated that *O. sanctum* extracts alleviate neuropathic pain. The method of preparation was similar in most study designs: dried tulsi leaves were reduced to coarse powder and then extracted with methanol and water (3:1) [189, 190] in order to obtain an oral preparation. 50 mg/kg b.w. of *O. sanctum* extract attenuated transection-induced axonal degeneration, reduction of nociceptive threshold, and motor in-coordination [190]. Kaur et al. orally administered 100 or 200 mg/kg b.w. of *O. sanctum* to rats that underwent chronic constriction injury in the sciatic nerve and found that the saponins, bavonoids, and flavonoids alleviated cold-induced hyperalgesia, mechanical allodynia, and paw-heat hyperalgesia [196]. In another study, a 200 mg/kg b.w. dose of *O. sanctum* extract was used, and the authors concluded that it is effective in preventingvincristine-induced neuropathic pain in rats [189]. The same group demonstrated the efficacy of the aforementioned essential oil for increasing paw withdrawal latency in the hot-plate decreasing formalin-induced hind paw inflammation and pain-evoked behaviors [201]. Another team used the essential oil of *O. gratissimum* for a model of visceral pain (the writhing test) and in the formalin test with equally favorable results [202]. Similar analgesic activity was achieved by *O. gratissimum* aqueous and hydroalcoholic extracts in two animal pain models: the acetic acid writhing test and the hot-plate test, indicating that it is efficient in nociceptive, neuropathic and inflammatory pain.

**3.9.2. Ocimum gratissimum**

*Ocimum gratissimum* L. is widely found in several geographical regions in South America and Africa [198, 199] and still used as a medicine with analgesic activity [198]. It contains several proanthocyanidins, which have been shown to exhibit significant antioxidant activities, saponins, steroids, alkaloids, terpenoids, flavonoids, phenols, and cardiac glycosides [200]. *O. gratissimum* essential oil was orally administered to mice with chronic constriction injury and effectively alleviated neuropathic pain most likely due to eugenol's antihyperalgesic action [203]. The same group demonstrated the efficacy of the aforementioned essential oil for increasing paw withdrawal latency in the hot-plate decreasing formalin-induced hind paw inflammation and pain-evoked behaviors [201]. Another team used the essential oil of *O. gratissimum* for a model of visceral pain (the writhing test) and in the formalin test with equally favorable results [202]. Similar analgesic activity was achieved by *O. gratissimum* aqueous and hydroalcoholic extracts in two animal pain models: the acetic acid writhing test and the hot-plate test, indicating that it is efficient in nociceptive, neuropathic and inflammatory pain.

**3.9.3. Ocimum micranthum**

*Ocimum micranthum* Willd. or *Ocimum campechianum* Mill., more commonly known as Amazonian or Peruvian basil, has shown anti-inflammatory and antianalgesic effects in several animal models of pain, although it has not been reported as less effective on the hot-plate test decreasing leukotriene-induced paw edema [190]. The difference in efficacy between plants is most likely due to their different compositions that additionally vary according to the geographical area. While some authors believe that the saponins these plants contain are responsible for their effect on pain [189], others have suggested that the volatile oil eugenol is in fact the most potent antioxidant and anti-inflammatory compound [197].

**3.10. Lamium Genus**

*Lamium* genus contains almost 40 herbaceous plants, some of which have been used as remedies for various conditions such as putrescence, paralysis, leucorrhoea, hypertension, or inflammation [206]. The *Lamium* species contain different concentrations of flavonoids, phenylpropanoids, benzoazinoids, and essential oil [207], which vary according to species and geographical area. Although widely used in traditional medicine, there are only few studies that investigate the potential analgesic effects of this genus. One study screened several plants of the *Lamium* genus and concluded that *Lamium purpureum* has potent antioxidant effects, being able to scavenge free radicals in several *in vitro* assays [150].

Another screening study assessed potential anti-inflammatory and antinociceptive effects of different *Lamium* species and concluded that *L. garganicum* L. and *L. purpureum* L. extracts are as effective as indomethacin, a reference anti-inflammatory drug. In this study, they were prepared by methanolic extraction of air-dried and powdered aerial plant parts (25 g plant in 250 mL methanol), which was then dried, suspended in water, partitioned, and lyophilized. The study showed that 200 mg/kg body weight of *L. garganicum* and *L. purpureum* methanolic extracts alleviate inflammatory pain in a model of ear edema and in carrageenan-induced and prostaglandin E2-induced paw edema [206].

**3.11. Teucrium Genus**

*Teucrium* genus contains several mostly perennial plants commonly referred to as germanders.

**3.11.1. Teucrium polium**

*Teucrium polium* L. is a perennial wild-growing plant, widely spread in several regions such as South-Western Asia, Europe, and Africa [208], and has been used in traditional medicine for the treatment of inflammations, rheumatism, diabetes, and ulcers. Two major compounds in the dried leaf plant extract are flavons and flavonoids [209]; the essential oil contains α-pinene (25.769%) and myrcene (12.507%), and the methanolic extract contains sinapic acid (15.553 mg/g) and eugenol (6.805 mg/g) [210]. A preclinical study showed that administration of 100 or 200 mg/kg b.w. per day for two weeks reduced pain-related behavior in the diabetic rat formalin test [211]. Of 500 mg/kg body weight of ethanolic extract of *T. polium* inhibited carrageenan-induced inflammation and reduced granuloma formation [212].
Another study compared the effect of morphine and *T. polium* extract on the tail flick latency and found the two to be comparable in this test. Both the total extract and the essential oil of the plant exhibited analgesic effects on the acetic acid-induced writhing test, thus suggesting efficacy in visceral pain [214]. Subsequently, a triple-blind, randomized, clinical trial was designed in order to assess the plant's efficacy in 250 mg menstruation. Seventy female students were randomly assigned to receive either *T. polium* powder every six hours for the first three days of their menstrual cycle or 250 mg mefenamic acid. Study results indicated that the two are equally effective, thus concluding that *T. polium* is effective in this type of pain [209].

3.11.2. *Teucrium hyrcanicum*

*Teucrium hyrcanicum* L., also known as “Purple Tails” is a plant native to Iran, which has been also shown to exhibit analgesic and anti-inflammatory activities in carrageenan-induced paw edema, acetic acid-induced writhing, tail flick, and formalin pain tests [215]. A recent study used a methanolic extract of dried aerial parts of *T. hyrcanicum* and observed that the high flavonoid content of the plant has antioxidant effects [216].

3.11.3. *Teucrium chamaedrys*

*Teucrium chamaedrys* L., also known as “The wall germander,” is an evergreen subshrub native to the Mediterranean region of Europe and Africa, and to the Middle East. It has been used in traditional English medicine as part of the Portland Powder for treating rheumatism and gout [217]. A preclinical study identified teurcoside as the main active ingredient of the plant and concluded that it is effective in inhibiting calcineurin, suggesting that this plant may have antileishmanial action [219].

3.12. *Hyptis Genus*

*Hyptis* genus, also known in Brazil as “sambacaitá” or “canudinho,” is a genus of aromatic plants in the Lamiaceae family [219]. The genus contains the perennial herbs from the Lamiaceae family, native from Europe and Asia but cultivated and naturalized in many other places.

The aqueous extract of *H. pectinata* possesses antiedematogenic properties in the carrageenan-induced paw edema model. The aqueous extract of *H. pectinata* leaves at 200 mg/kg with intraoperative laser therapy can stimulate liver regeneration and cause a reduction in the mitochondrial respiratory function without altering its phosphorylative activity [225].

The antinociceptive effects of *H. pectinata* can be seen in the volatile oil [226]. The major constituents of oil are 1,8-cineole (12.05%), t-caryophyllene (12.52%), (20.51%), and β-pinene (13.54%). β-Pinene may be considered a partial agonist of µ-opioid receptors [227]. Franco et al. [228] suggested that the essential oils have both peripheral and central analgesic actions without opioid system influence, although the central activity was more discrete.

In 2011, Raymundo published the results that *H. pectinata* essential oil shows peripheral and central antinociceptive effects, like opioid and cholinergic receptors, and anti-inflammatory activity through the inhibition of nitric oxide and PGE2 production. The involvement of the opioid system in the antinociceptive activity of *H. pectinata* essential oil was evaluated in the hot-plate model in mice with an opioid antagonist, naltrexone. The results suggest that naloxone reversed the antinociceptive activity of the essential oil. Antinociceptive effects were observed in other tests like acetic acid or hot-plate [230].

3.13. *Melissa Genus*

*Melissa* genus contains the perennial herbs from the Lamiaceae family, native from Europe and Asia but cultivated and naturalized in many other places.

3.13.1. *Melissa officinalis* L., also known as lemon balm, English balm, garden balm, balm mint, common balm, melissa, sweet balm, and heart’s delight, is an aromatic herb from the mint family (Lamiaceae) that includes two subspecies: *Melissa officinalis* L. subsp. officinalis, the common lemon balm, and *Melissa officinalis* L. subsp. altissima, naturalized in New Zealand and known as bush balm. The first information of the plant was found in Greece, 2000 years ago. In 2007, Khare [231] published the results that the plant has antidepressant, antihistaminic, and antiviral properties and can be used in cases of anxiety, nervousness and headache, and hyperthyroidism.

The known major components of lemon balm are hydroxycinnamic acid derivatives, particularly rosmarinic acid, caffeic acids, cinnamic acid, and metric acid [232, 233], tannins [234], flavonoids, including luteolin, luteolin 7-O-beta-D-glucopyranoside, apigenin 7-O-beta-D-glucuronopyranoside, and luteolin 3’-O-beta-D-glucuronopyranoside [235, 236], monoterpene glycosides [237], sesquiterpene glycosides, including 238, and sesquiterpene lactones [239].

Antioxidant effects [240] and exhibits a major morphological diversity [241]. The *Melissa officinalis* subsp. *altissima* is a perennial herb native to the southern United States to Argentina [242] and exhibits a major morphological diversity [243]. Subsequently, a triple-blind, randomized, clinical trial was designed in order to assess the plant's effects on menstrual cycle or 250 mg mefenamic acid. Study results indicated that the two are equally effective, thus concluding that *T. polium* is effective in this type of pain [209].
caryophyllene and germacrene [237], triterpenes [238], and volatile oils, including citronellal, citral a (geraniol), citral b (neral), menthol, o-cymene, citronellol, geraniol, nerol, β-caryophyllene, β-caryophyllene oxide, linalool, and ethoric acid [239].

*M. officinalis* exhibit antiviral effects against Newcastle disease virus, Semliki forest virus, influenza virus, myxoviruses, vaccinia [240], herpes simplex virus types 1 and 2 [241], HIV-1 [242]. The antiviral effects are mediated by tannin and polyphenol constituents, rosmarinic acid, ferulic acids [240].

*M. officinalis* has antibacterial effects and can be used to treat oropharyngeal diseases produced by anaerobic and facultative aerobic bacteria like *Porphyromonas gingivalis*, *Prevotella* spp., *Fusobacterium nucleatum*, *Capnocytophaga gingivalis*, *Veillonella paracorodes*, *Peptostreptococcus micros*, and *Actinomyces odontolyticus* [243].

Engelberger suggests that rosmarinic acid has anti-inflammatory effects because it reduces paw edema induced by cobra venom factor [244], and inhibit passive cutaneous anaphylaxis in rats at doses of 1–100 mg/kg by mouth. The same author says that rosmarinic acid has antithrombotic effects because it inhibits the classical pathway convertase and the alternative pathway convertase [244].

*M. officinalis* has antihyperglycemic effects (inhibit the binding of bovine TSH to human thyroid plasma membranes and adenylate cyclase; extrathyroidal enzymatic T4-5′-deiodination to both T3 and T4-5′-deiodination) [245], spasmylytic effects (observed only in isolated duodenum of rat) [246], sedative effects (dose-dependent sedation, inducing sleep and potentiating subhypnotic and hypnotic activity) [247], and cardiovascular effects (significant reduction in the cardiac rate by the stimulation of cardiac muscarinic receptors) [248].

3.14. *Origanum* Genus

*Origanum* is a genus of herbaceous perennials and subshrubs in the Lamiaceae family, native to Europe, North Africa, and much of temperate Asia and can be found in open or mountainous environments. A few species also naturalized in North America and other regions. The genus includes *O. vulgare* (oregano) and *Origanum majorana* – sweet marjoram, the two species of *Origanum* that can be used with medicinal purposes.

3.14.1. *Origanum vulgare*

*O. vulgare* is an aromatic, woody-based perennial, native to the stony slopes and rocky mountain areas at a wide range of altitudes in the Mediterranean area (Portugal and Andalusia), Europe (including the British Isles), and south and central Asia [249].

The difference between these two plants is almost indistinguishable (taste aside) to the amateur gardener. In technical terms, the difference is almost the same, marjoram and *O. majorana* is used as infusion, decoction, and maceration for various purposes such as sedative, stomach tonic, heart tonic, and preserve food [250].

The major compound of *O. vulgare* oil is terpinen-4-ol (26%), cis-sabinene (13.3%), o-cymene (9.3%), g-terpinen (5.8%), trans-sabinene hydrate (5.1%), b-thujene (4.9%), and α-terpinen (3.5%). The extracts obtained by supercritical CO2 presented higher non-oxygenated monoterpenes, without significant differences between fractions 1 and 2. A study from Iran shows that the composition of *O. vulgare* was dominant in β-caryophyllene, germacrene D, and cis-sabinene hydrate [251]. Another study from Italy showed that the components of essential oil in the *O. vulgare* ssp. *vulgaris* were β-caryophyllene, thymol, terpinen-4-ol, and p-cymene [252]. The compounds of *O. majorana* are the essential oil and tannins. The difference between the essential oil obtained from *O. vulgare* and *O. majorana* was observed in quantity (0.67% and 1.5%) [253]. The maximum quantity was obtained in the full bowering stage. The major component is germacrene D and terpinen-4-ol for *O. majorana* [254].

In the folk medicine, *Origanum* was used to treat several illnesses such as spasmodic, antimicrobial, digestive, expectorant, and astringent effect, whooping and convulsive coughs [255, 256]. *O. vulgare* (oregano) and *O. majorana* (marjoram) inhibit the growth of the bacteria (inhibited the growth of *Candida albicans*) [257] and the synthesis of the microbial metabolites [258, 259]. The leaves of *O. vulgare* have been used as diuretic and suppresssecretory activity [260]. *O. majorana* has stimulatory properties and vasodilatory activity [261]. By acting also on cardiovascular system and being used as an adjuvant for diabetes control, *Origanum* subsp. could both prevent and treat more cardiovascular associated developed as: atrial fibrillation development [262–265].

3.15. *Ziziphora* Genus

*Ziziphora* genus is an aromatic herb of the Lamiaceae family, native to Ukraine, Russia, Siberia, Central Asia, Xinjiang, Afghanistan, Turkey, and Middle East. *Ziziphora* species were used as culinary herb in Iran [266].

In traditional medicine, *Ziziphora* is used as infusion, decoction, and maceration for various purposes such as sedative, stomachic, diuretic, expectorant, coughing, antiseptic, migraine, fever, and depressant effect. Essential oils are used for treating some diseases such as edema, insomnia, lung abscess, tracheitis, hemorrhoids, and hypertension [267]. Antimicrobial activity of the essential oil of *Salmonella typhi* Vi-positive makes it useful in the treatment of typhoid fever, too. The plant modulate immune response by induction of CD40 expression on DCs and cytokine production and inhibition of T-cell stimulation in dendritic cells in high concentration [268].

3.15.1. *Ziziphora tenuior*

*Ziziphora tenuior* L. may possess an antidepressant-like effect, and its effect is similar to fluoxetine [269]. The composition of the essential oil of *Ziziphora tenuior* contains two new flavonoids named as “ziziphorin A and ziziphorin B,” 1-hentetracontanol [270], ursolic acid
The composition of Z. tenuior essential oil may therefore vary with plant genetics, environmental conditions, extraction methods, origin, including climate, soil, elevation, and topography. The main components of Z. tenuior, which are identified by GC/MS extracts, are 53.977% of p-menth-3-en-8-ol, 38.481% of pulegone, and 1.651% of p-menth-3,8-diene. The essential oil also contains percentages of β-pinene; 4ααα-, 7αα-, and 7αααα- nepetalactone; α-thujene; caryophyllene oxide; limonene; E-caryophyllene; and terpin-3-en-8-ol and pulegone are the main components of Z. tenuior, and they are responsible for the antimicrobial activities of the essential oil. Essential oils of Z. tenuior aerial parts were characterized by high levels of oxygenated monoterpenes, especially pulegone [276].

3.16. *Salvia* Genus

*Salvia* genus belongs to the subfamily Nepetoideae in the Lamiaceae family. In traditional medicine, *Salvia* is one of the oldest herbs used by humans, and it is considered as a universal panacea, used for its antibacterial, antiviral, antioxidative, antimarialar, anti-diabetic, cardiovascular, and antitumor effects.

*Salvia* can be used as infusion, tincture with diuretic, hemostatic, and spasmodicolytic activities, volatile oils with antiseptic role, and crude extract for antimicrobial effect.

The pharmacological effects of *Salvia* essential oils are based on the presence of more than 100 active compounds, which can be classified as monoterpene hydrocarbons, oxygenated monoterpenes, sesquiterpene hydrocarbons, diterpenes, nonisoprenoid compounds sesquiterpenes [277, 278]. The most abundant components are 1,8-cineole, camphor, and a wide variety of thujenes [279].

Analysis made by spectrophotometry and HPLC shows that *Salvia officinalis* L. has the highest total content (1.785 g%) expected to be an equivalent caffeic acid, and the highest value for rosmarinic acid (728.68 mg%). Rosmarinic acid is the major component, and it has antioxidant, anti-inflammatory, antibacterial, and antiviral activity [280]. *S. officinalis* is the most valuable species in terms of biologically active contents compared to other species studied, followed by *Salvia verticillata* L. and *Salvia glutinosa* L. [281].

3.17. *Leonurus* Genus

*Leonurus* genus natively grows in the temperate zone of Asia and Europe and was lately adapted in America and Africa. About 24 species of *Leonurus* have been identified, of which 13 species are spread in China. Plants belonging to *Leonurus* genus are traditionally used for antipsychological disorder in East Asia, and as sedative in Europe. Chemical investigations of the genus enriched the natural products library and also enlarged the pharmacological applications of this traditional herb [282].

3.17.1. *Leonurus cardiaca*

*Leonurus cardiaca* L. is a perennial herb widespread in Europe, throughout the plains and hills, as well as in East Asia to the Himalayas, Siberia, Northern Africa, and North America [283]. The common name of *L. cardiaca* is motherwort, but it is also known as throw-wort, lion's tail. For centuries, motherwort extract has been used as a medicinal plant to treat cardiac and vascular diseases, especially associated with anxiety, tension, and stress, and also for hypertension to reduce the risk of thrombosis to inhibit artery calcification [284].

The ethanolic extract has been prepared by adding 96% ethanol over aerial parts of the plants for 24–36 hours. The supernatant was concentrated by vacuum distillation at a temperature of 50°C. The extract was completely dried under sterile conditions with temperatures lower than 50°C.

In the aerial parts of *L. cardiaca*, many compounds were identified: terpene compounds: monoterpenes (iridoids: leonuride, ajugoside, and reptoside) [285], diterpenes (of clerodane, furanolabdane, and labdane types) [286], triterpenes (ursolic acid, oleanolic acids, euscaphic acid, and 1lilatifol D) [287], nitrogen-containing compounds (leonurine, stachydrine, and amine choline), and phenylpropanoids (lavandulifolioside, as well as flavonoids, phenolic acids, volatile oils, sterols (β-sitosterol and stigmasterol), and tannins. The phenylpropanoid glycosides such as lavandulifolioside (arabinoside) [288], phenolic acids such as chlorogenic, rosmarinic, coumaric, p-hydroxybenzoic, vanillic, and ferulic acids, and phenolic glycoside [289]. The volatile oils mainly contain sesquiterpene germacrene D, epicedrol, β-caryophyllene, α-humulene, and spathulenol and monoterpenes such as α-pinene and dehydro-1,8 cineol. Of these, ursolic acid proved a stronger anti-inflammatory activity than indomethacin and acetylsalicylic acid, and furanolabdane inhibited abdominal cramps more effectively than the parallel-given aspirin or acetaminophen.

Pharmacological studies have established that *L. cardiaca* possesses additional antimicrobial [286, 292], antioxidant [289, 293], anti-inflammatory [286, 294, 295], antinociceptive [296], neuroprotective [297], sedative [298], and even anticancer effects [299]. The findings obtained by coworkers, using the formalin, tail flick, and hot-plate tests, assess that central and peripheral mechanisms are involved in the activity of the motherwort extract. According to the tail flick test of this study, *L. cardiaca* extract only at the maximum dose (500 mg/kg) alleviated the pain in all times of tail flick test, whereas the lower doses (125 and 250 mg/kg) reduced only late pain. The formalin test of the *L. cardiaca* extract at a dose of 500 mg/kg and 250 mg/kg was more effective in the first and second phases, suggesting peripheral antinociceptive mechanism. The second phase of the formalin test is related to a peripheral inflammatory process [296].

As a conclusion, the studies concerning the analgesic activity of *L. cardiaca* extract afford a justification for the use of this plant in inflammatory disorders. Further research should be accomplished for the isolation of new phytochemicals and to fully understand the antinociceptive mechanism exhibited by the plant extract.

As undesirable effects, one can mention the potential to increase the risk of bleeding due to its antithrombotic and antiplatelet synergistic sedative effect when associated with benzodiazepines, which may result in coma [300].

3.18. *Mentha* Genus
**Mentha** is a genus of plants in the Lamiaceae family, with an estimated number of 13 to 18 species, lacking the exact distinction [301]. Hybridization between some of the species occurs naturally. The genus has a wide distribution across Europe, Africa, Asia, and North America. While the *Mentha* species can be found in many environments, most grow best in wet surroundings and most stems grow 10–120 cm tall and tend to spread uncontrollably over an indeterminate area; hence, they are sometimes considered invasive common and popular mints for commercial cultivation are *Mentha piperita*, *Mentha spicata*, *Mentha arvensis*, *Mentha suaveolens*. Mint was originally used as a medicinal herb to relieve stomachache and chest pains [302].

### 3.18.1. Mentha piperita

*Mentha piperita* L. (peppermint) is a hybrid of *M. spicata* and *M. aquatica*. This plant was cultivated since the time of ancient Egyptians and was established in the Icelandic Pharmacopoeia of the thirteenth century. The list of benefits and uses of peppermint as a folk remedy for medical therapy include biliary maladies, dyspepsia, enteritis, flatulence, gastritis, intestinal colic, and spasms of the bile duct in gastrointestinal (GI) tract [303].

The phytochemical occurrence in peppermint leaves and oil depends on plant maturity, variety, geographical origin, and processing conditions [304–307]. As fatty acids, there have been found palmitic, linoleic, and linolenic acids [308]. The main components of the volatile oil of peppermint are menthol (33–60%), menthone (15–32%), isomenthone (2–8%), 1,8-cineole (eucalyptol) (5–13%), and cineole (11%), menthofuran (1–10%), limonene (1–7%), β-myrcene (0.1–1.7%), β-caryophyllene (2–4%), pulegone (0.5–1.6%), and carvacrol [309]. The fresh leaves contain 1.2–3.9% (v/w) of essential oil, while the dried leaves is reported to contain only 21% of the original oil [310].

Carotenoids, chlorophylls, α- and γ-tocopherols, and ascorbic acid have also been reported in the plant extract [311]. The major menthol and carvone polyphenols include K, Ca, Mg, and Na, along with smaller amounts of Fe, Mn, Zn, and Cu and trace amounts of Cr, I, and Se [312]. Polyphenols isolated from peppermint leaves include mainly eriocitrin and rosmarinic acid, luteolin 7-O-rutinoside, and hesperidin [313].

The extraction of essential oils has been approached through different techniques, of which hydrodistillation is still the most common method, and volatile oils from medicinal plants, including *Mentha* [315]. In order to diminish the extraction time and for higher extraction yields, increased quality extracts, a number of extraction procedures have also been implemented, such as microwave-assisted extraction, solvent extraction, supercritical fluid extraction, and ultrasound-assisted extraction [316–319].

**In vitro and in vivo** pharmacological studies have proved multiple therapeutic effects, which are mentioned as follows: antioxidant (scavenging capacity being higher than that of *M. aquatica* or *M. longifolia*) [46, 320], antitumor activity on different cell lines [321], antiallergic activity [322, 324], antiviral activity with significant results on herpes simplex viruses (HSV-1 and HSV-2) and immunodeficiency virus-1 (HIV-1) [242, 325–327], antibacterial activity against different bacterial strains, including Gram-positive and Gram-negative rods (e.g., *S. aureus*, *Salmonella enteritidis*, *Shigella sonnei*, some strains of *E. coli*, *Heli cobacter pylon*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and many other pathogens) [328–331], modulatory effects on hepatic and renal functions [332–334], nervous system actions as analgesic and local anesthetic, and anti-inflammatory actions [335, 336].

The antinociceptive activity of *M. piperita* aqueous extract has been investigated by Yousef A. Taher using in vivo tests on mice [337]. In these studies, the plant extract showed inhibition of acetic acid-induced abdominal constrictions in mice at both 200 and 400 mg/kg doses. The hot-plate test has shown that administration of *M. piperita* aqueous extract (using the same abovementioned doses) caused a significant response to thermal stimulation. The carrageenan-induced paw edema test disclosed an increase in paw thickness; hence, it is a noninflammatory pain reliever activity, in contrast with previous research when the phytochemical compounds were obtained by the ethanolic extraction [335]. On the other hand, the methanolic extract of different *Mentha* species displayed different effects, indicating that these effects are species- and extract-form dependent [337, 338]. These findings indicate that the phytochemicals in the *M. piperita* extract exhibit analgesic effect arising from both CNS and peripheral actions since the response appears to both thermal and chemical pain stimuli. A similar efficacy is characteristic of central analgesics, such as morphine, which inhibits equally inflammatory and noninflammatory pains. The results concerning analgesic effects produced by *M. piperita* strongly recommend this plant as pain management, and encourage further studies for a better understanding of the nociception mechanism in order to find new options in pain therapy.

Toxicology studies of peppermint oil and its components completed in animals have shown no adverse effects or histopathological changes. There are no chronic toxicity studies of peppermint in humans, although the use of peppermint oil has been reported as contraindicated in patients with bile duct, gallbladder, and liver disorders. The use of peppermint oil capsules in patients with GI reflux, hiatal hernia, or kidney stones needs also caution [339].

### 3.18.2. Mentha spicata

*Mentha spicata* L., also known as spearmint, originated in Bangladesh and is traditionally used as herbal remedy for various conditions. Yousuf et al. have performed a study which aimed at evaluating the analgesic, anti-inflammatory, and antipyretic effects of *M. spicata* species models, using hot-plate, acetic acid-induced writhing test, carrageenan-induced rat paw edema, and yeast-induced pyrexia methods. These plate results suggest a centrally antinociceptive action with a higher pain inhibition at 180 minutes after administration, being a standard drug. The acetic acid-induced writhing method evaluates the peripherally analgesic action, which took place through in peritoneal receptors, most probably by inhibition of cyclooxygenase activity. The anti-inflammatory effect was maintained at a significant 6-hour period, showing efficiency in the late phase of inflammation due to the presence of certain components that interfere with prostaglandins.

Many other research studies on *Mentha* species such as *M. longifolia* [341], *M. arvensis* [342], or *M. villosa* [343] were also carried out on analgesic activity. Although the phytochemical occurrence is not identical, different mechanisms have been consequently involved in antinociception, with competitive results.
Lavandula genus includes more than 39 known species, mostly distributed in Arabia, Mediterranean Coasts, Asia, Middle East, and Africa. *Lavandula officinalis*, *Lavandula angustifolia*, *Lavandula hybrida*, and *Lavandula vera* have been considered as antispasmodic, antiflatulent, antiemetic, diuretic, anticonvulsant, antibacterial, antiepileptogenic, antioxidant, antibacterial, antifungal, and gastroprotective effects [344–348]. Lavender comprised over 100 constituents, among which the primary polyphenols, anthocyanins, carotenoids, linalool and linalyl acetate, α-pinene, limonene, 1,8-cineole, cis- and trans-ocimene, 3-octanol, caryophyllene, terpinen-4-ol, and flavonoids [349, 350].

### 3.19. Lavandula Genus

*Lavandula* is one of the most famous aromatic and medicinal plants [351] used in fresh state or dry condition, or in volatile oils (monoterpenic compounds, alcohols, and esters), triterpenic acids, coumarins, flavones, resins, and polyphenols [352]. Activity, *L. angustifolia* extracts or essential oils possess antispastic, carminative, analgesic, sedative, hypotensive, antiseptic, antifungal, diuretic, and general tonic action, but little information on lavender analgesic properties is available in the literature.

#### 3.19.1. Lavandula angustifolia

*Lavandula angustifolia* Mill. is one of the most famous aromatic and medicinal plants [351] used in fresh state or dry condition, or in volatile oils (monoterpenic compounds, alcohols, and esters), triterpenic acids, coumarins, flavones, resins, and polyphenols [352]. Activity, *L. angustifolia* extracts or essential oils possess antispastic, carminative, analgesic, sedative, hypotensive, antiseptic, antifungal, diuretic, and general tonic action, but little information on lavender analgesic properties is available in the literature.

#### 3.19.2. Lavandula officinalis

*Lavandula officinalis* Chaix is used in traditional and herbal medicine for the treatment of pain and in the reduction of the inflammatory process. Pharmacological and biological tests, extracts, fractions, and essential oils of *L. officinalis* are reported to have analgesic effects. The literature data show that *L. officinalis* extract contains linalool, acetate linalool, monoterp, sesquiterpene, luteolin, ursolic acid, coumarin, and luteolin. Hajhashemi and Ghannadi [349] showed that the aquatic, alcoholic, and phenolic extracts have antinociceptive effects in the second phase of the formalin test, but only the phenolic and alcoholic extracts had been able to prevent the first phase of the formalin test. Barocelli et al. proved that *L. officinalis* leaves inhalation attenuates pain evoked by hot-plate test, and stomach graze induced by high-dose acetic acid, ethanol and ascorbic acid. Husseini et al. (2015) [354] demonstrated that *L. officinalis* hydroalcoholic extracts inhibit inflammation and pain induced by formalin and cyclooxygenase (COX) type 1 and 2 activity in mice, using the formalin and hot-plate tests. The administration of 200, 250, 300, 400, and 800 mg/kg, i.p.) has inhibitory effects on inflammation induced by formalin injection into the animals hind paw, equal to morphine, dexamethasone, and indomethacin. The extract in 100, 200, and 300 mg/kg significantly reduced heat-induced activity in dose-dependent manner.

#### 3.19.3. Lavandula hybrida

In 2004, Barocelli et al. [353] demonstrated the antinociceptive and the gastroprotective effects of orally administered (100 mg, *Lavandula hybrida* Reverchon “Grosso” essential oil, and its principal constituents linalool and linalyl acetate in rodents. In the hot-plate test, the analgesic activity was observed after oil inhalation was inhibited by naloxone, atropine, and mecamylamine pretreatment, involving of opioidergic as well as cholinergic pathways. Therefore, the lavender oil reveals an interesting analgesic activity mainly after inhalation, at doses devoid of sedative side effect, suggesting the interest for potential application of this oil in aromatherapy.

### 4. Identification of Secondary Metabolites

The identification of secondary metabolites from essential oils was achieved by gas chromatography coupled with mass spectrometry or liquid chromatography coupled with mass spectrometry. Due to the high selectivity and sensitivity of mass spectrometry coupled to separation techniques such as gas chromatography and liquid chromatography represents a valuable tool for the qualitative and quantitative analysis of chemical substances present in essential oils and plant extracts.

The determination of the chemical composition belonging to essential oils for the following 14 species of the Lamiaceae family of plants: *Plectranthus pectinatus* [357], *Lavandula angustifolia* [349], *Lavandula officinalis* [356], *Leonurus cardiaca* [290], *Lamium purpureum* [357], *Marrubium vulgare* [358], *Mentha spicata* [359], *Origanum vulgare* [360], *Ocimum basilicum* [362], *Rosmarinus officinalis* [364], *Satureja hortensis*, and *Thymbus vulgaris* [365], included in most of the scientific articles follow the same steps: (i) flowering aerial parts and drying of the plant material, (ii) hydrodistillation of the dried plant material using a Clevenger apparatus, (iii) drying the essential oil using anhydrous sodium sulfate (Na₂SO₄), storing the essential oil in the dark at 4°C, i.v. injection of essential oil in the capillary column of a gas chromatograph, and separation of the chemical compounds, (iv) ionization and detection of each volatile substance in a mass spectrometer, and (v) identification of the components performed based on their retention indices in relation with a series of *n*-alkanes (C₈–C₃₂) and based on the mass spectra stored in NIST 21, NIST 107, Wiley spectral libraries, and scientific articles.

The volatile substances isolated from the 14 species of plants and analyzed by gas chromatography coupled with mass spectrometry for each of the essential oils in Table 1.

| Table 1: Compounds identified by GC-MS in essential oil. |

The chemical compounds identified by LC-ESI-MS in extracts prepared for the 9 species of plants that are included in the Lamiaceae family are also presented in Table 2.
Yalçin and the collaborators showed, using HPLC-ESI-MS, that the n-butanol extract of Lamium garganicum subsp. Laevigatum previously shown to possess anti-inflammatory and antinociceptive activity, contains nine iridoid glycosides [366].

Taamalli and collaborators reported the analyses of the methanolic extract of Mentha pulegium performed using an UPLC-QTOF spectrometer coupled with a liquid chromatograph and detected metabolites from the following groups: hydroxybenzoic acids, hydroxycinnamic acids, flavanols, flavones, flavonols, organic acids, nucleosides, amino acids, and fatty acids [56]. In the methanolic extract of *M. pulegium*, the authors identified a very high amount of gallolic acid.

In the case of the plant Marrubium vulgare, Amessis-Ouchemoukh Nadia and collaborators prepared the methanolic extract and analyzed it using an UHPLC-ESI-QTOF mass spectrometer. The mass spectra were acquired in the negative-ion mode and showed the presence of compounds presented in Table 2 [369].

Anna Vallverdú-Queralt et al. identified the phenolic compounds present in the Ethanolic acidified extract of Origanum vulgare. After the first extraction with a hydroalcoholic solvent, the extracted plant material was centrifuged, dried, ground, and stored. An aliquot of the extracted and dried plant material was subjected to extraction, 3 times, with 5 mL of 50% aqueous ethanol containing 0.1% formic acid. Supernatants were combined, and the organic solvent was evaporated under nitrogen flow. The dried residue was dissolved in 0.1% formic acid and concentrated using a 0.22 µm membrane filter, and the samples were analysed by HPLC-ESI-MS [76].

Pandey and Kumar performed extraction of dried leaves of Ocimum basilicum using 80% aqueous methanol [371]. A liquid chromatograph coupled to an ESI-Q-TOF mass spectrometer was used for the identification of the compounds, and the results are summarized in Table 2 [56].

### 5. In Vivo Evaluation of Phytochemicals Analgesic Activity

Over the decades, just a few studies tried to find alternatives to the classical treatment of pain, such as the application of phytochemicals.

Marrubiin, the broadly known diterpenoid lactone, has been associated with the bitter principle of the horehound (Marrubium vulgare L., M. alysson, M. thessalum), and other traditionally important Lamiaceae species (Leonotis leonurus, L. nepetifolia, Brachotia bracteosa) [67, 374–379]. According to recent literature, extensive pharmacological studies have revealed that marrubiin shows a spectrum of actions such as antinociceptive, antispasmodic, antihypertensive, antidiabetic, gastroprotective, anti-inflammatory, antimicrobial, antioxidant, and antihepatotoxic [65, 67, 71–73, 75, 374, 376–378].

Marrubiin, the broadly known diterpenoid lactone, has been associated with the bitter principle of the horehound (Marrubium vulgare L., M. alysson, M. thessalum) and other traditionally important Lamiaceae species (Leonotis leonurus, L. nepetifolia, Brachotia bracteosa) [67, 374–379]. According to recent literature, extensive pharmacological studies have revealed that marrubiin shows a spectrum of actions such as antinociceptive, antispasmodic, antihypertensive, antidiabetic, gastroprotective, anti-inflammatory, antimicrobial, antioxidant, and antihepatotoxic [65, 67, 71–73, 75, 374, 376–378].

Over time, the antinociceptive profile of marrubiin was analyzed in some animal models of pain. De Jesus et al.'s [64] results showed that marrubiin reveals potent and dose-related antinociceptive effects in mice, whose calculated ED50 values (µmol/kg, i.p.) were as follows: 2.2 in the writhing test, 6.6 (first phase) and 6.3 (second phase) in the formalin-induced pain test, and 28.8 when evaluated over the capsaicin test. The data show that marrubiin is more potent than some other well-known analgesic drugs. The antinociception produced by the marrubiin is not reversed by naloxone when analyzed against the writhing test. Its exact mechanism of action remains however still to be determined, but the results suggest that marrubiin, like the hydroalcoholic extract of *M. vulgare*, does not interact with opioid systems.

Analgesic activity success was obtained by reducing lac-tonic function of the marrubiin, in the formation of marrubiinic acid and its derivatives, which have shown significant analgesic effect on the writhing test in mice [68, 374]. The pharmacological study of marrubiinic acid presents an important (p < 0.05) and dose-dependent antinociceptive effect, against the writhing test, in administration, with ID50 value of 12 µmol/kg, being about 11-fold more active than the standard drugs used as reference, but lower than marrubiin [64].

Marrubiinic acid, given orally, at a dose of 50 mg/kg, produced a marked analgesic effect, reducing 76 ± 0.9% of the number of contractions induced by acetic acid, which may recommend that it can be well absorbed by the gastrointestinal tract. However, it was not effective in abolishing pain in a nonopiod way, showing the lack of antinociceptive effects in the hot-plate test [64]. When verified against the classical treatment of pain, it provided more direct evidence of the analgesic potential on neurogenic pain, causing an inhibition of 37.3 ± 3.8% at 10 mg/kg.
induced licking, signifying its involvement with the antagonism of vanilloid receptor [74].

The specific mechanism underlying the antinociceptive action of maruubin acid has yet to be determined, but it is likely that it interacts with opioid peptides. Although marubin acid displayed lesser analgesic properties than marubin, it is used in some clinically used drugs. In summary, these results show that it could be used as a model to obtain new and more potent analgesic agents.

In 2013, the analgesic activity of the aqueous extracts obtained from leaves (AEL) and stems (AES) of Rosmarinus officinalis, as well as their major compound—rosmarinic acid (RA)—were analyzed by Lucarini et al. [379]. The analysis is based upon abdominal constriction and licking behaviors in mice. The extracts were used at doses of 100, 200, and 400 mg·kg$^{-1}$, and the compounds were tested at 10, 20, and 40 mg·kg$^{-1}$. Oral administration of AEL, AES, and RA were not significantly active at any of the doses tested during the abdominal constriction test; the acetyl ester of RA presented significant analgesic activity. This data recommend that the analgesic effects of the acetyl derivative of RA function through a peripheral-mediated mechanism. The acetyl ester derivative of RA is theoretically applicable as a new lead compound for the management of pain.

Takaki et al. [23] investigated the antinociceptive effects of rosemary essential oil (REO) using the acetic acid-induced writhing and hot-plate tests in mice. REO is very common in folk medicine because of its antispasmodic, analgesic, and antirheumatic properties. In the administration of REO in doses of 125, 250, and 500 mg/kg revealed unremarkable effects on response latency, whereas concomitant administration with meperidine induced significant antinociceptive effects.

Moreover, the REO inhibited licking and shaking induced by formalin injections. Instead, at doses of 70, 125, and 250 mg/kg, REO exhibited substantial antinociceptive effect in the acetic acid-induced abdominal writhing test compared with control animals. The results show that REO possesses peripheral antinociceptive activity. Similarly, Martinez et al. [363] described the antinociceptive effect of this essential oil in the formalin model of articular pain. The essential oil with intraperitoneal administration in doses of 100, 300, and 600 mg/kg determined a dose-dependent antinociceptive effect, manifested as a remarkable reduction of the dysfunction in the pain-induced functional impairment model in mice at high doses. Emami et al. [34] indicate that rosemary essential oil can inhibit carrageenan-induced paw edema tests in rats. They also revealed that the rosemary oil induced writhing model of visceral pain and hot-plate tests in mice, suggesting that rosemary essential oil possesses anti-inflammatory and peripheral antinociceptive activity [23, 380, 381].

Investigations of the effects of carnosol as one of the constituents of rosemary essential oil extract have also shown that carnosol stimulated nitric oxide production (LPS [lipopolysaccharide]) in RAW 264.7 cells and reduced inflammation [382]. Moreover, carrageenan-induced proinflammatory leukotrienes in intact polymorph nuclear leukocytes [383], inhibited 5-lipoxygenase, antagonized mobilization of calcium ions, and inhibited cyclooxygenase type 2 (COX2) in inflamed skin in male Balb/C mice [384].

A recent work demonstrated that extracts from Rosmarinus officinalis can control pain by inhibiting its progression during a persistent noxious stimulus. This also has an essential characteristic, rosemary extract prevents damage to the nervous system. Thus, rosemary applies effects on the origins of neuropathic pain and offers a mean to directly modulate nervous signaling. The antineuropathic effects are mainly due to the terpenoid compound—rosmarinic acid (RA)—were analyzed by Lucarini et al. [379].

Husseini et al. [355] analyzed the effects of L. officinalis hydroalcoholic extract on pain induced by formalin and also cyclooxygenase-2 (COX-2) activity in mice. The administration of the extract intraperitoneally in doses of 100, 200, 250, 300, 400, and 800 mg/kg, respectively, produced a significant analgesic and anti-inflammatory activity in the chronic phase of the formalin test and also in hot-plate test in mice with no noted effect on the acute phase of the formalin test.

Moreover, this inhibitory effect is equal to the effects of morphine (10 mg/kg, s.c.), dexamethasone (10 mg/kg, i.p.), and indomethacin (10 mg/kg, i.p.). The extract in doses of 100, 200, and 300 mg/kg significantly reduced heat-induced pain and also reduced COX activity in a dose-dependent manner, where the inhibitory effect on COX1 activity was 33% and on COX2 activity was 45%. Therefore, these results indicate that RA possesses peripheral antinociceptive activity of the extract may be through modulation of COX2 activity.

Other studies [349] have also revealed that the extract of L. officinalis leaves might inhibit the formalin-induced chronic pain, abdominal constriction, and carrageenan-evoked edema. High doses of the essential oils and polyphenolic fraction of L. officinalis have similar effects by inhibiting acid-evoked pain [353]. This pharmacological activity could be derived from the contribution of various active principles composing the extract, such as linalool, myrcene, and 1–8 cineole, previously proved to possess antinociceptive properties [387–389]. However, administering the essential oil with naloxone, atropine, and mecamylamine could eliminate the analgesic effect of the extract, which indicates that the anti-inflammatory activity of the extract is dependent on cholinergic and opioid systems [349].

The antinociceptive and analgesic effects of the essential oil of Mentha spp. (EOM) leaves and its major constituent, piperitenone oxide (PO), were investigated in mice [390]. After an oral administration of 200 mg/kg of EOM and PO, the antinociceptive activity was demonstrated by an increase in the number of writhings and the second phase of the formalin test, while in the similar study, they did not interfere with the nociception associated with the hot-plate and tail immersion tests. The hot-plate and tail immersion tests were reported to be useful tests in discriminating analgesic agents acting primarily at the spinal medulla level and at higher central nervous system levels (positive results) from those acting through peripheral mechanisms (negative results) [391].

These findings show that EOM and PO are acting by peripheral mechanisms. In addition, EOM caused a reduction in the paw withdrawal time in the second phase of the formalin test, when administered at higher doses (100 and 200 mg/kg). At 100 and 200 mg/kg, PO reduced the swelling phase to 8.3 ± 2.7 s (N = 12) and 3.0 ± 1.2 s (N = 10), respectively. The antinociceptive activity induced by EOM and PO in the formalin tests was not altered by naloxone, demonstrating that their actions do not depend on opioid receptors [392], supporting their antinociceptive and anti-inflammatory hypothesis for their mechanism of action. Thus, it is reasonable to suggest that EOM and PO have an analgesic action that is probably indirect and attributed to the anti-inflammatory activity, which does not involve the central nervous system [393].
The Lamiaceae family includes numerous known species that are used as traditional medicine. The present review summarizes their traditional uses, pharmacology, and in vitro and in vivo studies of Betonica officinalis, Glechoma hederacea, Hystis pectinata, Leonurus cardiaca, Lamium genus, Melissa officinalis, Mentha genus, Marrubium vulgare, Origanum genus, Ocimum genus, Rosmarinus officinalis genus, Salvia genus, Satureja hortensis, Stachys lavandulifolia, Scutellaria lateriflora, Sideritis genus, Teucrium genus, and Ziziphus genus, belonging to Lamiaceae botanical genus. The above-referred studies reported that the abovementioned medicinal plants have potent antinociceptive activity. The findings of this review are promising, regarding new potential therapeutic agents with possible novel therapy. Most of the extracts identified did not present any toxic capabilities or known side effects and were at least as efficient as currently used synthetic drugs. Overall, although promising information evidence the efficacy of Lamiaceae genus in the treatment of pain associated disorders, the data are too preliminary and mostly fail to explain the exact cellular and molecular mechanisms of action and the respective active compounds. Therefore, future studies should be focused on investigating mechanisms of actions, realistic dosages, clinical efficacy, and safety of active compounds in pain treatment. This review covers a useful approach for further identification of new compounds from various medicinal plants, which may be effective in pain management.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors’ Contributions

All authors contributed equally to this work.

References

1. R. Masuda, J. Ajimi, and T. Murata, "Pharmacotherapy for neuropathic pain in Japan," *Journal of Nippon Medical School*, vol. 84, no. 4, pp. 258–267, 2017. View at Publisher · View at Google Scholar

2. B. I. Tamba, M.-M. Leon, and T. Petreus, "Common trace elements alleviate pain in an experimental mouse model," *Journal of Trace Elements in Medicine and Biology*, vol. 91, no. 4, pp. 554–561, 2013. View at Publisher · View at Google Scholar · View at Scopus

3. A. Iuliana Alexa, A. Cantemir, A. Ciobica et al., "Preliminary data regarding decreased catalase specific activity in the tear fluid in response to environmental stress," *Revista de Chimie-Bucharest*, vol. 68, no. 1, 2017. View at Google Scholar

4. K. Zorina-Lichtenwalter, M. Parisien, and L. Diatchenko, "Genetic studies of human neuropathic pain conditions," *Pain*, p. 1, 2017. View at Publisher · View at Google Scholar

5. F. Gedin, M. Skeppholm, K. Burström, V. Sparling, M. Tessma, and N. Zethraeus, "Effectiveness, costs and cost-effectiveness of spine care and physiotherapy compared with spino surgery in the treatment of non-specific chronic low back pain: study protocol for a randomized controlled trial," *Trials*, vol. 18, no. 1, p. 613, 2017. View at Publisher · View at Google Scholar · View at Scopus

6. I. D. Alexa, A. G. Pancu, A. I. Moroşanu et al., “The impact of self-medication with NSAIDS/analgescics in a north-eastern county of Romania,” *Farmacia*, vol. 62, 2014. View at Google Scholar

7. A. Scurrah, J. T. Shiner, J. A. Stevens, and S. G. Faux, “Regional nerve blockade for early analgesic management of elderly patients following fracture—a narrative review,” *Anaesthesia*, 2017, In press. View at Publisher · View at Google Scholar · View at Scopus

8. I. Gardikiotis, D. Azoicai, M. Popa, A. M. Manole, and M. Iorga, “The impact of body image and self-perceived physical ability in patients being after mastectomy without reconstruction,” *Journalul de Chirurgie*, vol. 11, no. 4, pp. 143–149, 2015. View at Publisher · View at Scopus

9. A. Luca, T. Alexa, A. Dondaş, I.-M. Crăcană, M. Bădescu, and C. Bohotin, “The effects of riboflavin and methylene blue on visceral pain,” *Revista Medico-Chirurgicala a Societatii De Medici Si Naturalisti Din Iasi*, vol. 119, no. 2, pp. 466–472, 2015. View at Publisher · View at Scopus

10. R. Cobzaru, A.-M. Dumitrescu, A. Glodeanu, M. Leon, S. Constantin, and M. Luca, “Pain and physical deformity after sentinel node biopsy,” *Medico-Chirurgicala a Societatii De Medici Si Naturalisti Din Iasi*, vol. 117, no. 2, pp. 29–32, 2013. View at Publisher · View at Google Scholar · View at Scopus

11. D. M. Iurea (Rata), M. Popa, J.-F. Chailan, B. I. Tamba, I. Tudorancea, and C. A. Peptu, “Ibuprofen-loaded chitosan/poly(maleic anhydride-alt-vinyl acetate) submicronic capsules for pain treatment,” *Journal of Bioactive and Compatible Polymers*, vol. 28, no. 4, pp. 143–149, 2013. View at Publisher · View at Google Scholar · View at Scopus

12. M. Iorga, L.-Z. Sztankovszky, C. Soponaru, and I. Gardikiotis, "Pharmacists’ attitude and practices about drug dispensing in Romania," *Journal of Nippon Medical School*, vol. 84, no. 6, pp. 601–606, 2015. View at Google Scholar

13. R. Ullah, S. Ahmad, A. Atiq et al., “Quantification and antibacterial activity of flavonoids in coffee samples,” *African Journal of Traditional, Complementary and Alternative Medicines*, vol. 12, no. 4, p. 84, 2015. View at Publisher · View at Google Scholar · View at Scopus

14. M. Ayaz, M. Junaid, F. Ullah et al., “Molecularly characterized solvent extracts and saponins from Polygonum hydropiper L. with antiplasmodial, antiangiogenic, anti-tumor, brine shrimp, and fibroblast NIH/3T3 cell line cytotoxicity,” *Frontiers in Pharmacology*, vol. 7, p. 718, 2016. View at Publisher · View at Google Scholar · View at Scopus

15. F. Haq, H. Ahmad, R. Ullah, and Z. Iqbal, “Species diversity and ethno botanical classes of the flora of Allai valley District, Swat, Pakistan,” *Pakistan Journal of Botany*, vol. 49, no. 3, pp. 1215–1221, 2017.
37. N. Okamura, H. Haraguchi, K. Hashimoto, and A. Yagi, “Flavonoids in alteration of cyclin A and cyclin B1 levels,” in *Nutritional Modulators of Pain in the Aging Population*, pp. 199–216, Elsevier, New York, NY, USA, 2017. View at Google Scholar

38. B. I. Tamba and T. Alexa-Stratulat, “Trace elements alleviate pain in mice and humans,” in *Nutritional Modulators of Pain in the Aging Population*, pp. 9–33, Elsevier, New York, NY, USA, 2017. View at Google Scholar

39. C. Peptu, R. Rotaru, L. Ignat et al., “Nanotechnology approaches for pain therapy through transdermal drug delivery,” *Journal of Pharmaceutical Design*, vol. 21, no. 42, pp. 6125–6139, 2015. View at Publisher · View at Google Scholar · View at Scopus

40. T. Alexa, A. Marza, T. Voloseniuc, and B. Tamba, “Enhanced analgesic effects of tramadol and common trace element coadjuvants in mice,” *Journal of Neuroscience Research*, vol. 93, no. 10, pp. 1534–1541, 2015. View at Publisher · View at Google Scholar · View at Scopus

41. B. I. Tamba, A. Dondas, M. Leon et al., “Silica nanoparticles: preparation, characterization and in vitro/in vivo biodistribution,” *European Journal of Pharmaceutical Sciences*, vol. 71, pp. 46–55, 2015. View at Publisher · View at Google Scholar · View at Scopus

42. M. Silion, F. Emami, H. Ali-Beig, S. Farahbakhs et al., “Hydroalcoholic extract of rosemary (*Rosmarinus officinalis*) leaves,” *Experimental and Pharmaceutical Design*, vol. 21, no. 42, pp. 6125–6139, 2015. View at Publisher · View at Google Scholar · View at Scopus

43. I. Takaki, L. E. Bersani-Amado, A. Vendruscolo et al., “Anti-inflammatory and antinociceptive effects of *Rosmarinus officinalis* in experimental animal models,” *Journal of Medicinal Food*, vol. 11, no. 4, pp. 741–746, 2008. View at Publisher · View at Google Scholar · View at Scopus

44. I. M. Jaba, D. Vasincu, G. Manolidis, I. Haulică, and O. C. Mungiu, “Experimental data regarding the implications of certain minimum structure enkephalin-like peptides in nociceptive processing,” *Romanian Journal of Physiology*, vol. 41, no. 1-2, pp. 119–123, 2012. View at Google Scholar

45. T. Alexa, A. Luca, A. Dondas, and C. R. Bobotin, “Preconditioning with cobalt chloride modifies pain perception in mice,” *European Journal of Pain Therapy*, vol. 9, no. 10, pp. 1465–1469, 2015. View at Publisher · View at Google Scholar · View at Scopus

46. A. Luca, T. Alexa, A. Dondas, and C. R. Bobotin, “Pain modulation by curcumin and ascorbic acid in mice,” *Revista de Chimie*, vol. 55, no. 5, pp. 1718–1723, 2007. View at Google Scholar

47. B. I. Tamba, T. Petreus, M.-M. L. Constantin, C. Rezu, M. Florea, and E. Rezu, “Heavy metal trace elements induced antinociceptive effects in an experimental mouse model,” *Revista de Chimie*, vol. 66, no. 7, pp. 976–982, 2015. View at Google Scholar

48. B. B. Kakoti, P. Pradhan, S. Borah, K. Mahato, and M. Kumar, “Analgesic and anti-inflammatory activities of the methanolic stem bark extract of *Nyctanthes arbor-tristis* Linn,” *BioMed Research International*, vol. 2013, Article ID 826295, 6 pages, 2013. View at Google Scholar · View at Scopus

49. M. Bahmani, M. Shirzad, M. Majlesi, N. Shahinfar, and M. Rafieian-Kopaei, “A review study on analgesic applications of Iranian medicinal plants,” *Asian Pacific Journal of Tropical Medicine*, vol. 7, pp. S43–S53, 2014. View at Publisher · View at Google Scholar · View at Scopus

50. M. Bekut, S. Brkić, N. Kladar, G. Dragović, N. Gavarić, and B. Božin, “Potential of selected Lamiaceae plants in anti(retro)viral therapy,” *Pharmacological Research*, 2017, In press. View at Publisher · View at Google Scholar · View at Scopus

51. M. R. al-Sereiti, K. M. Abu-Amr, and P. Sen, “Pharmacology of rosemary (*Rosmarinus officinalis* Linn.) and its therapeutic applications,” *Indian Journal of Experimental Biology*, vol. 37, no. 2, pp. 124–130, 1999. View at Google Scholar

52. G. Altinier, S. Sosa, R. P. Aquino, T. Mencherini, R. Della Loggia, and A. Tubaro, “Characterization of topical antiinflammatory activity of *Rosmarinus officinalis* L. by bioassay,” *Journal of Agricultural and Food Chemistry*, vol. 55, no. 5, pp. 1718–1723, 2007. View at Publisher · View at Google Scholar

53. F. Emami, H. Ali-Beig, S. Farahbakhs et al., “Hydroalcoholic extract of rosemary (*Rosmarinus officinalis* L.) and its constituent carnosol inhibit formalin-induced pain and inflammation in mice,” *Pakistan Journal of Biological Sciences*, vol. 16, no. 7, pp. 309–314, 2013. View at Publisher · View at Google Scholar · View at Scopus

54. J. I. Sotelo-Félix, D. Martinez-Fong, P. Muriel, R. L. Santillán, D. Castillo, and P. Yahuaca, “Evaluation of the effectiveness of *Rosmarinus officinalis* (Lamiaceae) in the alleviation of carbon tetrachloride-induced acute hepatotoxicity in the rat,” *Journal of Ethnopharmacology*, vol. 81, no. 2, pp. 145–154, 2002. View at Publisher · View at Google Scholar · View at Scopus

55. J. M. Visanji, D. G. Thompson, and P. J. Padfield, “Induction of G2/M phase cell cycle arrest by carnosol and carnosic acid is correlated to alteration of cyclin A and cyclin B1 levels,” *Cancer Lett.*, vol. 237, pp. 130–136, 2006. View at Publisher · View at Google Scholar · View at Scopus

56. N. Okamura, H. Haraguchi, K. Hashimoto, and A. Yagi, “Flavonoids in *Rosmarinus officinalis* leaves,” *Phytochemistry*, vol. 37, no. 5, pp. 124–130, 1994. View at Publisher · View at Google Scholar · View at Scopus
80. C. H. Peng, J.-D. Su, C.-C. Chyau et al., "Supercritical fluid extracts of rosemary leaves exhibit potent anti-inflammatory effects," *Bioscience, Biotechnology, and Biochemistry*, vol. 71, no. 9, pp. 2223–2232, 2007. View at Publisher · View at Google Scholar · View at Scopus

59. M. M. Chan, C. T. Ho, and H. I. Huang, "Effects of three dietary phytochemicals from tea, rosemary and turmeric on inflammatory nitrite production," *Cancer Letters*, vol. 96, no. 1, pp. 23–9, 1995. View at Publisher · View at Google Scholar · View at Scopus

K.-I. Inoue, H. Takano, A. Shiga et al., "Effects of volatile constituents of a rosemary extract on allergic airway inflammation and dust mite allergen in mice," *International Journal of Molecular Medicine*, vol. 16, pp. 315–319, 2005. View at Google Scholar

K. Inoue, H. Takano, A. Shiga et al., "Effects of volatile constituents of rosemary extract on lung inflammation induced by nanoparticles," *Basic Clinical Pharmacology Toxicology*, vol. 99, no. 1, pp. 52–57, 2006. View at Google Scholar

M. E. González-Trujano, E. I. Peña, A. L. Martínez et al., "Evaluation of the antinociceptive effect of *Rosmarinus officinalis* in different experimental models in rodents," *Journal of Ethnopharmacology*, vol. 111, no. 3, pp. 476–482, 2007. View at Google Scholar · View at Scopus

C. Meyre-Silva and V. Cechinel-Filho, "A review of the chemical and pharmacological aspects of the genus *Marrubium*." *Pharmaceutical Design*, vol. 16, no. 31, pp. 3503–3518, 2010. View at Publisher · View at Google Scholar · View at Scopus

R. A. De Jesus, V. Cechinel-Filho, A. E. Oliveira, and V. Schlemper, "Analysis of the antinociceptive properties of marrubiin in *Marrubium vulgare*," *Phytotherapy*, vol. 7, no. 2, pp. 111–115, 2000. View at Publisher · View at Google Scholar · View at Scopus

C. A. Rodrigues, A. O. S. Savi, V. Schlemper, F. Reynaud, and V. Cechinel-Filho, "An improved extraction of marrubiin from *Marrubium vulgare*," *Chromatographia*, vol. 47, no. 7–8, pp. 449–450, 1998. View at Publisher · View at Google Scholar · View at Scopus

M. M. de Souza, R. A. P. de Jesus, V. Cechinel-Filho, and V. Schlemper, "Analgesic profile of hydroalcoholic extract of *Marrubium vulgare*," *Phytotherapy*, vol. 5, no. 2, pp. 103–107, 1997. View at Publisher · View at Google Scholar · View at Scopus

C. Meyre-Silva, R. A. Yunes, V. Schlemper, F. Campos-Buzzi, and V. Cechinel-Filho, "Analgesic potential of marrubiin derivatives: a diterpene present in *Marrubium vulgare* (Lamiaceae)," *Il Farmaco*, vol. 60, no. 4, pp. 321–326, 2005. View at Publisher · View at Google Scholar · View at Scopus

O. Popoola, A. Elbagory, F. Ameer, and A. Hussein, "Marrubiin," *Molecules*, vol. 18, no. 8, pp. 9049–9060, 2013. View at Publisher · View at Google Scholar · View at Scopus

K. Yousefi, S. Hamedeyazdan, M. Torbati, and F. Fathiazad, *Chromatographic fingerprint analysis of marrubiin in Marrubium vulgare leaf extracts using HPTLC Technique*, vol. 6, Tabriz Univ. Med. Sci, 2016. View at Publisher · View at Google Scholar · View at Scopus

A. P. Novaes, C. Rossi, C. Poffo et al., "Preliminary evaluation of the hypoglycemic effect of some Brazilian medicinal plants," *Pak J Pharm Sci*, vol. 26, no. 4, pp. 427–430.

H. K. Stulzer, M. P. Tagliari, J. A. Zampi, V. Cechinel-Filho, and V. Schlemper, "Antioedematogenic effect of marrubiin in *Marrubium vulgare*," *Journal of Ethnopharmacology*, vol. 108, no. 3, pp. 379–84, 2006. View at Publisher · View at Google Scholar · View at Scopus

A. Herrera-Arellano, L. Aguilar-Santamaría, B. García-Hernández, P. Nicasio-Torres, and J. Tortoriello, "Clinical trial of *Cecropia obtusifolia* and *Marrubium vulgare* leaf extracts on blood glucose and serum lipids in type 2 diabetics," *Phytotherapy*, vol. 11, no. 7, pp. 233–239, 2004. View at Publisher · View at Google Scholar · View at Scopus

I. E. Orhan, R. Belhattab, F. S. Şenol, A. R. Gülpinar, S. Hoşbaş, and M. Kartal, "Profiling of cholinesterase inhibitory activities of *Artemisia absinthium*, *A. herba-alba*, *A. fragrans*, *Marrubium vulgare*, *M. astranicum*, *Origanum vulgare* subsp. glaucum and *Gaultheria glandulosum* essential oil analysis of two Artemisia species," *Industrial Crops and Products*, vol. 32, no. 3, pp. 566–571, 2010. View at Publisher · View at Google Scholar · View at Scopus

D. Julius, M. J. Caterina, M. A. Schumacher, M. Tominaga, T. A. Rosen, and J. D. Levine, "The capsaicin receptor: a heat channel in the pain pathway," *Nature*, vol. 389, no. 6653, pp. 816–824, 1997. View at Publisher · View at Google Scholar · View at Scopus

G. Çitoğlu and F. Aksit, "Occurrence of marrubiin and ladanein in *Marrubium trachyticum* Boiss. from Turkey," *Biochemical System and Ecology*, vol. 30, no. 9, pp. 885–886, 2002. View at Publisher · View at Google Scholar · View at Scopus

B. Janeska, M. Stefova, and K. Alipieva, "Assay of bavonoid aglycones from the species of genus *Sideritis* (Lamiaceae) from *Sideritis glandulosum*," *Acta Pharmacologica*, vol. 57, no. 3, 2007. View at Publisher · View at Google Scholar · View at Scopus

R. Knörle, "Extracts of *Sideritis scardica* as triple monoamine reuptake inhibitors," *Journal of Neural Transmission*, vol. 119, no. 9, pp. 1479–1482, 2012. View at Publisher · View at Google Scholar · View at Scopus

J. Hofrichter, M. Krohn, T. Schumacher et al., "Alzheimer’s β-amyloidosis mouse models and aged C57Bl/6 mice," *Journal of Alzheimer’s Disease*, vol. 53, no. 3, pp. 967–980, 2016. View at Publisher · View at Google Scholar · View at Scopus

J. P. Stanoeva and M. Stefova, "Evaluation of the ion trap MS performance for quantification of flavonoids and comparison to pinch ions," *Journal of Mass Spectrometry*, vol. 47, no. 11, pp. 1395–1406, 2012. View at Publisher · View at Google Scholar · View at Scopus

V. Samanidou, A. Tsagiannidis, and I. Sarakatsianos, "Simultaneous determination of polyphenols and major purine alkaloids in..."
1. Schmidt, J. Wanner, M. Hiiferl et al., “Chemical composition, olfactory analysis and antibacterial activity of ROS generation,” Natural Product Research, vol. 21, no. 9, pp. 819–823, 2007. View at Publisher · View at Google Scholar · View at Scopus

2. J. Petreska, G. Stefkov, S. Kulevanova, K. Alipieva, V. Bankova, and M. Stefova, “Phenolic compounds of mountain tea from LC/DAD/ESI/MSn profile and content,” Natural Product Communications, vol. 6, no. 1, pp. 21–30, 2011. View at Google Scholar

3. A. B. Trendafilova, M. N. Todorova, L. N. Evstatieva, and D. V. Antonova, “Variability in the essential-oil composition of Sideritis from native Bulgarian Populations,” Chemistry & Biodiversity, vol. 10, no. 3, pp. 484–492, 2013. View at Publisher · View at Google Scholar · View at Scopus

4. B. Qazimi, G. Stefo, M. Karapandzova, I. Cvetkovikj, and S. Kulevanova, “Aroma compounds of mountain tea (Sideritis raeseri) from western Balkan,” Natural Product Communications, vol. 9, pp. 1369–72, 2014. View at Google Scholar

5. J. Petreska Stanoeva and M. Stefova, “Assay of urinary excretion of polyphenols after ingestion of a cup of mountain tea (Sideritis scardica) measured by HPLC-DAD-ESI-MS/MS,” Journal of Agricultural and Food Chemistry, vol. 61, no. 44, pp. 10488–10497, 2013. View at Publisher · View at Google Scholar · View at Scopus

6. E. González-Burgos, M. E. Carretero, and M. P. Gómez-Serranillos, “Sideritis spp.: uses, chemical composition and pharmacology—a review,” Journal of Ethnopharmacology, vol. 135, no. 2, pp. 209–225, 2011. View at Publisher · View at Google Scholar · View at Scopus

7. C. M. Ghiciuc, L. C. Dima-Cozma, R. M. Bercea et al., “Imbalance in the diurnal salivary testosterone/cortisol ratio in men with obstructive sleep apnea: an observational study,” Brazilian Journal of Otorhinolaryngology, vol. 82, no. 5, pp. 529–535, 2016. View at Publisher · View at Google Scholar · View at Scopus

8. W. Dimpfel, "Pharmacological classification of herbal extracts by means of comparison to spectral EEG signatures induced by drugs in the freely moving rat," Journal of Ethnopharmacology, vol. 149, no. 2, pp. 583–589, 2013. View at Publisher · View at Google Scholar · View at Scopus

9. O. Mitu, M. Roca, M.-M. Leon, A. Gherasim, M. Graur, and F. Mitu, “Association of health-related quality of life with cardiovascular risk factors and subclinical atherosclerosis in non-diabetic asymptomatic adults,” Biomedical Research, vol. 27, 2016. View at Google Scholar

10. V. Tadić, D. Bojović, I. Arsić et al., “Chemical and antimicrobial evaluation of supercritical and conventional Sideritis scardica Lamiaceae extracts,” Molecules, vol. 17, no. 3, pp. 2683–2703, 2012. View at Publisher · View at Google Scholar · View at Scopus

11. F. Danesi, S. Saha, P. A. Kroon et al., “Bioactive-rich Lamiaceae extracts,” Food and Chemical Toxicology, vol. 50, pp. 608–615, 2012. View at Publisher · View at Google Scholar · View at Scopus

12. D. Ö. Yavuz, “Optimization of regeneration conditions and in vitro propagation of Sideritis Stricta Boiss & Heldr.,” Zeitschrift für Naturforschung C, vol. 62, no. 7-8, pp. 519–525, 2007. View at Google Scholar · View at Publisher · View at Scopus

13. C.-H. Kang, I. M. N. Molagoda, Y. H. Choi, C. Park, D.-O. Moon, and G.-Y. Kim, “Apigenin promotes TRAIL-mediated apoptosis of ROS generation,” Food and Chemical Toxicology, vol. 111, pp. 623–630, 2018. View at Publisher · View at Google Scholar · View at Scopus

14. B. Qazimi, G. Stefo, M. Karapandzova, I. Cvetkovikj, and S. Kulevanova, “Aroma compounds of mountain tea (Sideritis raeseri) from western Balkan,” Natural Product Communications, vol. 9, pp. 1369–72, 2014. View at Google Scholar

15. O. Mitu, M. Roca, M.-M. Leon, A. Gherasim, M. Graur, and F. Mitu, “Association of health-related quality of life with cardiovascular risk factors and subclinical atherosclerosis in non-diabetic asymptomatic adults,” Biomedical Research, vol. 27, 2016. View at Google Scholar

16. V. Tadić, D. Bojović, I. Arsić et al., “Chemical and antimicrobial evaluation of supercritical and conventional Sideritis scardica Lamiaceae extracts,” Molecules, vol. 17, no. 3, pp. 2683–2703, 2012. View at Publisher · View at Google Scholar · View at Scopus

17. F. Danesi, S. Saha, P. A. Kroon et al., “Bioactive-rich Lamiaceae extracts,” Food and Chemical Toxicology, vol. 50, pp. 608–615, 2012. View at Publisher · View at Google Scholar · View at Scopus

18. D. Ö. Yavuz, “Optimization of regeneration conditions and in vitro propagation of Sideritis Stricta Boiss & Heldr.,” Zeitschrift für Naturforschung C, vol. 62, no. 7-8, pp. 519–525, 2007. View at Google Scholar · View at Publisher · View at Scopus

19. C.-H. Kang, I. M. N. Molagoda, Y. H. Choi, C. Park, D.-O. Moon, and G.-Y. Kim, “Apigenin promotes TRAIL-mediated apoptosis of ROS generation,” Food and Chemical Toxicology, vol. 111, pp. 623–630, 2018. View at Publisher · View at Google Scholar · View at Scopus

20. E. Schmidt, J. Wanner, M. Hiiferl et al., “Chemical composition, olfactory analysis and antibacterial activity of Thymus vulgaris.”
geraniol, 4-thujanol/terpinen-4-ol, thymol and linalool cultivated in southern France,” *Natural Product Communications*, vol. 41, pp. 1098–1103, 2012. View at Google Scholar

10. V. Vičiūlytė, R. Butkiūnienė, and K. Ložienė, “Effects of meteorological conditions and plant growth stage on the accumulation of its precursors in *Thymus pulegioides*,” *Phytochemistry*, vol. 128, pp. 20–26, 2016. View at Publisher · View at Google Scholar

11. P. Satyal, B. L. Murray, R. L. McFeeters, and W. N. Setzer, “Essential oil characterization of *Thymus vulgaris* from various locations,” *Foods*, vol. 5, no. 4, p. 78, 2016. View at Publisher · View at Google Scholar

12. H. Tsuchiya, “Hironori, anesthetic agents of plant origin: a review of phytochemicals with anesthetic Activity,” *Molecules*, vol. 22, no. 13, pp. 2639–2662, 2017. View at Publisher · View at Google Scholar · View at Scopus

13. M. Akram and A. Rashid, “Anti-coagulant activity of plants: mini review,” *Journal of Thrombosis and Thrombolysis*, vol. 44, no. 3, pp. 401–411, 2017. View at Publisher · View at Google Scholar · View at Scopus

14. K. Okazaki, K. Kawazoe, and Y. Takaishi, “Human platelet aggregation inhibitors from thyme (*Thymus vulgaris* L.),” *Phytotherapy Research*, vol. 16, no. 4, pp. 398–399, 2002. View at Publisher · View at Google Scholar · View at Scopus

15. M. Soosaraei, M. Fakhar, S. Hosseini Teshnizi, H. Ziaei Hezarjaribi, and E. S. Banimostafavi, “Medicinal plants with antifebrilemanial activity in Iran: a systematic review and meta-analysis,” *Annals of Medicine and Surgery*, vol. 21, pp. 63–69, 2017. View at Publisher · View at Google Scholar · View at Scopus

16. A. Ebadollahi, J. J. Sendi, and A. Aliakbar, “Efficacy of nanoencapsulated *Thymus eriocalyx* and *Thymus kotschyanus* essential oil mesoporous material MCM-41 against *Tetranychus urticae* (Acari: Tetranychidae),” *Journal of Economic Entomology*, vol. 110, no. 2, pp. 2411–2420, 2017. View at Publisher · View at Google Scholar · View at Scopus

17. K. Schönknecht, H. Krauss, J. Jambor, and A. M. Fal, “Treatment of cough in respiratory tract infections—the effect of combination of active compounds with thymol,” *Wiadomosci Lekarskie*, vol. 69, no. 6, pp. 791–798, 2016. View at Publisher · View at Google Scholar · View at Scopus

18. H. Ayrlé, M. Mevissen, M. Kaske et al., “Medicinal plants–prophylactic and therapeutic options for gastrointestinal and respiratory infections in calves and piglets? A systematic review,” *BMC Veterinary Research*, vol. 12, no. 1, p. 89, 2016. View at Publisher · View at Google Scholar · View at Scopus

19. L. Wan, D. Meng, H. Wang et al., “Preventive and therapeutic effects of thymol in a lipopolysaccharide-induced acute lung injury model,” *Inflammation*, vol. 41, no. 1, 2017. View at Publisher · View at Google Scholar · View at Scopus

20. E. Vigo, A. Cepeda, R. Perez-Fernandez, and O. Gualillo, “In-vitro anti-inflammatory effect of *Eucalyptus globulus* and 2-nitric oxide inhibition in J774A.1 murine macrophages,” *Journal of Pharmacy and Pharmacology*, vol. 56, no. 2, pp. 257–261, 2014. View at Publisher · View at Google Scholar · View at Scopus

21. M. Kindl, B. Blaže kovič, F. Bucar, and S. Vladimir-Knežević, “Antioxidant and anticholinesterase potential of six *Thymus* species,” *Phytochemistry*, vol. 91, pp. 1–11, 2013. View at Publisher · View at Google Scholar · View at Scopus

22. M. Alabdullatif, I. Boujezza, M. Mekni et al., “Enhancing blood donor skin disinfection using natural oils,” *Transfusion*, vol. 57, no. 11, pp. 2920–2927, 2017. View at Publisher · View at Google Scholar

23. E. Basch, C. Ulbricht, P. Hammerness, A. Bevins, and D. Sollars, “Thyme (*Thymus vulgaris* L.), thymol,” *Journal of Herbal Pharmacology*, vol. 4, no. 1, pp. 49–67, 2004. View at Publisher · View at Google Scholar · View at Scopus

24. E. A. El Zayyat, M. I. Soliman, N. A. Elleboudy, and S. E. Ofaa, “Bioefficacy of some Egyptian aromatic plants on *Culex p. (Culicidae)* adults and larvae,” *Journal of Arthropod-Borne Diseases*, vol. 11, no. 1, pp. 147–155, 2017. View at Google Scholar · View at Scopus

25. M. I. Qadir, A. Parveen, K. Abbas, and M. Ali, “Analgesic, anti-inflammatory and anti-pyretic activities of *Thymus linearis*,” *Journal of Pharmaceutical and Biomedical Analysis*, vol. 59, no. 5, pp. 1109–1114, 2012. View at Publisher · View at Google Scholar · View at Scopus

26. A. A. Taherian, M. Babaei, A. A. Vafaei, M. Jarrahi, M. Jadidi, and H. Sadeghi, “Antinoceptive effects of hydroalcoholic extract of *Thymus vulgaris*,” *Pakistan Journal of Pharmaceutical Sciences*, vol. 22, pp. 83–89, 2009. View at Google Scholar · View at Scopus

27. H. Salvan tan, R. Saghebi, A. A. Moghadamnia et al., “Comparative effect of *Thymus vulgaris* and ibuprofen on primary triple-blind clinical study,” *Caspian Journal of Internal Medicine*, vol. 5, no. 2, pp. 82–88, 2014. View at Google Scholar

28. M. Orlowska, I. Stanimirova, D. Staszek, M. Sajewicz, T. Kowalska, and M. Waks mundzka-Hajnos, “Optimization of extraction thin-layer chromatographic fingerprints of common thyme,” *Journal of AOAC International*, vol. 97, no. 5, pp. 1274–1284, 2015. View at Publisher · View at Google Scholar · View at Scopus

29. E. Pinto, C. Pina-Vaz, L. Salgueiro et al., “Antifungal activity of the essential oil of *Thymus pulegioides* on *Candida, Dermatophyte* species,” *Journal of Medical Microbiology*, vol. 55, no. 10, pp. 1367–1373, 2006. View at Publisher · View at Google Scholar · View at Scopus

30. S. Vitalini, M. Iriti, C. Puricelli, D. Ciuchi, A. Segale, and G. Fico, “Traditional knowledge on medicinal and food plants of Giacomo (Sondrio, Italy)—an alpine ethnobotanical study,” *Journal of Ethnopharmacology*, vol. 145, no. 2, pp. 517–529, 2012. View at Publisher · View at Google Scholar · View at Scopus
124. S. Schaffer, G. P. Eckert, W. E. Müller et al., “Hypochlorous acid scavenging properties of local Mediterranean plant foods,” Life, vol. 12, pp. 1239–1247, 2004. View at Publisher · View at Google Scholar · View at Scopus

125. K. Stalińska, A. Guzdek, M. Rokicki, and A. Koj, “Transcription factors as targets of the anti-inflammatory treatment. A case study with extracts from some Mediterranean diet plants,” Journal of Physiology and Pharmacology, vol. 56, no. 1, pp. 157–169. View at Google Scholar

126. J. Novak, L. Bahoo, U. Mittregger, and C. Franz, “Composition of individual essential oil glands of savory (Satureja hortensis L.) from Syria,” Flavour and Fragrance Journal, vol. 21, no. 4, pp. 731–734, 2006. View at Publisher · View at Google Scholar · View at Scopus

127. S. Monztz and M. Abdollahi, “An update on pharmacology of Satureja species; from antioxidant, antimicrobial, anti-inflammatory, hypolipidemic to reproductive stimulation,” International Journal of Pharmacology, vol. 6, pp. 454–461, 2010. View at Publisher · View at Google Scholar

128. B. Tepe and M. Cilkiz, “A pharmacological and phytochemical overview on Satureja,” Pharmaceutical Biology, vol. 54, no. 10, 2016. View at Publisher · View at Google Scholar · View at Scopus

129. F. Nikaein, S. Babajafari, S. Mazloomi et al., “The effects of Satureja hortensis L. Dried leaves on serum sugar, lipid profiles, blood pressure in metabolic syndrome patients: a double-blind randomized clinical trial,” Iranian Red Crescent Medical Journal, vol. 4, no. 1, pp. 109–114, 2009. View at Publisher · View at Google Scholar · View at Scopus

130. P. Mašković, V. Veličković, M. Mićić et al., “Summer savory extracts prepared by novel extraction methods resulted in enhanced biological activity,” Industrial Crops and Products, vol. 109, pp. 875–881, 2017. View at Publisher · View at Google Scholar · View at Scopus

131. S. Ceker, G. Agar, L. Alpsoy, G. Nardemir, and H. E. Kizil, “Antagonistic effects of Satureja hortensis essential oil against lymphocytes in vitro,” Cytology and Genetics, vol. 48, no. 5, pp. 327–332, 2014. View at Publisher · View at Google Scholar · View at Scopus

132. V. Hajhashem, B. Zolfaghari, and A. Yousefi, “Antinociceptive and anti-inflammatory activities of Satureja hortensis seed hydroalcoholic and polyphenolic extracts in animal models,” Medical Principles and Practice, vol. 21, no. 2, pp. 178–182, 2012. View at Publisher · View at Google Scholar · View at Scopus

133. M. Mohammadhosseini, A. Akbarzadeh, and H. Hashemi-Moghaddam, “Gas chromatographic-mass spectrometric analysis obtained by HS-SPME-GC-MS technique from Stachys lavandulifolia and evaluation for biological activity: a review,” Journal of Essential Oil Bearing Plants, vol. 19, no. 6, pp. 1300–1327, 2016. View at Publisher · View at Google Scholar · View at Scopus

134. K. Javidnia, F. Mojab, and S. A. Mojahedi, “Chemical constituents of the essential oil of Stachys lavandulifolia Vahl from different locations,” Essential Oil Bearing Plants, vol. 19, no. 6, pp. 174–178, 2003. View at Publisher · View at Google Scholar · View at Scopus

135. A. G. Pirbalouti and M. Mohammadi, “Phytochemical composition of the essential oil of different populations of Stachys lavandulifolia from Syria,” Asian Pacific Journal of Tropical Biomedicine, vol. 3, no. 2, pp. 123–128, 2013. View at Publisher · View at Google Scholar · View at Scopus

136. L. Rouzbeh, “Antimicrobial activity and chemical composition of essential oils of Stachys lavandulifolia Vahl. from Mashhad, Iran,” Journal of Medicinal Plants Research, vol. 6, no. 24, pp. 4149–4158, 2012. View at Publisher · View at Google Scholar

137. M. Oztürk, M. E. Duru, F. Aydoğan-Oztürk et al., “GC-MS analysis and antimicrobial activity of essential oil of Stachys smyrnææa,” Natural Product Communications, vol. 4, no. 1, pp. 109–114, 2009. View at Google Scholar

138. B. Minae, M. Sardari, H. Sharifi, M. Sedigh Rahim Abadi, and O. Sadeghpour, “Stachys lavandulifolia Vahl. and its relation to traditional manuscripts,” Iranian Red Crescent Medical Journal, vol. 17, no. 11, p. e19932, 2015. View at Publisher · View at Google Scholar · View at Scopus

139. M. Modarres, L. Hosseinzadeh, N. Nematy, Z. M. Siavash-Haghighi, and K. Ghanbari, “Acute and subchronic toxicological effects of Stachys lavandulifolia aqueous extract in Wistar rats,” Research in Pharmacological Sciences, vol. 9, no. 3, pp. 165–72, 2014. View at Publisher · View at Google Scholar

140. V. Hajhashemi, A. Ghannadi, and S. Sedighifar, “Analgesic and anti-inflammatory properties of the hydroalcoholic, polyphenolic, and hydrophobic extracts of Stachys lavandulifolia,” Research in Pharmaceutical Sciences, vol. 1, pp. 92–98, 2007. View at Google Scholar

141. R. S. S. Barreto, J. S. S. Quintans, R. K. L. R. S. Amarante et al., “Evidence for the involvement of TNF-α and IL-1β in the anti-inflammatory activity of Stachys lavandulifolia Vahl. (Lamiaceae) essential oil and (-)-α-bisabolol, its main compound,” Journal of Ethnopharmacology, vol. 191, pp. 9–18, 2016. View at Publisher · View at Google Scholar · View at Scopus

142. E. Házagny-Radnai, Á. Balogh, S. Czigle, I. Máthé, J. Hohmann, and G. Blazsó, “Antiinflammatory activities of Hungarian Satureja cretica species from traditional manuscripts,” Phytotherapy Research, vol. 26, no. 4, pp. 505–509, 2012. View at Publisher · View at Google Scholar · View at Scopus

143. H. D. Skalska, C. Demetzos, D. Lazari, and M. Sokovic, “Essential oil analysis and antimicrobial activity of eight Stachys species,” Phytochemistry, vol. 64, no. 3, pp. 743–752, 2003. View at Publisher · View at Google Scholar · View at Scopus

144. G. Paun, E. Neagu, C. Albu, V. Moroeanu, and G.-L. Radu, “Antioxidant activity and inhibitory effect of polyphenolic-rich extracts from Betonica officinalis and Impatiens noli-tangere herbs on key enzyme linked to type 2 diabetes,” Journal of the Taiwan Institute of Engineers, vol. 60, pp. 1–7, 2016. View at Publisher · View at Google Scholar · View at Scopus
146. I. Stümpfli, P. R. Venskutonis, M. Murkovic, and O. Ragažinskienė, “Antioxidant properties and phenolic composition (Betonica officinalis L., syn. Stachys officinalis L.),” Industrial Crops and Products, vol. 50, pp. 715–722, 2013. View at Publisher · View at Google Scholar · View at Scopus

147. E. Russo, Handbook of Psychotropic Herbs: A Scientific Analysis of Herbal Remedies for Psychiatric Conditions, Haworth Press, Binghamton, NY, USA, 2001.

148. F. Conforti, F. Menichini, C. Formisano et al., “Comparative chemical composition, free radical scavenging and cytotoxic effects of essential oils of six Stachys species from different regions of the Mediterranean area,” Food Chemistry, vol. 116, no. 4, pp. 898–905, 2010. View at Publisher · View at Google Scholar · View at Scopus

149. G. Paun, E. Neagu, V. Moroeanu et al., “Phytochemical analysis and in vitro biological activity of Betonica officinalis and its extracts,” Romanian Biotechnological Letters, vol. 22, no. 4, 2017. View at Google Scholar

150. A. Matkowski and M. Piotrowska, “Antioxidant and free radical scavenging activities of some medicinal plants from Lamiaceae family,” Fitoterapia, vol. 77, no. 5, pp. 346–353, 2006. View at Publisher · View at Google Scholar · View at Scopus

151. N. Maleki, A. Garjani, H. Nazemiyeh et al., “Potent anti-inflammatory activities of hydroalcoholic extract from aerial parts of Stachys byzantina on rats,” Journal of Ethnopharmacology, vol. 75, no. 2–3, pp. 213–218, 2001. View at Publisher · View at Google Scholar · View at Scopus

152. M. Khanavi, M. Sharifzadeh, A. Hadjiaakhoondi, and A. Shafiee, “Phytochemical investigation and anti-inflammatory activity of Stachys byzantina C. Koch,” Journal of Ethnopharmacology, vol. 97, no. 3, pp. 463–468, 2005. View at Publisher · View at Google Scholar · View at Scopus

153. Y.-Y. Wang, S.-Y. Lin, W.-Y. Chen et al., “Glechoma hederacea extracts attenuate cholestatic liver injury in a bile duct-ligated rat model,” Journal of Ethnopharmacology, vol. 204, pp. 58–66, 2017. View at Publisher · View at Google Scholar · View at Scopus

154. J. Kim, S. Song, I. Lee et al., “Anti-inflammatory activity of constituents from Glechoma hederacea var. longituba,” Bioorganic & Medicinal Chemistry Letters, vol. 21, no. 11, pp. 3483–3487, 2011. View at Publisher · View at Google Scholar · View at Scopus

155. H. Ohigashi, H. Takamura, K. Koshimizu, H. Tokuda, and Y. Ito, “Search for possible antitumor promoters by inhibition of tetradecanoylphorbol-13-acetate-induced Epstein-Barr virus activation; ursolic acid and oleanolic acid from an anti-inflammatory Chinese medicinal plant, Glechoma hederacea L.,” Cancer Letters, vol. 30, no. 2, pp. 143–151, 1986. View at Publisher · View at Google Scholar · View at Scopus

156. H. Kühn, R. Wiesner, L. Alder, and T. Schewe, “Occurrence of free and esterified lipoxygenase products in leaves of Glechoma hederacea and other Lamiaceae,” European Journal of Biochemistry, vol. 186, no. 1-2, pp. 155–62, 1989. View at Publisher · View at Google Scholar · View at Scopus

157. T. Singh, J. H. Wu, W. J. Peumans et al., “Carbohydrate specificity of an insecticidal lectin isolated from the leaves of Glechoma hederacea (ground ivy) towards mammalian glycoconjugates,” Biochemical Journal, vol. 393, no. 1, pp. 331–41, 2006. View at Publisher · View at Google Scholar · View at Scopus

158. Y. Kumarasamy, P. J. Cox, M. Jaspars, L. Nahar, and S. D. Sarker, “Biological activity of Glechoma hederacea,” Fitoterapia, vol. 73, pp. 721–723, 2002. View at Publisher · View at Google Scholar · View at Scopus

159. H.-J. An, H.-J. Jeong, J.-Y. Um, H.-M. Kim, and S.-H. Hong, “Glechoma hederacea inhibits inflammatory mediator release in IFN-γ and LPS-stimulated mouse peritoneal macrophages,” Journal of Ethnopharmacology, vol. 106, no. 3, pp. 418–424, 2006. View at Publisher · View at Google Scholar · View at Scopus

160. J. K. Hwang, M. Erkhambaatar, D. R. Gu et al., “Glechoma hederacea suppresses RANKL-mediated osteoclastogenesis,” Journal of Research, vol. 93, no. 7, pp. 685–690, 2014. View at Publisher · View at Google Scholar · View at Scopus

161. M. Milovanovic, D. Zivkovic, and B. Vucelic-Radovic, “Antioxidant effects of Glechoma hederacea as a food additive,” Communications, vol. 5, no. 1, pp. 61–63, 2010. View at Google Scholar

162. A. Belščak-Cvitanić, K. Durgo, A. Bušić, J. Franek, and D. Komes, “Phytochemical attributes of four conventionally extra plants and cytotoxic evaluation of their extracts on human laryngeal carcinoma (HEp2) cells,” Journal of Medicinal Food, vol. 7, no. 2-3, pp. 206–217, 2014. View at Publisher · View at Google Scholar · View at Scopus

163. I. Miron, S. Diaconescu, G. Aprodu, I. Ioniuc, M. R. Diacsonescu, and L. Miron, “Diagnostic difficulties in a pediatric insulinoma,” Romanian Journal of Medicine, vol. 95, no. 11, p. e3045, 2016. View at Publisher · View at Google Scholar · View at Scopus

164. C. Brock, J. Whitehouse, I. Tewfik, and T. Towell, “American skullcap (Scutellaria lateriflora): a randomised, double-blind placebo crossover study of its effects on mood in healthy volunteers,” Phytotherapy Research, vol. 28, no. 5, pp. 692–698, 2014. View at Publisher · View at Google Scholar · View at Scopus

165. C. Brock, J. Whitehouse, I. Tewfik, and T. Towell, “American skullcap (Scutellaria lateriflora): an ancient remedy for today’s mental health,” Journal of Wellbeing, vol. 1, no. 4, pp. 25–30, 2010. View at Publisher · View at Google Scholar

166. J. Gao, A. Sanchez-Medina, B. A. Pendry, M. J. Hughes, G. P. Webb, and O. Corcoran, “Validation of a HPLC method for biomarkers in skullcap (Scutellaria) and its use to illustrate wide variability in the quality of commercial tinctures,” Journal of Pharmaceutical Sciences, vol. 11, no. 1, pp. 77–87, 2008. View at Publisher · View at Google Scholar
167. J. Li, Y.-H. Wang, T. J. Smillie, and I. A. Khan, “Identification of phenolic compounds from Scutellaria lateriflora by liquid chromatography with ultraviolet photodiode array and electrospray ionization tandem mass spectrometry,” Journal of Pharmaceutical Analysis, vol. 63, pp. 120–127, 2012. View at Publisher · View at Google Scholar · View at Scopus

168. J. L. Rhudy and M. W. Meagher, “Fear and anxiety: divergent effects on human pain thresholds,” Pain, vol. 84, no. 1, pp. 65–72, 2000. View at Publisher · View at Google Scholar · View at Scopus

169. M. Lohani, M. Ahuja, M. A. Buabeid et al., “Anti-oxidative and DNA protecting effects of flavonoids-rich Scutellaria lateriflora extracts and its active components, baicalin, baicalein and wogonin,” American Journal of Chinese Medicine, vol. 24, no. 1, pp. 31–36, 1996. View at Publisher · View at Google Scholar · View at Scopus

170. C.-C. Lin and D.-E. Shieh, “The anti-inflammatory activity of Scutellaria rivularis extracts and its active components, baicalein and wogonin,” American Journal of Chinese Medicine, vol. 24, no. 1, pp. 31–36, 1996. View at Publisher · View at Google Scholar · View at Scopus

171. S. Yoo, S. Han, Y. S. Park, J.-H. Lee, U. Oh, and S. W. Hwang, “Lipoxygenase inhibitors suppressed carrageenan-induced Fos expression in the spinal nerve ligation rats,” Journal of the Formosan Medical Association, vol. 113, no. 8, pp. 513–520, 2014. View at Publisher · View at Google Scholar · View at Scopus

172. S. Hu, Y. Chen, Z.-F. Wang et al., “The analgesic and antineuroinflammatory effect of baicalein in cancer-induced bone pain, complement,” Alternative Medicine, vol. 2015, Article ID 973524, 8 pages, 2015. View at Publisher · View at Google Scholar · View at Scopus

173. A. C. Pinzariu, S. A. Pasca, A. Sindilar et al., “Adipose tissue remodeling by prolonged administration of high dose of vitamin D3 treated to prevent sarcopenia,” Aging & Disease, vol. 8, no. 1, pp. 1–11, 2017. View at Publisher · View at Google Scholar · View at Scopus

174. I. Wakabayashi, “Inhibitory effects of baicalein and wogonin on lipopolysaccharide-induced nitric oxide production in macrophages,” Toxicology & Applied Pharmacology, vol. 146, no. 1, pp. 1–11, 1998. View at Publisher · View at Google Scholar · View at Scopus

175. K. J. Woo, J. H. Lim, S.-I. Suh et al., “Differential inhibitory effects of baicalein and baicalin on LPS-induced cyclooxygenase-2 expression through inhibition of C/EBPβ DNA-binding activity,” Immunobiology, vol. 211, no. 5, pp. 359–368, 2006. View at Publisher · View at Google Scholar · View at Scopus

176. M. Kumar, E. R. Kasala, L. N. Bodduluru, V. Dahiya, and M. Lahkar, “Baicalein protects isoproterenol induced myocardial ischemic injury in rats,” Immunology, vol. 94, no. 3, pp. 481–487, 1998. View at Publisher · View at Google Scholar · View at Scopus

177. Y. Xie, X. Song, X. Sun et al., “Identification of baicalein as a ferroptosis inhibitor by natural product library screening,” Biophysical Research Communications, vol. 473, no. 4, pp. 775–780, 2016. View at Publisher · View at Google Scholar · View at Scopus

178. R. S. M. de Carvalho, F. S. Duarte, and T. C. M. de Lima, “Involvement of GABAergic non-benzodiazepine sites in the anxiolytic-like and sedative effects of the flavonoids baicalein in mice,” Behavioural Brain Research, vol. 221, no. 1, pp. 75–82, 2011. View at Publisher · View at Google Scholar · View at Scopus

179. H. Yin, J. P. Bhattacharai, S. M. Oh, S. J. Park, D. K. Ahn, and S. K. Han, “Baicalein activates glycine and γ-aminobutyric acid receptor subunits gelatinous cells of the trigeminal subnucleus caudalis in juvenile mice,” American Journal of Chinese Medicine, vol. 44, no. 3, pp. 403–411, 2016. View at Publisher · View at Google Scholar · View at Scopus

180. A. Woo, C. Cheng, and M. Waye, “Baicalein protects rat cardiomyocytes from hypoxia/reoxygenation damage via a prooxidant mechanism,” Cardiovascular Research, vol. 65, no. 1, pp. 244–253, 2005. View at Publisher · View at Google Scholar · View at Scopus

181. N. Mahajan, S. Rawal, M. Verma, M. Poddar, and S. Alok, “A phytopharmacological overview on Ocimum species with special reference to Ocimum sanctum,” Biomedicine & Preventive Nutrition, vol. 3, no. 2, pp. 185–192, 2013. View at Publisher · View at Google Scholar · View at Scopus
S. Bahramikia and R. Yazdanparast, “Phytochemistry and medicinal properties of
Lamium galeobdolon (Lamiaceae),” Journal of Brachial Plexus and Peripheral Nerve Injury, vol. 5, p. 3, 2010. View at Publisher · View at Google Scholar · View at Scopus

A. Muthuraman, V. Diwan, A. S. Jaggi, N. Singh, and D. Singh, “Ameliorative effects of Ocimum sanctum in sciatic nerve transection-induced neuropathy in rats,” Journal of Ethnopharmacology, vol. 120, no. 1, pp. 56–62, 2008. View at Publisher · View at Google Scholar · View at Scopus

P. Bhattacharyya and A. Bishayee, “Ocimum sanctum Linn. (Tulsi): an ethnomedicinal plant for the prevention and treatment of a variety of ailments,” Anti-Cancer Drugs, vol. 24, no. 7, pp. 659–66, 2013. View at Publisher · View at Google Scholar · View at Scopus

S. Mondal, S. Varma, V. D. Bamola et al., “Double-blinded randomized controlled trial for immunomodulatory effects of Ocimum sanctum Linn.) leaf extract on healthy volunteers,” Journal of Ethnopharmacology, vol. 136, pp. 452–456, 2011. View at Publisher · View at Google Scholar · View at Scopus

S. Choudhury, L. Bashyam, N. Manthapuram, P. Bitla, P. Kollipara, and S. D. Tetali, “Ocimum sanctum leaf extracts attenuate oxidative damage and neurological deficits following focal cerebral ischemia/reperfusion injury in rats,” Anais da Academia Brasileira de Ciências, vol. 87, no. 1, pp. 417–429, 2015. View at Publisher · View at Google Scholar · View at Scopus

S. Singh, D. K. Majumdar, and H. M. Rehan, “Evaluation of anti-inflammatory potential of fixed oil of Ocimum sanctum (holy basil) in zymosan-induced peritoneal exudate and possible mechanism of action,” Journal of Ethnopharmacology, vol. 54, no. 1, pp. 19–26, 1996. View at Publisher · View at Google Scholar · View at Scopus

D. Gupta, D. Bhaskar, R. Gupta et al., “A randomized controlled clinical trial of Ocimum sanctum and chlorhexidine mouth plaque and gingival inflammation,” Journal of Ayurveda and Integrative Medicine, vol. 5, p. 109, 2014. View at Publisher · View at Google Scholar · View at Scopus

G. Kaur, A. Bali, N. Singh, and A. S. Jaggi, “Ameliorative potential of Ocimum sanctum in chronic constriction injury-induced neuropathic pain in rats,” Anais da Academia Brasileira de Ciências, vol. 87, no. 1, pp. 417–429, 2015. View at Publisher · View at Google Scholar · View at Scopus

A. Ahmad, M. M. Khan, S. S. Raza et al., “Ocimum sanctum attenuates oxidative damage and neurological deficits following ischemia/reperfusion injury in rats,” Neurological Sciences, vol. 33, no. 6, pp. 1239–1247, 2012. View at Publisher · View at Google Scholar · View at Scopus

N. Okiemy-Andissa, M. Miguel, A. Etou, J. Ouamba, M. Gbeassor, and A. Abena, “Analgesic effect of aqueous and hydroalcoholic extracts of Nauclea latifolia,” African Journal of Traditional, Complementary and Alternative Medicines, vol. 8, no. 9, pp. 1613–1615, 2004. View at Publisher · View at Google Scholar · View at Scopus

L. Paula-Freire, G. Molska, M. Andersen, and E. Carlini, “Ocimum gratissimum essential oil and its isolated compounds (eugenol and trans-myrcene) reduce neuropathic pain in mice,” Planta Medica, vol. 82, no. 3, pp. 211–216, 2015. View at Publisher · View at Google Scholar · View at Scopus

E. O. Igbinosa, E. O. Uzunuigbe, I. H. Igbinosa, E. O. Edjadjare, N. O. Igiehon, and O. A. Emuedo, “In vitro assessment of antioxidant, phytochemical and nutritional properties of extracts from the leaves of Ocimum gratissimum Linn.,” African Journal of Traditional, Complementary and Alternative Medicines, vol. 10, no. 5, pp. 292–298, 2013. View at Publisher · View at Google Scholar · View at Scopus

L. Paula-Freire, M. L. Andersen, G. R. Molska, D. O. Köhn, and E. L. A. Carlini, “Evaluation of the antinociceptive activity of Ocimum gratissimum L. (Labiatae) essential oil and its isolated active principles in mice,” Phytotherapy Research, vol. 27, no. 8, pp. 1220–1224, 2013. View at Publisher · View at Google Scholar · View at Scopus

M. Rabelo, E. P. Souza, P. M. G. Soares, A. V. Miranda, F. J. A. Matos, and D. N. Criddle, “Antinociceptive properties of the Ocimum micranthum (Lamiaceae) essential oil and its isolated compounds (eugenol and trans-myrcene) reduce neuropathic pain in mice,” Brazilian Journal of Medical and Biological Research, vol. 46, no. 11, pp. 990–996, 2013. View at Publisher · View at Google Scholar · View at Scopus

L. Paula-Freire, M. L. Andersen, V. S. Gama, G. R. Molska, and E. L. A. Carlini, “The oral administration of trans-myrcene of trans-myrcene attenuates acute and chronic pain in mice,” Phytomedicine, vol. 21, no. 3, pp. 356–362, 2014. View at Publisher · View at Google Scholar · View at Scopus

S. Katsuyama, H. Mizoguchi, H. Kuwahata et al., “Involvement of peripheral cannabinoid and opioid receptors in β-caryophyllene-induced antinociception,” European Journal of Pain, vol. 17, no. 5, pp. 664–675, 2013. View at Publisher · View at Google Scholar · View at Scopus

J. de Pinho, A. Silva, B. Pinheiro et al., “Antinociceptive and antispasmodic effects of the essential oil of Ocimum micranthum in inflammatory properties,” Planta Medica, vol. 78, no. 7, pp. 681–685, 2012. View at Publisher · View at Google Scholar · View at Scopus

E. K. Akkol, F. N. Yalcın, D. Kaya, İ. Çalış, E. Yesilada, and T. Ersöz, “In vivo anti-inflammatory and antinociceptive actions of Ocimum micranthum species,” Journal of Ethnopharmacology, vol. 118, no. 1, pp. 166–172, 2008. View at Publisher · View at Google Scholar · View at Scopus

K. Alipiæva, L. Evtiatieva, N. Handijeva, and S. Popov, “Comparative analysis of the composition of flower volatiles from Lamiastrum galeobdolon and Lamiastrum galeobdolon Heist. ex Fabr.,” Z. Naturforsch. C., vol. 58, no. 11-12, pp. 779–782, 2003. View at Google Scholar · View at Scopus

S. Bahramikia and R. Yazdanparast, “Phytochemistry and medicinal properties of Teucrium polium L. (Lamiaceae),” Phytother. Res., vol. 22, no. 7, pp. 869–876, 2008. View at Publisher · View at Google Scholar · View at Scopus
T. Baluchnejadmojarad, M. Roghani, and F. Roghani-Dehkordi, "Antinociceptive effect of *Teucrium polium* leaf extract in formalin test," *Journal of Ethnopharmacology*, vol. 97, no. 2, pp. 207–210, 2005. View at Publisher · View at Google Scholar · View at Scopus

M. Tariq, A. M. Ageel, M. A. al-Yahya, J. S. Mossa, and M. S. al-Said, "Anti-inflammatory activity of *Teucrium polium*," *International Journal of Tissue Reactions*, vol. 11, no. 4, pp. 185–188, 1989. View at Google Scholar

M. Shahraei, H. MirShekari, and M. J. Palan, "The comparison of noiceptive effect of *Teucrium polium* and morphine,” *Horizons Medical Science*, vol. 12, no. 1, pp. 10–14, 2006. View at Google Scholar

M. Abdollahi, H. Karimpour, and H. R. Monsef-Esfahani, "Antinociceptive effects of *Teucrium polium* I. total extract and rats," *Phyisol Pharmacol*, vol. 14, no. 1, pp. 78–84, 2010. View at Google Scholar

F. Golfakhrabadi, F. Yousef beyk, T. Mirnezami, P. Laghaei, M. Hajimahmoodi, and M. Khanavi, “Antioxidant and antiacetylcholinesterase activity of *Teucrium hyrcanicum*,” *Pharmacognosy Research*, vol. 7, no. 5, pp. S15–S19, 2015. View at Publisher · View at Scopus

C. Nencini, P. Galluzzi, F. Pippi, A. Menchiari, and L. Micheli, “Hepatotoxicity of *Teucrium chamaedrys* L. decoction: role of harvesting area and preparation method,” *Indian J. Pharmacol*, vol. 46, no. 2, pp. 181–184, 2014. View at Publisher · View at Scopus

T. A. K. Prescott, N. C. Veitch, and M. S. J. Simmonds, "Direct inhibition of calcineurin by caffeoyl phenylethanoid glycosides of *Teucrium chamaedrys* and *Nepeta cataria*," *Journal of Ethnopharmacology*, vol. 137, no. 3, pp. 1306–1310, 2011. View at Publisher · View at Google Scholar · View at Scopus

R. A. Falcao, P. L. A. do Nascimento, S. A. de Souza et al., “Antileishmanial phenylpropanoids from the leaves of *Hyptis pectinata*,” *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, p. 460613, 2013. View at Publisher · View at Google Scholar · View at Scopus

S. A. da L. Bordignon, "*Hyptis tetracephala* (Labiatae), nova espécie do sul do Brasil," *Napaea*, vol. 8, pp. 1–3, 1992. View at Google Scholar

R. Harley, in *Evolution and distribution of Erione (Labiatae) and its relation in Brazil*, P. Vanzolini and W. Heyer, Eds., Proc. a Work. Neotrop. Distrib. Patterns, pp. 71–121, Academia Brasileira de Ciências, Rio de Janeiro, Brazil, 1988.

M. D. Bispo, R. H. Mourão, E. M. Franzotti et al., “Antinociceptive and antiedematogenic effects of the aqueous extract of *Teucrium polium* leaves in experimental animals,” *Journal of Ethnopharmacology*, vol. 76, no. 1, pp. 81–86, 2001. View at Publisher · View at Google Scholar · View at Scopus

M. S. Paixão, M. S. Melo, N. P. Damascena et al., “*Hyptis pectinata* gel prevents alveolar bone resorption in experimental rats,” *Revista Brasileira de Farmacognosia*, vol. 25, no. 1, pp. 35–41, 2015. View at Publisher · View at Google Scholar · View at Scopus

M. S. Paixão, M. S. Melo, M. G. B. Oliveira et al., “*Hyptis pectinata*: redox protection and orofacial antinociception,” *Phytotokia*, vol. 27, no. 9, pp. 1328–1333, 2013. View at Publisher · View at Google Scholar · View at Scopus

G. B. Melo, R. L. Silva, V. A. Melo et al., “Enhancement of liver regeneration by the association of *Hyptis pectinata* with *Buddleja davidii*.”, *Digestive Diseases and Sciences*, vol. 50, no. 5, pp. 949–954, 2005. View at Publisher · View at Google Scholar · View at Scopus

M. F. Arrigoni-Blank, R. Silva-Mann, D. A. Campos et al., “Morphological, agronomical and pharmacological characterization of *Hyptis pectinata* (L.) Poit germplasm,” *Revista Brasileira de Farmacognosia*, vol. 15, no. 4, pp. 298–303, 2005. View at Publisher · View at Google Scholar

C. Liapi, G. Anifandis, G. Anifantis et al., “Antinociceptive properties of 1,8-cineole and beta-pinene, from the essential oil of *Camaldulensis* leaves, in rodents,” *Planta Medica*, vol. 73, no. 12, pp. 1247–54, 2007. View at Publisher · View at Google Scholar · View at Scopus

C. R. P. Franco, Â. R. Antoniolli, A. G. Guimarães et al., “Bioassay-guided evaluation of antinociceptive properties and chemical composition of the essential oil of *Hyptis fruticosa*,” *Phytotherapy Research*, vol. 25, no. 11, pp. 1693–1699, 2011. View at Publisher · View at Google Scholar · View at Scopus
251. J. F. Sarmento-Neto, L. G. Do Nascimento, C. F. B. Felipe, and D. P. De Sousa, “Analgesic potential of essential oils,” *Molecules*, vol. 29, 2016. [View at Publisher] [View at Google Scholar] [View at Scopus]

252. C. P. Khare, *Indian Medicinal Plants*, Springer New York, New York, NY, USA, 2007. [View at Publisher] [View at Google Scholar]

253. I. Agata, H. Kusakabe, T. Hatano, S. Nishibe, and T. Okuda, “Melitric acids A and B, new trimeric caffeic acid derivatives from *Melissa officinalis*,” *Chemical & Pharmaceutical Bulletin*, vol. 41, no. 9, pp. 1608–1611, 1993. [View at Publisher] [View at Google Scholar] [View at Scopus]

254. K. Triantaphyllou, G. Blekas, and D. Boskou, “Antioxidative properties of water extracts obtained from herbs of the species *Lippia alba*,” *International Journal of Food Sciences and Nutrition*, vol. 52, no. 4, pp. 313–317, 2001. [View at Publisher] [View at Google Scholar] [View at Scopus]

255. M. Felková, L. Nátherová, and K. Dusková, “Tannin compounds in leaves of *Melissa officinalis* L., invaded by *Septoria Ceskoslovenska Farmacie*, vol. 18, no. 9, pp. 457–460, 1969. [View at Google Scholar]

256. M. Mrliánová, D. Tekelová, M. Felková, V. Reinöhl, and J. Töth, “The influence of the harvest cut height on the quality of the essential oil of *Melissa folium* and *Melissa herba*,” *Planta Medica*, vol. 68, no. 2, pp. 178–80, 2002. [View at Publisher] [View at Google Scholar] [View at Scopus]

257. J. Patora, T. Majda, J. Góra, and B. Klimek, “Variability in the content and composition of essential oil from lemon balm (*Melissa officinalis* L.) cultivated in Poland,” *Acta Poloniae Pharmaceutica*, vol. 60, no. 5, pp. 395–400, 2003. [View at Google Scholar]

258. J. Mikus, M. Harkenthal, D. Steverding, and J. Reichling, “In vitro effect of essential oils and isolated mono- and sesquiterpenes on *Leishmania major* and *Trypanosoma brucei*,” *Planta Medica*, vol. 66, no. 4, pp. 366–368, 2000. [View at Publisher] [View at Google Scholar] [View at Scopus]

259. C. H. Brieskorn and W. Krause, “Further triterpenes from *Melissa officinalis* L. (author’s transl),” *Archiv der Pharmazie*, vol. 306, pp. 603–12, 1974. [View at Publisher] [View at Google Scholar] [View at Scopus]

260. E. C. Herrmann and L. S. Kucera, “Antiviral substances in plants of the mint family (Labiatae). II. Nontannin polyphenols of *Melissa officinalis*,” *Proceedings of the Society for Experimental Biology and Medicine*, vol. 124, pp. 869–874, 1967. [View at Google Scholar]

261. M. S. Lawrence, P. Stojanov, P. Polak et al., “Mutational heterogeneity in cancer and the search for new cancer-associated genes,” *Acta Poloniae Pharmaceutica*, vol. 57, no. 1, pp. 89-96, 2000. [View at Publisher] [View at Google Scholar] [View at Scopus]

262. K. Yamasaki, M. Nakano, T. Kawahata et al., “Anti-HIV-1 activity of herbs in Labiatae,” *Biological & Pharmaceutical Bulletin*, vol. 21, pp. 829–833, 1998. [View at Publisher] [View at Google Scholar] [View at Scopus]

263. L. Iauk, A. M. Lo Bue, I. Milazzo, A. Rapisarda, and G. Blandino, “Antibacterial activity of medicinal plant extracts against periodontopathic bacteria,” *Biological & Pharmaceutical Bulletin*, vol. 26, no. 6, pp. 599–604, 2003. [View at Publisher] [View at Google Scholar] [View at Scopus]

264. W. Englberger, U. Hadding, E. Etschenberg et al., “Rosmarinic acid: a new inhibitor of complement C3-convertase with anti-inflammatory activity,” *Endocrinology*, vol. 125, no. 2, pp. 680–687, 1988. [View at Publisher] [View at Google Scholar]

265. R. Gazola, D. Machado, C. Ruggiero, G. Singi, and M. Macedo Alexandre, “*Lippia alba, Melissa officinalis* and *Cymbopogon citratus* as antioxidants,” *Pharmacological Research*, vol. 50, no. 5, pp. 477–480, 2004. [View at Publisher] [View at Google Scholar] [View at Scopus]

266. T. Anca, P. Alin Constantin, C. Roxana Gabriela et al., “Toxic effects of magnesium nitrate on cardiac muscle tissue of Gallus domesticus embryos and chicks,” *Revista de Chimie-Bucharest*, vol. 68, pp. 1343–1349, 2017. [View at Google Scholar]

267. F. Sahin, M. C. Güllice, D. Daferera et al., “Biological activities of the essential oils and methanol extract of *Origanum vulgare* L. subspecies of various strains from the Anatolia region of Turkey,” *Food Control*, vol. 15, no. 7, pp. 549–557, 2004. [View at Publisher] [View at Google Scholar] [View at Scopus]

268. J. F. Sarmento-Neto, L. G. Do Nascimento, C. F. B. Felipe, and D. P. De Sousa, “Analgesic potential of essential oils,” *Molecules*, vol. 29, 2016. [View at Publisher] [View at Google Scholar] [View at Scopus]

269. M. Barazandeh, “Identification of the essential oil composition from *Origanum majorana* L.,” *Journal of Pajohesh & Sazandegi*, vol. 38–40, 2000. [View at Google Scholar]

270. M. Melegari, F. Severi, M. Bertoldi et al., “Chemical characterization of essential oils of some *Origanum vulgare* L. subspecies of various strains from the Anatolia region of Turkey,” *Revista Brasileira de Plantas Medicinais*, vol. 16, no. 4, pp. 21–28, 1995. [View at Publisher] [View at Google Scholar] [View at Scopus]
A. G. Pirbalouti, A. Amirkhosravi, F. Bordbar, and B. Hamedi, "Diversity in the chemical composition of essential oils of Zizyphus officinalis L. grown in different environmental conditions," Food and Chemical Toxicology, vol. 55, pp. 42–47, 2013. View at Google Scholar

Z. H. Fu, H. Wang, X. Hu, Z. Sun, and C. Han, "The pharmacological properties of Salvia essential oils," Journal of Applied Science, vol. 3, no. 7, pp. 122–127, 2013. View at Publisher · View at Google Scholar · View at Scopus

K. Szentmihályi, C. Csédo, and M. Then, "Comparative study on tannins, flavonoids, terpenes and mineral elements of some species of Acta Horticulturae, vol. 629, pp. 463–470, 2004. View at Google Scholar

A. Russo, C. Formisano, D. Rigano et al., "Chemical composition and anticancer activity of essential oils of Mediterranean Leonurus cardiaca L. grown in different environmental conditions," Food and Chemical Toxicology, vol. 55, pp. 42–47, 2013. View at Google Scholar · View at Scopus

M. Coisin, R. Necula, V. Grigoras, E. Gille, E. Rosenhech, and M. Zamfirache, "Phytochemical evaluation of some Salvia species, "Biologie vegetală, vol. 58, no. 1, pp. 35–44, 2012. View at Google Scholar

A.-V. Pop (Cuceu), T. Maria, S. A. Sonia et al., "Comparative study regarding the chemical composition of essential oils of some species," Hop and Medicinal Plants, 2014. View at Google Scholar

R.-H. Zhang, Z.-K. Liu, D.-S. Yang, X.-J. Zhang, H.-D. Sun, and W.-L. Xiao, "Phytochemistry and pharmacology of the genus Leonurus herb to benefit the mothers and more," Phytochemistry, vol. 147, pp. 167–183, 2018. View at Publisher · View at Google Scholar · View at Scopus

K. Wojtyniak, M. Szymański, and I. Matlawska, "Leonurus cardiaca L. (Motherwort): a review of its phytochemistry and pharmacology," Phytotherapy Research, vol. 27, no. 8, pp. 1115–1120, 2013. View at Publisher · View at Google Scholar · View at Scopus

Motherwort Benefits, Uses and Side Effects, Assessment report on Leonurus cardiaca L., herba EMA/127430/2010, 2014. View at Google Scholar

M. Wichtl, Herbal Drugs and Phytopharmaceuticals: A Handbook for Practice on a Scientific Basis, Medpharm, Guildford, UK, 2005.

V. Agnihotri, H. ElSohly, T. Smillie, I. Khan, and L. Walker, "New Labdane diterpenes from Leonurus cardiaca," Planta Medica, vol. 68, pp. 1288–1290, 2002. View at Publisher · View at Google Scholar · View at Scopus

J. Bernatoniene, A. Kucinskaite, R. Masteikova, Z. Kalveniene, G. Kasparaviciene, and A. Savickas, "The comparison of the kinetic in vitro of the fluid extract from maidenhair tree, motherwort and hawthorn," Acta Poloniae Pharmaceutica, vol. 66, no. 3, pp. 419–421, 2009. View at Google Scholar

K. Morteza-Semnani, M. Saeedi, and M. Akbarzadeh, "The essential oil composition of Leonurus cardiaca L.," Journal of Essential Oil Research, vol. 20, pp. 107–109, 2008. View at Publisher · View at Google Scholar · View at Scopus

D. Mockutė, G. Bernotienė, and A. Judžentienė, "Storage-induced changes in essential oil composition of Leonurus cardiaca growing wild in Vilnius and of commercial herbs," Chemija, vol. 16, no. 2, pp. 29–32, 2005. View at Google Scholar

A. A. Sattar, V. Bankova, A. Kujumgiev et al., "Chemical composition and biological activity of leaf exudates from some Lamiaceae species, "Biologia vegetală, vol. 50, pp. 62–65, 1995. View at Google Scholar

S. Jafari, A. Moradi, A. Salaritabar, A. Hadiakhoondi, and M. Khanavi, "Determination of total phenolic and flavonoid contents of Leonurus cardiaca L. in compare with antioxidant activity," Research Journal of Biological Sciences, vol. 5, pp. 484–487, 2010. View at Google Scholar

M. S. Ali, S. A. Ibrahim, S. Jalil, and M. I. Choudhary, "Ursolic acid: a potent inhibitor of superoxides produced in the mammalian respiratory burst," Phytotherapy Research, vol. 21, no. 6, pp. 558–561, 2007. View at Publisher · View at Google Scholar · View at Scopus

X. Song, T. Wang, Z. Zhang et al., "Leonurine exerts anti-inflammatory effect by regulating inflammatory signaling pathways in LPS-induced mouse mastitis," Inflammation, vol. 38, pp. 79–88, 2015. View at Publisher · View at Google Scholar · View at Scopus

R. A. S. A. Al-Jubair, O. A. H. Al-Jubair, J. F. C. F. Al-Jubair, and M. A. A. Al-Jubair, "The inhibitory effect of Leonurus cardiaca L. on 5-lipoxygenase activity," Phytotherapy Research, vol. 20, no. 5, pp. 419–421, 2006. View at Publisher · View at Google Scholar · View at Scopus

J. Qi, Z. Y. Hong, H. Xin, and Y. Z. Zhu, "Neuroprotective effects of leonurine on ischemia/reperfusion-induced mitochondrial dysfunction in rat cerebral cortex," Biomedical & Pharmaceutical Bulletin, vol. 33, no. 12, pp. 1958–1964, 2010. View at Publisher · View at Google Scholar · View at Scopus

J. Tao, P. Zhang, G. Liu et al., "Cytotoxicity of Chinese motherwort (YiMuCao) aqueous ethanol extract is non-apoptosis receptor independent on human breast cancer cells," Journal of Ethnopharmacology, vol. 122, pp. 234–239, 2009. View at Publisher · View at Google Scholar · View at Scopus

A. Tachjian and V. Maria, "Use of herbal products and potential interactions in patients with cardiovascular diseases..." View at Publisher · View at Google Scholar · View at Scopus
Pharmaceutical Bulletin

T. Inoue, Y. Sugimoto, H. Masuda, and C. Kamei, "Antiallergic effect of bavonoid glycosides obtained from Mentha arvensis, P. Ferreira, T. Cardoso, F. Ferreira, M. Fernandes-Ferreira, P. Piper, and M. J. Sousa, "Antioxidants, S. Dragland, H. Senoo, K. Wake, K. Holte, and R. Blomhoff, "Several culinary and medicinal herbs are important sources of dietary non-volatile organic compounds of boldo leaves. From lab to industrial scale, L. Petigny, S. Périno, M. Minuti, F. Visinoni, J. Wajsman, and F. Chemat, "Simultaneous microwave extraction and separation of volatile and non-volatile organic compounds of boldo leaves. From lab to industrial scale, M. Gavahian, A. Farahnaky, R. Farhoosh, K. Javidnia, and F. Shahidi, "Extraction of essential oils from Mentha arvensis, W. Zheng and S. Y. Wang, "Antioxidant activity and phenolic compounds in selected herbs, E. Capecka, A. Mareczek, and M. Leja, "Antioxidant activity of fresh and dry herbs of some Lamiaceae species, B. Fatih, K. Madani, M. Chibane, and P. Duez, "Chemical composition and biological activities of Mentha species, in Medicinal Plants–Back to Nature, InTech, Bronx, NY, USA, 2017. E. Cano, A. Mareczek, and M. Leja, "Antioxidant activity of fresh and dry herbs of some Lamiaceae species, Food Chemistry, 2, pp. 223–226, 2005. A. Lozak, K. Sołtyk, P. Ostapczuk, and Z. Fijałek, "Determination of selected trace elements in herbs and their infusions, Science of the Total Environment, 289, no. 1–3, pp. 33–40, 2002. F. M. ScienceDirect, P. Valentão, P. B. Andrade, F. Ferreres, and R. M. Seabra, Food Chemistry, Applied Science Publishers, 2001. W. Zheng and S. Y. Wang, "Antioxidant activity and phenolic compounds in selected herbs, Journal of Agricultural and Food Chemistry, 49, no. 11, pp. 5165–5170, 2001. M. Gavahian, A. Farahnaky, R. Farhoosh, K. Javidnia, and F. Shahidi, "Extraction of essential oils from Mentha arvensis, Food and Bioproducts Processing, vol. 94, pp. 50–58, 2015. B. Kaufmann and P. Christen, "Recent extraction techniques for natural products: microwave-assisted extraction and pressurized solvent extraction, Phytochemical Analysis, vol. 13, no. 2, pp. 105–113, 2002. L. Wang and C. L. Weller, "Recent advances in extraction of nutraceuticals from plants, Trends in Food Science and Technology, 17, pp. 300–312, 2006. T. J. Mason, F. Chemat, and M. Vinatouru, "The extraction of natural products using ultrasound or microwaves, Current Organic Agriculture, vol. 15, no. 2, pp. 237–247, 2011. L. Petigny, S. Périno, M. Minuti, F. Visinoni, J. Wajsman, and F. Chemat, "Simultaneous microwave extraction and separation of non-volatile organic compounds of boldo leaves. From lab to industrial scale, International Journal of Molecular Sciences, vol. 15, pp. 7183–7198, 2014. S. Dragland, H. Senoo, K. Wake, K. Holte, and R. Blomhoff, "Several culinary and medicinal herbs are important sources of antioxidants, Journal of Nutrition, vol. 133, no. 5, pp. 1286–1290, 2003. S. K. G. Abrami and P. Nirmala, "A comparative–invitro study of anticancer effect of Mentha piperita, Ocimum basilicum, Ocimum aromaticus against human laryngeal epidermoid carcinoma (HEP-2) cell lines, Journal of Medicinal Plants Studies, vol. 2, no. 2, Google Scholar. P. Ferreira, T. Cardoso, F. Ferreira, M. Fernandes-Ferreira, P. Piper, and M. J. Sousa, "Mentha piperita essential oil induces apoptosis associated with both cytosolic and mitochondrial ROS-mediated damage, FEMS Yeast Research, vol. 14, 2014. T. Inoue, Y. Sugimoto, H. Masuda, and C. Kamei, "Antiallergic effect of flavonoid glycosides obtained from Mentha piperita L., Pharmaceutical Bulletin, vol. 25, no. 2, pp. 256–259, 2002.
A. Sato and H. Tamura, "High antiallergic activity of 5,6,4′-tri hydroxy-7,8,3′-trimethoxy flavone and 5,6-dihy-
teramethoxy flavone from eau de cologne mint (Mentha × piperita citrata)," *Fitoterapia*, vol. 102, pp. 74–83, 2015. View at Publisher · View at Scopus

A. Schuhmacher, J. Reichling, and P. Schnitzler, "Virucidal effect of peppermint oil on the enveloped viruses herpes simplex type 2 in vitro," *Phytomedicine*, vol. 10, no. 6–7, pp. 504–510, 2003. View at Publisher · View at Google Scholar · View at Scopus

J. Omidian, F. Sheikh-Shoshtari, and M. Fazeli, "Inhibitory effect of *Mentha Piperita* extracts against herpes simplex virus infection," *Iranian Journal of Virology*, vol. 8, no. 1, pp. 35–41, 2014. View at Publisher · View at Scopus

R. Singh, M. A. M. Shushni, and A. Belkheir, "Antibacterial and antioxidant activities of *Mentha piperita L.*," *Arabian Journal of Chemistry*, vol. 8, no. 3, pp. 322–328, 2015. View at Publisher · View at Google Scholar · View at Scopus

P. Horváth and J. Koščová, "In vitro antibacterial activity of *Mentha* essential oils against *Staphylococcus aureus*," *Folia Veterinarium* 3, pp. 71–77, 2017. View at Publisher · View at Google Scholar

S. Inouye, H. Yamaguchi, and T. Takizawa, "Screening of the antibacterial effects of a variety of essential oils on respiratory pathogens using a modified dilution assay method," *Journal of Infection and Chemotherapy*, vol. 7, no. 4, pp. 251–254, 2001. View at Google Scholar · View at Scopus

Y. Shahbazi, "Chemical composition and in vitro antibacterial activity of *Mentha spicata* essential oil against common respiratory pathogens bacteria," *Journal of Pathogens*, vol. 2015, Article ID 916305, 5 pages, 2015. View at Publisher · View at Google Scholar · View at Scopus

I. Rasooli, P. Owlia, M. Taghizadeh, S. D. A. Astaneh, and S. M. Sharafi, "Protective effects of bioactive phytochemicals from *Agastache foeniculum* with multiple health potentials," *Pharmacognosy Magazine*, vol. 6, no. 23, pp. 147–153, 2010. View at Publisher · View at Google Scholar · View at Scopus

O. Bobiş, L. A. Mărghitaş, D. Dezmirean, M. Duda, R. Mărgăoan, and S. C. Duda, "Changes in major bioactive compounds with antioxidant activity in *Mentha piperita* leaf, foliar and root plant tissue extracts," *British Journal of Pharmaceutical Research*, vol. 4, no. 10, pp. 792–797, 2014. View at Publisher · View at Google Scholar · View at Scopus
ESI/MS, "F. N. Alçin, D. Kaya, I. Çaliş, T. Ersöz, and E. Palaska, "Determination of iridoid glycosides from four Turkish
3, pp. 241–251, 2016.

M. Moosavi-Nasab, M. J. Saharkhiz, E. Ziaee, F. Moayedi, R. Koshani, and R. Azizi, "Chemical compositions and antibacterial activities of
essential oils, "

L. De Martino, V. De Feo, and F. Nazzaro, "Chemical composition and in vitro antimicrobial and mutagenic activities of some
essential oils," Molecules, vol. 14, no. 10, pp. 4213–4230, 2009.

M. Moosavi-Nasab, M. J. Saharkhiz, E. Ziaee, F. Moayedi, R. Koshani, and R. Azizi, "Chemical compositions and antibacterial
of five selected aromatic plants essential oils against food-borne pathogens and spoilage bacteria," Journal of Essential Oil Res.
3, pp. 241–251, 2016.

F. N. Yalçın, D. Kaya, I. Çalış, T. Ersöz, and E. Palaska, "Determination of iridoid glycosides from four Turkish Lavandula sp.
and Melissa officinalis ethanolic extract on memory, learning and nociception," Biomedicine and Aging Pathology, vol. 4, no. 1, pp. 71–77.

A. Kadri, Z. Zarai, A. Békir, N. Gharsallah, and M. Damak, "Chemical composition and antioxidant activity of Marrubium vulgare essential oil from Tunisia," African Journal of Biotechnology, vol. 10, no. 19, pp. 3908–3914, 2011.

G. De Mastro, W. Tarraf, L. Verdini, G. Brunetti, and C. Ruta, "Essential oil diversity of Origanum vulgare L. populations from Italy," Food Chemistry, vol. 235, pp. 1–6, 2017.

D. Benedec, I. Oniga, R. Opren, and M. Tamas, "Chemical composition of the essential oils of Ocimum basilicum L. cultivated in Hungary," Planta Medica, vol. 57, pp. 625–629, 2009.

A. L. Martinez, M. E. González-Trujano, F. Pellicer, F. J. López-Muñoz, and A. Navarrete, "Antinociceptive effect and GCR
of Rosmarinus officinalis L. essential oil from its aerial parts," Planta Medica, vol. 75, no. 5, pp. 508–511, 2009.

Survey of the Antimicrobial and Antioxidant Effects of Different Lavender (Lavandula officinalis L.) Varieties, vol. 3, no. 3, pp. 142–152, 2014.

G. Flamini, P. L. Cioni, and I. Morelli, "Composition of the essential oils and in vivo emission of volatiles of four Lamium species:
L. purpureum, L. hybridum, L. bifidum and L. amplexicaule," Food Chemistry, vol. 91, no. 1, pp. 63–68, 2005.

Y. El Ouadi, M. Manssouri, A. Bouyaneur et al., "Essential oil composition and antifungal activity of Melissa officinalis cultivated in north-east Morocco, against postharvest phytopathogenic fungi in apples," Microbial Pathogenesis, vol. 107, pp. 321–326, 2017.

I. Chrysargyris, C. Panayiotou, and N. Tzortzakis, "Nitrogen and phosphorus levels affected plant growth, essential oil composition and antioxidant status of lavender plant (Lavandula angustifolia Mill.)," Industrial Crops and Products, vol. 83, pp. 577–586, 2016.

S. Gavanji, E. Mohammadi, B. Larki, and A. Bakhtari, "Antimicrobial and cytotoxic evaluation of some herbal essential oils in comparison with common antibiotics in bioassay condition," Microbial Pathogenesis, vol. 75, no. 5, pp. 508–511, 2009.

E. Barocelli, F. Calcina, M. Chiavarini et al., "Antinociceptive and gastroprotective effects of inhaled and orally administered Reverchon "grosso" essential oil," Life Sciences, vol. 76, no. 2, pp. 213–223, 2004.

L. Pistelli, B. Najar, S. Giovanelli, L. Lorenzini, S. Tavarini, and L. G. Angelini, "Agronomic and phytochemical evaluation of lavender cultivars cultivated in the Tyrrenian area of Tuscany (Italy)," Industrial Crops and Products, vol. 109, pp. 37–44, 2016.
A: Applied Mathematics and Physics

M. V. Ivan, A. Zala, A. Agop et al., “Several aspects about fractalitaty role in the dynamics of complex systems,” Food and Function, vol. 6, pp. 2240–2248, 2015. View at Publisher · View at Google Scholar · View at Scopus

M. Cirlini, P. Mena, M. Tassotti et al., “Phenolic and volatile composition of a dry spear mint (Mentha spicata L.) extract,” Molecules, vol. 16, pp. 1–15, 2016. View at Publisher · View at Google Scholar · View at Scopus

R. Pandey and B. Kumar, “HPLC-QTOF-MS/MS-based rapid screening of phenolics and triterpenic acids in leaf extracts of and their interspecies variation,” Journal of Liquid Chromatography and Related Technologies, vol. 39, no. 4, pp. 225–238. View at Publisher · View at Google Scholar · View at Scopus

P. Mena, M. Cirlini, M. Tassotti, K. A. Herrlinger, C. Dall’Asta, and D. Del Rio, “Phytochemical profiling of flavonoids, terpenoids, and volatile fraction of a rosemary (Rosmarinus officinalis L.) extract,” Molecules, vol. 21, no. 11, pp. 1–15. View at Publisher · View at Google Scholar · View at Scopus

B. F. Zimmermann, S. G. Walch, L. N. Tinzoh, W. Stühlinger, and D. W. Lachenmeier, “Rapid UHPLC determination of free catechins in aqueous infusions of Salvia officinalis L. (sage tea),” Journal of Chromatography B, vol. 879, no. 24, pp. 2459–2464, 2011. View at Publisher · View at Google Scholar · View at Scopus

M. Marrelli, F. Conforti, D. Rigano et al., “Cytotoxic properties of Marrubium globosum ssp. libanoticum and its bioactive compounds,” Natural Product Communications, vol. 8, no. 5, pp. 567–569, 2013. View at Google Scholar

N. Mnonopi, R. Levendal, M. T. Davies-Coleman, and C. L. Frost, “The cardioprotective effects of marrubin, a diterpenoid from Leonotis leonurus extracts,” Journal of Ethnopharmacology, vol. 138, no. 1, pp. 67–75, 2011. View at Google Scholar

N. Zaabat, A.-E. Hay, S. Michalet et al., “Antioxidant and antigenotoxic properties of compounds isolated from Marrubium vulgare L. (Lamiaceae),” Journal of Pharmaceutical and Biomolecular Analysis, vol. 63, no. 9, pp. 1230–1237, 2011. View at Publisher · View at Google Scholar · View at Scopus

R. Lucarini, W. A. Bernardes, D. S. Ferreira et al., “In vivo analgesic and anti-inflammatory activities of Rosmarinus officinalis L. aerial parts extract on morphine withdrawal syndrome,” Phytomedicine, vol. 17, no. 8, pp. 938–941, 2010. View at Publisher · View at Google Scholar · View at Scopus

H. Hosseinzadeh and M. Nourbakhsh, “Effect of Rosmarinus officinalis L. aerial parts extract on morphine withdrawal syndrome,” Phytotherapy Research, vol. 17, no. 8, pp. 938–941, 2003. View at Publisher · View at Google Scholar · View at Scopus

C. Chen, H. Chen, C. Hsieh, Y. Yang, and B. Wung, “Upregulation of NF-E2-related factor-2-dependent glutathione by carnosol provokes a cytoprotective response and enhances cell survival,” Acta Pharmacologica Sinica, vol. 32, no. 1, pp. 62–69, 2011. View at Publisher · View at Google Scholar · View at Scopus

C.-F. Kuo, J.-D. Su, C.-H. Chiu et al., “Anti-inflammatory effects of supercritical carbon dioxide extract and its isolated carnosic acid from Rosmarinus officinalis leaves,” Pharmaceutical Biology, vol. 51, no. 9, pp. 1087–1090, 2013. View at Publisher · View at Google Scholar · View at Scopus

Y. Shingai, A. Fujimoto, M. Nakamura, and T. Masuda, “Structure and function of the oxidation products of polyphenols and potent lipoxigenase inhibitors from fe-catalyzed oxidation of resveratrol,” Journal of Agricultural and Food Chemistry, vol. 59, no. 8, pp. 3674–3685, 2011. View at Publisher · View at Google Scholar · View at Scopus

E. S. Mengoni, G. Vicheria, L. A. Rigano et al., “Suppression of COX-2, IL-1β and TNF-α expression and leukocyte infiltration in skin by bioactive compounds from Rosmarinus officinalis L.,” Fitoterapia, vol. 82, no. 3, pp. 414–421, 2011. View at Publisher · View at Google Scholar · View at Scopus

L. D. C. Mannelli, L. Micheli, M. Maresca et al., “Anti-neuropathic effects of Rosmarinus officinalis L. terpenoid fractions and their bioactive components,” Scientific Reports, vol. 6, pp. 1–15, 2016. View at Publisher · View at Google Scholar · View at Scopus

M. V. Ivan, A. Zala, A. Agop et al., “Several aspects about fractalitaty role in the dynamics of complex systems,” UPB Scientific A: Applied Mathematics and Physics, vol. 79, no. 3, pp. 235–246, 2017. View at Google Scholar

A. T. Peana, P. S. D’Aquila, F. Panin, G. Serra, P. Pippa, and M. D. L. Moretti, “Anti-inflammatory activity of linalool and...
388. A. T. Peana, P. S. D'Aquila, M. L. Chessa, M. D. L. Moretti, G. Serra, and P. Pippia, “(−)-Linalool produces antinociception in two experimental models of pain,” *European Journal of Pharmacology*, vol. 460, no. 1, pp. 37–41, 2003. View at Google Scholar

389. V. S. Rao, A. M. Menezes, and G. S. Viana, “Effect of myrcene on nociception in mice,” *Journal of Pharmacy and Pharmacology*, vol. 460, no. 1, pp. 37–41, 2003. View at Google Scholar

390. P. J. C. Sousa, C. F. B. M. Linard, D. Azevedo-Batista, A. C. Oliveira, A. N. Coelho-de-Souza, and J. H. Leal-Cardoso, “Antinociceptive effects of the essential oil of *Mentha x villosa* leaf and its major constituent piperitenone oxide in mice,” *Brazilian Journal of Medical Research*, vol. 42, no. 7, pp. 655–659, 2009. View at Google Scholar

391. D. Le Bars, M. Gozariu, and S. W. Cadden, “Animal Models of Nociception,” *Pharmacological Reviews*, vol. 53, no. 4, pp. 597–652, 2001.

392. E. Williamson, D. Okpako, and F. Evans, *Selection, Preparation and Pharmacological Evaluation of Plant Material*, John Wiley & Sons, Hoboken, NJ, USA, 1996.

393. A. W. Bannon and A. B. Malmberg, *Models of Nociception: Hot-Plate, Tail-Flick, and Formalin Tests in Rodents*, in: *Curr. Protoc. Neurosci.* John Wiley & Sons, Inc., Hoboken, NJ, USA, 2007. View at Publisher · View at Google Scholar