Abstract

Recently, numerous side effects of synthetic drugs have lead to using medicinal plants as a reliable source of new therapy. Pain is a global public 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 specific implications 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 chronical pathologies along with it, the prevalence of accompanying pain is expected to increase yearly in elderly patients, where the treatment is also more sensitive [6, 7]. Considering the above, new therapeutic agents with increased efficacy, less side effects, and lower costs 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.
information holds guarantees for the finding of new therapeutic agents capable of inhibiting, decreasing, or relieving pain. They 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 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 The most known members of this family are a variety of aromatic spices like thyme, mint, oregano, basil, sage, savory, rosemary, salad, 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 modification and 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 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; hortensis; Stachys lavandulifolia; Scutellaria lateriflora; Sideritis; Teucrium; Thymus; Ziziphea tenuior] + [Lamiaceae; botanical genus case studies, in vivo and in vitro relevant studies, and comparative studies were included in this search strategy. Additionally, potentially 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 the first months of the next year (Figure 1).

![Figure 1: Number of publications according to ScienceDirect.](image)

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 Mediterranean Basin.

3.1.1. *Rosmarinus officinalis*

*R. officinalis* L., commonly called rosemary, is a Mediterranean shrubby herb and widely spread in European, American countries. It is a common spice used worldwide for culinary, medicinal, and commercial uses, including the fragrance and food industry. Leaves of rosemary (fresh or dries) are used for their characteristic aroma in cooking or consumed in small amounts as herbal tea, 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 verbinol. Rosemary, a 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 oleanolic and ursolic acid and carnosol. Phenols in rosemary comprise caffeic, chlorogenic, labiatic, neochlorogenic, and rosmarinic acids. Rosemary covers high amounts of salicylates [42–48].

Modern pharmacological studies have indicated that rosemary and its constituents, especially caffeic acid derivatives such as rosmarinic various traditional uses in ethnomedicine including analgesic, anti-inflammatory, anticarcinogenic, antiinflammatory, spasmylocytic, atherosclerotic, carminative, and choleric applications [44–54], protection against UV and gamma radiation, and amelioration of The powdered leaves are used as an effective natural flea and tick repellent. Activity against certain bacteria including *Staphylococcus albus*, *Vibrio cholerae*, *Escherichia coli*, and *Corynebacterium* has been observed. One study found that rosemary oil is effective the "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 it can be associated with toxicity characterized by stomach and intestinal irritation and kidney damage. While rosemary oil is irritating to rabbit skin,
Bioactive compounds such as flavonoids, diterpenes, phenols, and triterpenes from plant sources have been traditionally extracted using conventional solid-liquid extraction. Nevertheless, this extraction technique presents several disadvantages, mainly because it is an energy-consuming process that requires a high consumption of solvents, and in some cases provides low recovery. For that reason, new promising 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 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]. Marrubiinic acid inhibited the time mice spent licking and shaking induced by formalin injections. Nevertheless, the extract did not display any analgesic or 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, preclinical studies 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 injection, 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, being listed as an endangered plant. Although the use in traditional medicine has been extensive in the abovementioned places, recent studies have shown some effects on type II diabetes [63], because medical literature are offering data mostly on the species M. vulgare, 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 vasorelaxant activity [66–68].

Marrubiin, the main active ingredient of M. vulgare, seems to be generated as an artifact from premarrubiin during the extraction process, as 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, and their effects in various experimental models of pain and inflammation have been confirmed in modern research and clinical trials. Marrubiin with the formation of marrubiinic acid and two esterified derivatives has conditioned the successful antinociceptive effect influencing writhes in mice. Marrubiinic acid exhibited a high analgesic effect that has been long established in other experimental models of pain, suggesting great potencies observed in the writhing test and formalin-induced pain test propose that marrubiin acts by some peripheral mechanism. In vivo experimental studies have documented an LD50 of 370 mg/kg body weight [56, 57], 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 Africa, and even Norway, with apparent differences in composition between the same species corresponding to the geographic provenience [76]. The species have been used as flavoring agents, widely as ingredients for tea preparation or with medicinal purposes, areas being listed as an endangered plant. Although the use in traditional medicine has been extensive in the abovementioned countries, species have reduced usage in western medicine [78], because medical literature are offering data mostly on the scardica, lotsy, and S. scardica

S. scardica Gris. is also known as “Greek tea” or “mountain tea.” The components of scardica have been studied through various methods in order to highlight their 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, 4′-methylepicatein, isoscutellarein, and 4′-O-methylisoscultellarein [79], and also other components like sterols and triterpenoids.
flavonoids, essential oil, iridoids, terpenoids, and glycosides [76]. The presence of phenolic antioxidants (catechins) correlating to 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, region to region. In the oil from Macedonia, for example, α-cadinol is predominant as compared to the Bulgarian version of the plant which contains mostly diterpenic compounds and octadecenoil. Interestingly, none contained menthol, nerol, or geraniol, which are components in the S. scardica 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 chromatography with diode-array detection. The analysis found that it contains 90% phenylethanol glycosides and flavonoid acetyl esters. Turkish S. scardica oil has β-pinene in abundance as compared to the Greek version which contains α-pinene primarily. Both the plants are mainly rich in monoterpenic hydrocarbons unlike the ones from Macedonia and Bulgaria, which are poor in these compounds. Differences in components have also been proven between the fresh and dried versions of the plant material [84].

An analysis of urine samples from humans who received oral administration of S. scardica showed that the flavonoid metabolites were present in human and that hypolaetin and isocosutellarein had the largest number of metabolites (methylhyprolaetin 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]. Accordingly, in rats showed that S. scardica extract administered 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 superior to hydrodistillation and is attributed partially to diterpenes and fatty acids and their derivates and also to other momentarily unknown compounds 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 benefits and implications in pain treatment proving a possible valuable agent in limiting the use of analgesics, anti-inflammatory, and anti-anxiety drugs [6,91].

In vivo models demonstrated the anti-inflammatory effects of S. scardica over a model of carrageenan-induced rat paw edema, gastroprotective activity over ethanol-induced acute stress ulcer in rats and also a promising cytotoxic activity [92], attributing in part to its constituents (apigenin and luteolin) that can induce cell-cycle arrest and cellular apoptosis in vitro [93]. In vivo models demonstrated that S. scardica over αβ-epoxykaurane has a capacity to inhibit human serotonin transporter (hSERT) greater than in rat models. Similarly to S. scardica, the acetone extract of S. stricta is demonstrated to have anti-inflammatory and emedema-reducing capabilities with important implications in pain modulation and other pathologies [92].

The usage of S. scardica in traditional and modern medicine has demonstrated various degrees of effectiveness with promising 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 pathologies (common cold, lung emphysema, bronchitis, and asthma) [85], and also as an effective cytotoxic activity [99]. Inflammatory and emedema-reducing capabilities should be considered as the basis for further studies of S. scardica implication in pain.
Thymus genus, part of the Lamiaceae family, consists of over 350 species of aromatic plants with evergreen leaves. Geographically, it 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 oncological pathologies 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 the chemotype and composition [103], which was demonstrated by a study comparing essential oils from two regions of France (linalool chemotype with 41.0% linalool and thymol chemotype with 47.1% thymol) and two regions of Serbia (geraniol chemotype with 59.8% geraniol and sabinene chemotype with 30.8% cis-sabinene hydrate) [104].

The terpenoids associated with T. vulgaris anesthetic capabilities are thymol (2-isopropyl-5-methylphenol) and eugenol (4-allyl-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 Tet [108, 109]. T. vulgaris also has a spasmylocytic, 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, spasmylocytic 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 therapeutic 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 properties of T. vulgaris extracts [113]. Also, because of the antioxidant capabilities and being an inhibitor of acetylcholinesterase, T. vulgaris could be a promising 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 conditions like 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, and antipyretic activity in mouse 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 pain 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 antibiotic 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 effect and the chelating activity of T. pulegioides are moderate to high, with an increased acetylcholinesterase inhibition [114]. A study in vivo demonstrated among the first medicinal plants in traditional medicine and the second most relevant in respiratory pathologies usage [120].

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]; however, more data 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 rosemaries and thyme. It is native to the North western 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 [126]. The floral parts and leaves from 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, α-terpine, p-cymene, α-terpinene, and myrcene. The only notable sesquiterpene is bisabolene [126].
Regarding the biological activity, extracts from *Stachys hortensis* are covering a large spectrum of pathological conditions. Antinociceptive activity, antioxidant activity, cytotoxic activity, insecticidal activity, fungicidal toxicity, insect repellent activity, anticonvulsant and an antileishmanial activity, genotoxic activity, anti-inflammatory activity, effects on immune system, effects on productive performance, activity, antidiarrheal activity, relaxant effect (antispasmodial activity), antigonotoxic activity, antihepatic activity, contain triterpenoids, effect on vitality and healthiness of cereals, molluscicidal activity, larvicidal activity, antithrombocyte activity, inhibition of hemadherence, aggregation and secretion, effect on rhinosinusitis, amyloid beta protein aggregation inhibitory activity, and matrix metalloproteinase inhibitory activity.

Concerning the analgesic activity, *Stachys hortensis* extracts (hydroalcoholic extract, polyphenolic fraction, and essential oil of the aerial parts) were evaluated by use of tail flick, formalin, and acetic acid-induced writhing tests in mice. Results showed that, in the light tail flick test, neither the essential oil nor the extracts could exert any significant effect. The hydroalcoholic extract (2000 mg/kg, p.o.) and the essential oil (400 mg/kg, p.o.) inhibited the mice writhing responses caused by acetic acid. In the formalin test, hydroalcoholic extract (500–2000 mg/kg, p.o.) and polyphenolic fraction (250–1000 mg/kg, p.o.), and the essential oil (50–200 mg/kg, p.o.) showed analgesic activity, and pretreatment with naloxone (1 mg/kg, i.p.) or caffeine (20 mg/kg, i.p.) failed to reverse this antinociceptive activity. Authors suggested that antinociceptive effect could be due to the involvement of opioid and adenosine receptors in the antinociception mediator.

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 vary 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 climate including diverse areas of Europe, Asia, Africa, and Australia. The plant is known as Chay-e-Kouhi in Persian, whereas in English it is called 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 were germacrene-D (13.2%), β-phellandrene (12.7%), β-pinene (10.2%), myrcene (9.4%), α-pinene (8.4%), and Z-β-cimene (5.8%). In another study, 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 *Stachys lavandulifolia* is used in antipyretic, anti-inflammatory, spasmyloytic, sedative, and anticonvulsion 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 *Stachys lavandulifolia* were signaled, and the main of those being possibility of abortion depending on the dosage in animals, useful in controlling premenstrual syndrome (PMS) and primary dysmenorrhea symptoms, helps in strengthening stomach, 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 for antipyretic and spasmyloytic effects. As an undesired effect, it gives rise to failure in fetus survival and, consequently, abortion may be induced [139]. 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 *Stachys lavandulifolia* and their analgesic effects were studied in mice using formalin, acetic acid-induced writhing, and light tail flick tests. Results showed that all 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 *Stachys lavandulifolia* extracts, the implication of essential oil (EOS 1) and (−)-α-bisabolol (BIS), its main compound, was studied in algogen-induced orofacial nociceptive behavior in mice. Authors have shown that the treatment with EOS 1 and 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* (both aerial and aerial parts) were used in traditional folk medicine for numerous purposes, either internally as tea or externally as compress. Important medicinal effects and implications in the treatment of respiratory tract, gastrointestinal tract, nervous and cardiac systems, and gynecological disorders were also observed. Also, a variety of *Betonica* species are used in food industry to improve the taste in preparation of jelly or yogurt, or as seasonings and flavorings [148].

The chemical composition of *Betonica officinalis* includes polyphenols such as tannins, phenolic acids, flavonoids, alkaloids to stachydrine (a pyrrolidine alkaloid), iridoids, diterpenes, phenylethanoid glycosides, fatty acids, betaine, volatile oils, and choline. According to the literature data, phenylethanoid glycosides, triterpenoids, and flavonoids are considered to be the active components for the biological actions of the genus *Stachys*, but the anti-inflammatory or analgesic effects, or components of it, have not been completely so far.
A hydroalcoholic extract of *Stachys in?ata* Benth., one of the *Stachys* species from Iran, induced anti-inflammatory and anti-inflamma-
tory effects in vitro. The extract was shown to be capable of attenuating both early and delayed phases of carrageenan-induced inflammation with a dose-related inhibitor of the late phase (inflammatory component) (50–200 mg/kg). Compared to a standard nonsteroidal anti-inflammatory drug, indomethacin, the hydroalcoholic extract of *S. in?ata* was 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 the synthesis of cyclooxygenase products and polymorphonuclear leukocytes accumulation determined by myeloperoxidase activity. *Stachys in?ata* (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 components of the extract. Several components quantified in *Stachys* extracts demonstrated in vivo anti-inflammatory and antinociceptive activity against carrageenan-induced paw edema and p-benzoquinone-induced abdominal constriction tests.

### 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 Georgia, play a significant role in the inhibition of pain and inflammatory processes by using two inflammatory models, namely, for carrageenan-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 diterpene ester (phytlyl nonadecanoate), two normal alkanes (tritriacontane and hentriacontane), one fatty acid (oleic acid), and two sterols (stigmasterol and lawsonitol). Structures were established by conventional methods of analysis and confirmed by ¹H, ¹³C NMR, and mass spectral analysis. All three doses of acetone/methanol extracts of *Stachys byzantina* (50, 100, and 200 mg/kg), administered by intraperitoneal injection, significantly inhibited the pain associated with the second phase (inflammatory component) of the formalin test, and the effect of the low dose was the most predominant. Compared to indomethacin (high dose of 5 mg/kg) as a nonsteroidal anti-inflammatory drug, the extracts decreased the pain associated with the late phase significantly, with the maximum inhibitory response obtained with 50 mg/kg of the extract.

The authors assumed that the analgesic effects of the extracts are probably mediated by interactions with inflammatory mediators (arachidonic acid metabolites), since the antiinflammatory activities were observed in late phase (20 min after formalin injection). In the carrageenan-induced paw edema, both extracts revealed dose-related inhibitory effects, in both early and delayed phases, over the dose range 50–200 mg/kg, and dose of indomethacin (5 mg/kg). The present data demonstrated that the anti-inflammatory activity of acetone and methanol extracts of *S. byzantina* is probably related to the inhibition of the synthesis or release of COX2 products.

### 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 north Europe and the neighboring regions of 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 herb 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 traditional medicine as a remedy for several digestive, pulmonary, skeletal, and inflammatory conditions [153]. Active components include polyphenols such as chlorogenic acid, caffeic acid, rutin, genistin, rosmarinic acid, quercetin, or genistein [153] and triterpenoids as ursolic acid and oleanoic acid [154, 155]. Additionally, studies report that *G. hederacea* leaves contain polyunsaturated fatty acids and a novel 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 have been shown to exhibit antibacterial, anticancer, insecticidal, and platelet-stimulating activity [157, 158]. Currently, there are no studies specific for ground ivy's effect on pain. However, existing data point out that the plant has potent anti-inflammatory effects. An *in vitro* study demonstrated that incubating activated macrophages with a ground ivy decoction (3 h in boiling distilled water) led to a significant decrease in NO production. Furthermore, the authors noted that the expression of some inflammatory cytokines such as IL-12p70 and TNFα was also decreased [159]. Similarly, Kim et al. demonstrated that several compounds found in *G. hederacea* inhibit NF-κB production [160]. Hot water *G. hederacea* extract was shown to have an anti-inflammatory effect 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 activation in liver. 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 an anti-inflammatory include its effects on extracellular calcium release and on oxidation. Purified ethyl acetate extracts of ground ivy showed a strong antioxidant activity when used as a food additive to protect types of food (pork lard and sunflower oil) [161].

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 adding 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 used 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 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 2016, the same research group published the results of a larger randomized controlled clinical trial designed to assess the effect of a S. lateriflora extract on normal volunteers. Results indicated that global mood was significantly enhanced in individuals who received 350 mg of plant extract without any significant side effects on energy and cognition [164]. Taking into account the fact that anxiety is a well-known enhancer of depression, panic attacks, and fibromyalgia [164, 167], 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 extract), and glutamine (31 mg/g in H₂O extract) [170]. Other flavonoids found in S. lateriflora include oroxylin A, genkwanin, hesperetin, quercetin, rutin, naringenin, chrysos, and daidzein [167]. While its anti-inflammatory effects are probably due to some of the flavonoids that bind to one of the serotonin receptors [171], S. lateriflora's antioxidant activity is most likely due to baicalin and its glucuronide, baicalein.

Baicalein can be extracted from S. lateriflora through alkali solution and acid isolation methods; for a high-purity extract (99.35% purity), baicalein and column chromatography purification can be used [172]. As an isolated compound, baicalein has shown not only analgesic activity but also significant anti-inflammatory activity in several in vitro and in vivo models, which has made it an interesting drug to be developed as an analgesic.

One study used several extracts from a plant of the Scutellaria genus and found that baicalein has a significant analgesic effect in the formalin-induced rat paw inflammatory model [173]. Similarly, baicalein was found to significantly decrease pain-related behavior and c-fos expression (a surrogate marker for pain intensity) in the spinal dorsal horn of animals exposed to painful stimuli [174]. A combination of baicalin and catechins was assessed in onchically used animal pain models and was found to have analgesic effects in visceral, nociceptive, and inflammatory pain.

Baicalin 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, baicalin significantly enhanced the effect of analgesic agents in neuropathic animals, most likely by suppressing histone deacetylase 1 expression in the spinal dorsal horn [176]. The compound was also shown to be effective in cancer-induced bone pain: both intrathecal and oral baicalin administration reduced cytokine expression and inhibited pain-related signals 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 effects may partly be explained by its inhibitory effects on lipoxigenases—enzymes that play a key role in leukotriene and lipoxin synthesis, the inflammatory response. Deschamps et al. found that baicalein inhibits both human platelet 12-lipoxygenase and human neutrophil lipoxygenase-1 [179]. Additionally, Hsieh et al. showed that baicalein inhibits IL-1β and TNF-α through modulation of the NK-K receptor, while other authors found that it inhibits protein expression of inducible nitric oxide synthase [181] and COX2 gene expression [182]. Pretreatment with baicalein increased the concentration of antioxidant enzymes such as SOD, catalase, and GSH in an in vivo model of cerebral ischemic injury [183] and protected cells against lipid membrane peroxidation [184]. However, it is very likely that, taking into account the fact 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 receptor, which has a modulatory effect on pain because GABA is the main inhibitory neurotransmitter. When directly injected into the central nervous system, baicalein has strong sedative and anxiolytic effects due to GABA binding [185]. Also, a recent review article indicated that through GABA modulation, baicalein could be used in orofacial pain modulation [186]. Another study also indicated that baicalein modulates both intracellular and extracellular calcium levels [178], 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, antianxiety, antiulcer, antiabetic, hepatoprotective, chemoprotective, antihyperlipidemic, cardioprotective, antiaging, radioprotective, memory enhancing, antiarthritic, antifertility, antihypertensive, anticoagulant, anthelmintic, and antinociceptive activity [188]. As such, several members of the genus such as Ocimum sanctum, Ocimum gratissimum, or Ocimum micranthum play a 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%), eugenol (8–30%), and methyl chavicol (15–25%). Minor constituents are (+)-delta-cadinene, 3-carene, α-humulene, citral, and caryophyllene [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 an extract of O. sanctum on healthy volunteers and concluded that the drug has immunomodulatory effects and can be given for up to four weeks without any significant side effects [192]. Although less numerous, there are some studies that have assessed the effect of O. sanctum, with wide variability depending on the manufacturer and species of Ocimum used [166].
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 production and decreasing TNF-α secretion [193]. Different types of dried leaf extracts were also shown to be effective in reducing carrageenan-induced inflammation and leukotriene-induced paw edema [194]. More recently, a triple-blind randomized clinical study compared an ethanolic extract of Ocimum gratissimum mouthwash in regards to their effect on dental plaque and gingival inflammation and found that the two were equivalent, with the O. sanctum extract being 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. One screening study assessed potential anti-inflammatory and antinociceptive effects of different dried leaf extracts of Ocimum gratissimum, Lamium purpureum, Ocimum micranthum, and Ocimum sanctum. 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 transsection-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 essential oil of the same plant 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 administered in rats with surgically induced focal cerebral ischemia/reperfusion injury and was shown to reduce both neurological deficit and oxidative damage [197].

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 medicinal plant with analgesic activity [198]. It contains several proanthocyanidins, which have been shown to exhibit significant antioxidant activity, 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 [199]. A different team demonstrated the efficacy of the aforementioned essential oil for increasing paw withdrawal latency in the hot-plate test and decreasing formalin-induced hind paw inflammation and pain-evoked behaviors [201]. Another team used the essential oil of O. gratissimum to model visceral pain (the writhing test) and in the formalin test with equally favorable results [202]. Similar analgesic activity was observed in mice 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 effective in nociceptive, neuropathic and inflammatory pain.

trans-Caryophyllene, a sesquiterpene from O. gratissimum, was shown to have dose-dependent analgesic effects in several experimental pain models. It acts as an acute and chronic pain suppressor and was found to be effective in relieving pain in the formalin test, chronic constriction injury, and the hot-plate test. The authors evaluated the mechanisms responsible for the substance's properties and found that the analgesic effect was reversed by several types of antagonists, indicating the involvement of both the opioid and endocannabinoid system [204].

3.9.3. Ocimum micranthum

Ocimum micranthum Willd. or Ocimum campechianum Mill., more commonly known as Amazonian or Peruvian basil, has anti-inflammatory and antianalgesic effects in several animal models of pain, although it has been reported as less effective on the hot-plate test compared to other Ocimum species [205]. 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 dysmenorrhea, paralysis, leucorrhea, 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.[206] 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, a methanolic extract prepared by methanolic extraction of air-dried and powdered aerial plant parts (25 g plant in 250 mL methanol), which was then filtered, dried, suspended in water, partitioned, and lyophilized. The study showed that 200 mg/kg body weight of L. garganicum L. 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 active ingredients of the dried leaf plant extract are flavans 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 oral 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]. Administration of 500 mg/kg body weight of ethanolic extract of T. polium inhibited carrageenan-induced inflammation and reduced granuloma formation [209].
Another study compared the effect of morphine and *T. polium* extract on the tail flick latency and found the two to be comparable in effect. Both the total extract and the essential oil of the plant exhibited analgesic effects on the acetic acid-induced writhing test, thus suggesting it to be effective in visceral pain [214]. Subsequently, a triple-blind, randomized, clinical trial was designed in order to assess the pain relief during the first menstrual cycle or 250 mg mefenamic acid. Study results indicated that the two are equally effective, thus concluding that *T. polium* can be used for the treatment of dysmenorrhea. 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* can be used for the treatment of dysmenorrhea.

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 study used a methanolic extract of dried aerial parts of *T. hyrcanicum* and observed that the high flavonoid content of the plant has antiproliferative 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 teucrioside as the main active ingredient of the plant and concluded that it is effective in inhibiting the inflammatory response, thus potentially playing a role in reducing inflammatory states [218].

3.12. *Hyptis Genus*

*Hyptis* genus, also known in Brazil as “sambacáia” or “canudinho,” is a genus of aromatic plants in the Lamiaceae family [219]. This genus consists of approximately 400 species distributed from the southern United States to Argentina [220] and exhibits a major morphology in the Brazilian Cerrado [221].

3.12.1. *Hyptis pectinata*

*Hyptis pectinata* L. Poit. is present very common in gardens, and it is frequently used as tea (decoctions or infusions) and montone for the management of diabetes, hypertension, and other metabolic diseases due to the presence of hydroxycinnamic acid derivatives, particularly rosmarinic acid, caffeic acids, chlorogenic acid, and caftaric acid [222].

Hyptis *pectinata*, bavonoids, including luteolin, luteolin 7-O-beta-D-glucopyranoside, apigenin 7-O-beta-D-glucopyranoside, and luteolin 3’-O-beta-D-glucuronopyranoside, have anti-inflammation due to being considered a natural antiphlogistic. In Brazilian folk medicine, the infusion of the fresh leaves is used to treat the relief of menstrual pain, dysmenorrhea, and other pain conditions and wound healing [222], fungal infections, and HIV.

Also, the plant has cytotoxicity and insecticide properties [223]. *H. pectinata* has an important neurogenic and inflammatory antinociceptive effects, without interference in the motor performance. The mechanism is currently unknown but seems to be related to glutamate receptors. The opioid system seems unlikely to participate in the antinociception caused by the extract [224]. The local application of *H. pectinata* leaves at 200 mg/kg with intraoperative laser therapy can stimulate liver regeneration and cause a release of 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 (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 not evident. GC-MS analysis showed that β-caryophyllene (40.90%) and caryophyllene oxide (30.05%) were the major compounds present in the essential oil.

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 [229]. The involvement of the opioid system in the antinociceptive activity of *H. pectinata* essential oil was evaluated in the hot-plate model, and mice with an opioid antagonist, naloxone. The results suggest that naloxone reversed the antinociceptive activity of the essential oil, whereas 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* subsp. *officinalis*, the common lemon balm, and *Melissa officinalis* subsp. *altissima*, naturalized in New Zealand and known as bush balm. The first information about 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, neurosis and nervous excitability, palpitation and headache.

The known major components of lemon balm are hydroxycinnamic acid derivatives, particularly rosmarinic acid, caffeic acids, chlorogenic acid, and metelic acid [232, 233], tannins [234], flavonoids, including luteolin, luteolin 7-O-beta-D-glucopyranoside, apigenin glucopyranoside, and luteolin 3’-O-beta-D-glucuronopyranoside [235, 236], montonepene glycosides [237], sesqui-
caryophyllene and germacrene [237], triterpenes [238], and volatile oils, including citronellal, citral a (geraniol), citral b (neral), menthol, ocimene, citronellol, geraniol, nerol, \( \beta \)-caryophyllene, \( \beta \)-caryophyllene oxide, linalool, and etheric oil [239].

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

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

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

*M. officinalis* has antithyroid actions (inhibit the binding of bovine TSH to human thyroid plasma membranes and adenylate cyclase, inhibit the TSH-induced release of the thyroid hormones and the \( T_3 \)-deiodination to both \( T_3 \)-and \( T_4 \)-5′-deiodination) [245], spasmylytic effects (observed only in the isolated duodenum of rat) [246], sedative effects (dose-dependent sedation, inducing sleep and potentiating subhypnotic and hypnotic doses of pentobarbital) [246], 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 strongly aromatic leaves and abundant tubular flowers with long-lasting coloured bracts. The genus includes *O. vulgare* marjoram and *O. majorana* L. or 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 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 between marjoram and oregano is based on the shape of the calyx and not the leaves, how hairy they are, or the growth habit. There are a lot of information about *Origanum*. So, Hippocrates used *O. majorana* as an antiseptic agent. The ancient Greeks considered the plant a symbol of love, honour, and happiness. Aristotle declares that *Origanum* is an antipoison. The people from old Egypt used *Origanum* to preserve food [250].

The major compound of *O. vulgare* oil is terpinen-4-ol (26%), \( \alpha \)-sabinene (13.3%), \( \alpha \)-cymene (9.3%), g-terpinen (5.8%), \( \alpha \)-thujene (5.1%), \( \alpha \)-terpinene (4.9%), and \( \alpha \)-terpinene (3.5%). The extracts obtained by supercritical \( \mathrm{CO}_2 \) presented higher content of monoterpenes, without significant differences between fractions 1 and 2. A study from Iran shows that the composition in *O. vulgare* was dominant in \( \beta \)-caryophyllene, germacrene D, and \( \alpha \)-sabinene hydrate [251]. Another study from Italy shown the components of essential oil in the *O. vulgare* ssp. *vulgaris* were \( \beta \)-caryophyllene, thymol, terpinen-4-ol, and \( \alpha \)-cymene [252]. Compounds of *O. majorana* are the essential oil and tannins. The difference between the essential oil obtained from *O. vulgare* and *O. majorana* in quantity (0.67% and 1.5%) [253]. The maximum quantity was obtained in the full flowering stage. The major component is germacrene, 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 anti-scorbutic effect. The 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* are used as a sedative, hypnotic, and spasmolytic effect; brain and central nervous systems disorders, common cold, inflammation, carminative, diarrhea, expectorant, coughing, antiseptic, migraine, fever, and depressant effect. The essential oils are used for treating some diseases such as edema, insomnia, lung abscess, tracheitis, hemorrhoids, and hypertension. The antimicrobial activity of the essential oil of *Salmonella typhi* Vi-positive makes it useful in the treatment of typhoid fever, too. The g-terpinen-4-ol modulate immune response by induction of CD40 expression on DCs and cytokine production and inhibition of T-cell stimulation when used in high concentration [260].

### 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, stomach disorders, common cold, inflammation, carminative, diarrhea, expectorant, coughing, antiseptic, migraine, fever, and depressant effect. The essential oils are used for treating some diseases such as edema, insomnia, lung abscess, tracheitis, hemorrhoids, and hypertension. The antimicrobial activity of the essential oil of *Salmonella typhi* Vi-positive makes it useful in the treatment of typhoid fever, too. The g-terpinen-4-ol modulate immune response by induction of CD40 expression on DCs and cytokine production and inhibition of T-cell stimulation when used 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], uricosic 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; 4α-α, 7α-α, and 7αa-nepeta lactone; *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 medicinal plants used by humans, and it is considered as a universal panacea, used for its antibacterial, antiviral, antioxidant, antimalarial, antidiabetic, cardiovascular, and antitumor effects. *Salvia* can be used as infusion, tincture with diuretic, hemostatic, and spasmodic activities, volatile oils with antiseptic role, and essential oil with antimicrobial effect.

The pharmacological effects of *Salvia* essential oils are based on the presence of more than 100 active compounds, which can be classified into terpene hydrocarbons, oxygenated monoterpenes, sesquiterpene hydrocarbons, diterpenes, nonisoprenoid compounds, and sterols [286]. 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 %) expressed as equivalent caffeic acid, and the highest value for rosmarinic acid (728.68 mg %). Rosmarinic acid is the major compound, and it shows anti-inflammatory, antibacterial, and antiviral activity [278]. *S. officinalis* is the most valuable species in terms of biologically active constituents 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 antineurological 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 [272].

#### 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 thorn or 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 repetside) [285], diterpenes (of clerodane, furoarbolabane, and labdane types) [286], triterpenes (ursolic acid, oleanolic acids, and euc sapiac acid, and ileilatifol D) [287], nitrogen-containing compounds (leunorine, stachydrine, and amine choline), and phenols (lavandulifolioside), as well as flavonoids, phenolic acids, volatile oils, sterols (β-sitosterol and stigmasterol), and tannins. The phenolic compounds comprise polyphenol glycosides such as lavandulifolioside (arabinoside) [288], phenolic acids such as chlorogenic, rosmarinic, gallic, and caffeic acids, and phenolic glycoside [289]. The volatile oils mainly contain sesquiterpenes (germacrene D, epidedrol, β-caryophyllene, α-humulene, and spathulenol and monoterpenes such as α-pinene and dehydro-1,8 cineole). Of these, ursolic acid proved a stronger anti-inflammatory activity than indomethacin and acetylsalicylic acid, and furanodabane 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], antiinflammatory [290, 294, 295], antinociceptive [296], neuroprotective [297], sedative [298], and even antianxiety 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 antinociceptive 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) alleviates 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 *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 elucidate 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].
**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 moist stems grow 10–120 cm tall and tend to spread uncontrollably over an indeterminate area; hence, they are sometimes considered invasive plants.

The common and popular mints for commercial cultivation are *Mentha piperita*, *Mentha spicata*, *Mentha gracilis*, *Mentha arvensis*, and *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 established in the Icelandic Pharmacopoeia of the thirteenth century. The list of benefits and uses of peppermint as a folk remedy or alternative medical therapy include biliary maladies, dyspepsia, enteritis, flatulence, gastritis, intestinal colic, and spasms of the bile duct and 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%), menthifuran (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 volatile peppermint leaves 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. 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], antiallergenic activity [322, 323], antiviral activity with significant results on herpes simplex viruses (HSV-1 and HSV-2) and immunodeficiency virus-1 (HIV-1) [242, 324–326], 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 pylori*, *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, 338]. 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 valuable tool to study the anti-inflammatory potential of a test substance. An aqueous extract has a noninflammatory pain reliever activity, in contrast with previous research when the phytochemicals were obtained by the ethanolic extraction [335]. On the other hand, the methanolic extract of different *Mentha* species displayed different analgesic 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 nociceptive pain. The results concerning analgesic effects produced by *M. piperita* strongly recommend this plant as a potential source of analgesics, and hence, 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 GI reflux, hiatal hernia, or kidney problems; hence, 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* L. [341], using hot-plate, acetic acid-induced writhing test, carrageenan-induced rat paw edema, and yeast-induced pyrexia methods. The hot-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 inhibition of local prostaglandin 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. The analgesic activity. Although the phytochemical occurrence is not identical, different mechanisms have been consequently involved in antinociception, with competitive results.
3.19. Lavandula Genus

*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, anti-inflammatory, antiseptic, antibacterial, antifungal, antispasmodic, 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].

3.19.1. Lavandula angustifolia

*Lavandula angustifolia* Mill. is one of the most famous aromatic and medicinal plants [351] used in fresh state or dry condition, containing volatile oils (monoterpenic compounds, alcohols, and esters), triterpenic acids, coumarins, flavones, resins, and polyphenols [352]. Lavender comprises over 100 volatile substances isolated from the 14 species of plants and analyzed by gas chromatography coupled with mass spectrometry. Washington et al. [353] demonstrated that *L. officinalis* leaves extraction attenuates pain evoked by hot-plate test, and stomach graze induced by high-dose acetic acid and ethanol and ascorbic acid. Huseini et al. (2015) [354] demonstrated that *L. officinalis* hydroalcoholic extracts inhibit inflammation and shock by formic acid and cyclooxygenase (COX) type 1 and 2 activity in mice, using the formalin and hot-plate tests. The administration of *L. officinalis* extracts contain linalool, acetate linalool, monotril, sesquiterpene, luteolin, ursolic acid, coumarin, and umbelliferone. The extract in 100, 200, 250, 300, 400, and 800 mg/kg, i.p. has inhibitory effects on inflammation induced by formic acid injection in the animals; as well as dexamethasone and indomethacin. The extract in 100, 200, and 300 mg/kg significantly reduced heat-induced activity in dose-dependent manner.

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 response [355]. The volatile oils (monoterpenic compounds, alcohols, and esters), triterpenic acids, coumarins, flavones, resins, and polyphenols [356] of *Lavandula officinalis* essential oils are reported to have analgesic effects. The literature data showed that *L. officinalis* extract contains linalool, acetate linalool, monotril, sesquiterpene, luteolin, ursolic acid, coumarin, and umbelliferone. Huseini et al. (2015) [354] demonstrated that *L. officinalis* hydroalcoholic extracts inhibit inflammation and shock by formic acid and cyclooxygenase (COX) type 1 and 2 activity in mice, using the formalin and hot-plate tests. The administration of *L. officinalis* extracts (in 100, 200, 250, 300, 400, and 800 mg/kg, i.p.) has inhibitory effects on inflammation induced by formic acid injection in the animals; as well as 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. [355] demonstrated the antinociceptive and the gastroprotective effects of orally administered (100 mg/kg, i.p.) *Lavandula hybrida* Reverchon “Grosso” essential oil, and its principal constituents linalool and linalyl acetate in rodents. In the hexagenic activity was observed after oil inhalation was inhibited by naloxone, atropine, and mecamylamine pretreatment, involvement of opioidergic as well as cholinergic pathways. Therefore, the lavender oil reveals an interesting analgesic activity main 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 by liquid chromatography coupled with mass spectrometry. Due to the high selectivity and sensitivity, 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: *Satureja pectinata* [357], *Lavandula angustifolia* [349], *Lavandula officinalis* [356], *Leonurus cardiaca* [290], *Lamium purpureum* [357], *Mentha spicata* [358], *Marrubium vulgare* [360], *Origanum vulgare* [361], *Ocimum basilicum* [362], *Rosmarinus officinalis* [364], *Satureja hortensis*, and *Thymus vulgaris* [365], included in most of the scientific articles follow the same steps: (i) collection of 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 the essential oil in the capillary column of a gas chromatograph, and separation of the chemical compounds, (iv) ionization and determination of the volatile substance in a mass spectrometer, and (v) identification of the components performed based on their retention indices and mass spectra stored in NIST 21, NIST 107, Wiley spectral libraries, or reported in scientific articles.

The volatile substances isolated from the 14 species of plants and analyzed by gas chromatography coupled with mass spectrometry are presented in Table 1.

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Identification</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Lavandula officinalis</em></td>
<td>[356]</td>
</tr>
<tr>
<td><em>Lavandula angustifolia</em></td>
<td>[349]</td>
</tr>
<tr>
<td><em>Leonurus cardiaca</em></td>
<td>[290]</td>
</tr>
<tr>
<td><em>Lamium purpureum</em></td>
<td>[357]</td>
</tr>
<tr>
<td><em>Mentha spicata</em></td>
<td>[358]</td>
</tr>
<tr>
<td><em>Marrubium vulgare</em></td>
<td>[360]</td>
</tr>
<tr>
<td><em>Origanum vulgare</em></td>
<td>[361]</td>
</tr>
<tr>
<td><em>Ocimum basilicum</em></td>
<td>[362]</td>
</tr>
<tr>
<td><em>Rosmarinus officinalis</em></td>
<td>[364]</td>
</tr>
<tr>
<td><em>Satureja hortensis</em></td>
<td></td>
</tr>
</tbody>
</table>
Yalçın 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].

The decoction prepared from Melissa officinalis dry leaves was filtered through a Whatman no. 4 filter paper, frozen and lyophilized, and the compounds were separated and analyzed by HPLC coupled with an ESI-triple quadrupole-ion trap mass spectrometer using the negative-ion mode. The identification of the phenolic compounds was carried out based on the comparison of their retention time, UV-Vis, and with those obtained from solutions prepared with standard substances. For the compounds for which no standard substance was available, the identification was performed based on the scientific literature [367].

Based on the UHPLC-ESI-MS data reported by Martina Cirlini et al. [368], the methanolic extract of Mentha spicata contains 88% salvinianolic acids when calculating the amount of rosmarinic acid derivatives as percentage of the total amount of detected phenols was calculated.

Taamalli and collaborators reported the analyses of the methanolic extract of Mentha pulegium performed using an UPLC-HRMS spectrometer coupled with a liquid chromatograph and detected metabolites from the following groups: hydroxybenzoic acids, hydroxycinnamic acids, flavonols, flavones, flavanones, flavonols, organic acids, nucleosides, amino acids, and fatty acids [56]. In the methanolic extract of pulegium, the authors identified a very high amount of gallic 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 instrument. The mass spectra were acquired in the negative-ion mode and showed the presence of some compounds not presented in Table 2 [369].

Anna Vallverdú-Queralt et al. identified the phenolic compounds present in the ethanolic acidified extract of Ocimum vulgare. After the first extraction with a hydroalcoholic solvent, the extracted plant material was centrifuged, dried, ground, and stored. An aliquot of the 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 used for the separation and mass spectrometric analyses performed using an UPLC-ESI-TOF mass spectrometer couple with a liquid chromatograph and detected metabolites from the following groups: hydroxybenzoic acids, hydroxycinnamic acids, bavone, bavanones, bavonols, organic acids, nucleosides, amino acids, and fatty acids [57].

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

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 Ayurvedic phytochemicals. Marrubiin, the broadly known diterpenoid lactone, has been associated with the bitter principle of the horseradish (Marrubium vulgare de Noe, M. alysson, and M. thessalum) and other traditionally important Lamiaceae species (Leonotis leonurus, L. nepetfolia, and L. bracteosa) [67, 374–379]. According to recent literature, extensive pharmacological studies have revealed that marrubiin shows a suite of activities such as antinociceptive, antispasmodic, antihypertensive, anti-diabetic, 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 the marrubiin reveals potent and dose-related antinociceptive effects in mice, whose calculated ID50 values (µmol/kg, i.p.) were as follows: 2.2 (first phase) and 6.3 (second phase) in the formalin-induced pain test, and 28.8 when evaluated over the capsaicin test. The results showed that it is more potent than other well-known analgesic drugs. The antinociception produced by the marrubiin is not reversed when analyzed against the writhing test. Its exact mechanism of action remains however still to be determined, but the results suggest, like the hydroalcoholic extract of M. vulgare, does not interact with opioid systems.

Analgesic activity success was obtained by reducing lactonic function of the marrubiin, in the formation of marrubinic acid and its derivatives, which have shown significant analgesic effect on the writhing test in mice [68, 374]. The pharmacological studies revealed that marrubinic 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 still less active than marrubiin [64].

Marrubinic acid, given orally, at a dose of 50 mg/kg, produced a marked analgesic effect, reducing 76 ± 0.9% of the number of constrictions induced by acetic acid, which may recommend that it can be well absorbed by the gastrointestinal tract. However, it is very effective in abolishing pain in a nonopioid way, showing the lack of antinociceptive effects in the hot-plate test [64]. When verified against a novel method, it provided more direct evidence of the analgesic potential on neuropathic pain, causing an inhibition of 37.3 ± 3.8% at 10 mg/kg, and 47.5 ± 3.2% at 50 mg/kg of marrubinic acid, respectively [64].

Table 2: Compounds identified by HPLC-ESI-MS in aqueous and alcoholic extracts.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Percentage</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrubiin</td>
<td>88%</td>
<td>Antinociceptive</td>
</tr>
<tr>
<td>M. officinalis</td>
<td>56%</td>
<td>Antispasmodic</td>
</tr>
<tr>
<td>M. vulgare</td>
<td>65%</td>
<td>Antihypertensive</td>
</tr>
<tr>
<td>O. basilicum</td>
<td>73%</td>
<td>Antidiabetic</td>
</tr>
<tr>
<td>L. nepetfolia</td>
<td>75%</td>
<td>Gastroprotective</td>
</tr>
<tr>
<td>L. bracteosa</td>
<td>374%</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>L. leonurus</td>
<td>375%</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>L. thessalum</td>
<td>376%</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>L. leonurus</td>
<td>377%</td>
<td>Antihepatotoxic</td>
</tr>
</tbody>
</table>
Future Perspectives and Conclusions

The specific mechanism underlying the antinociceptive action of marrubiin has yet to be determined, but it is likely that this interaction of opioid peptides. Although marrubiin displayed lower analgesic properties than morphin, it is more often used as a clinical drug. In summary, these results show that it could be used as a model to obtain new and more potent analgesics.

In 2013, the analgesic activity of the aqueous extracts obtained from leaves (AEL) and stems (AES) of Rosmarinus officinalis, as well as the marrubiin compound—rosmarinic acid (RA)—were analyzed by Lucarini et al. [379]. The analysis is based on abdominal constriction and formalin tests 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 was the only compound that presented a significant analgesic activity. This data recommend that the analgesic effects of the acetyl derivative of RA function in 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 formalin tests in mice. REO is very common in folk medicine because of its antispasmodic, analgesic, antitumour, and carminative effects. In the administration of REO in doses of 125, 250, and 500 mg/kg revealed unremarkable effects on response latency, whereas the morphine 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 showed substantial antinociceptive effect in the acetic acid-induced abdominal writhing test compared with control animals. The results suggest that the compound possesses peripheral antinociceptive activity. Similarly, Martinez et al. [363] described the antinociceptive effect of this essential oil in the chronic phase of the formalin test in mice. The essential oil with intraperitoneal administration in doses of 100, 300, and 600 mg/kg determined a significant increase in the time duration of licking in mice at high doses. Emami et al. [34] indicate that rosemary essential oil can inhibit carrageenan-induced paw edema tests in rats using the formalin-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 representatives 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, carnosol has anti-inflammatory, 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 R. officinalis can control pain by inhibiting its progression during a persistent noxious stimulus. As an essential characteristic, rosemary extract prevents damage to the nervous system. Thus, rosemary applies effects on the origin of neuropathic pain and offers a mean to directly modulate nervous signaling. The antineuropathic effects are mainly due to the terpenoid fraction in a mecamylamine-reversed manner, suggesting a pharmacodynamic role of nicotinic acetylcholine receptors [385, 386].

Husseini et al. [355] analyzed the effects of L. officinalis hydroalcoholic extract on pain induced by formalin and also cyclooxygenase type 2 activity in mice. The administration of the extract intraperitoneally in doses of 100, 200, 250, 300, 400, and 800 mg/kg, respectively, demonstrated 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 the mechanism of analgesic and anti-inflammatory effects 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 blocking acetic acid evoked pain [353]. This pharmacological activity could be derived from the contribution of various active principles composed such as linalool, myrcene, and 1–8 cineole, previously proved to possess antinociceptive proprieties [378–380]. However, administering essential oil with naltrexone, atropine, and mecamylamine could eliminate the analgesic effect of the extract, which indicates that the 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, piperitene oil were investigated in mice [390]. After an oral administration of 200 mg/kg of EOM and PO, the antinociceptive activity was determined in the acetic acid-induced number of writhings and the second phase of the formalin test, while in the similar conditions, they did not interfere with the nociception associated with the hot-plate and tail immersion tests. The hot-plate and tail immersion tests reported to be useful tests in discriminating analgesic agents acting primarily at the spinal medulla level and at higher central nervous system (positive results) from those acting through peripheral mechanisms (negative results) [391].

These findings suggest that EOM and PO are acting by peripheral mechanisms. In addition, EOM caused a reduction in the paw withdrawal latency 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 paw withdrawal latency 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 an 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 the traditional uses, pharmacology, and in vitro and in vivo studies of Betonica officinalis, Glechoma hederacea, Hyptis pectinata, Leonurus cardiaca, Lamium genus, Melissa officinalis, Mentha genus, Marrubium vulgare, Origanum genus, Ocimum genus, Rosmarinus officinalis, Salvia genus, Satureja hortensis, Stachys lavandulifolia, Scutellaria lateriflora, Sideritis genus, Teucrium genus, Thymus genus, and Zingiber officinale, 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 mositure 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 valuable 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.

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