Review

Antispasmodic Effect of Essential Oils and Their Constituents: A Review

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Abstract: The antispasmodic effect of drugs is used for the symptomatic treatment of cramping and discomfort affecting smooth muscles from the gastrointestinal, biliary or genitourinary tract in a variety of clinical situations. The existing synthetic antispasmodic drugs may cause a series of unpleasant side effects, and therefore the discovery of new molecules of natural origin is an important goal for the pharmaceutical industry. This review describes a series of recent studies investigating the antispasmodic effect of essential oils from 39 plant species belonging to 12 families. The pharmacological models used in the studies together with the mechanistic discussions and the chemical composition of the essential oils are also detailed. The data clearly demonstrate the antispasmodic effect of the essential oils from the aromatic plant species studied. Further research is needed in order to ascertain the therapeutic importance of these findings.

Keywords: essential oils; aromatic plants; antispasmodic effect; isolated ileum; monoterpenes

1. Introduction

The antispasmodic (spasmolytic) effect of drugs is commonly used for the reduction of excessive smooth muscle contractility, responsible for cramping and discomfort in the abdominal area, caused by multiple conditions affecting the gastrointestinal, biliary or genitourinary tract [1]. Irritable bowel syndrome (IBS), biliary colic caused by gallstones, gastritis, colitis and pancreatitis or dysmenorrhea may affect large numbers of patients and usually require antispasmodic treatment for the relief of symptoms [1–3]. Additionally, antispasmodic compounds are also used for the reduction of discomfort caused by medical procedures like colonoscopy [4]. A variety of synthetic antispasmodic drugs have been authorized worldwide by the regulatory agencies, the most important being anticholinergic agents (butylscopolamine), direct smooth muscle relaxants (papaverine), calcium antagonists (pinaverium) or opioid receptor modulators (trimebutine) [1,2]. Despite their clinical efficacy, the use of these molecules is often limited by the development of unpleasant and sometimes severe side effects which may reduce patient compliance and impair treatment efficiency [1,4]. Historically, a long time before the golden age of medicinal chemistry, several aromatic plants were used in traditional medicine for the treatment of different ailments in some parts of the world. In Europe, aromatic plants like peppermint or thyme have been used for medical purposes since antiquity while in Chinese or Indian traditional medicine other
aromatic species like cinnamon or sandalwood were known for centuries [5]. Nowadays, antispasmodic botanical remedies are used by a constantly increasing number of patients for symptomatic treatment of functional dyspepsia, intestinal, colonic or ureteral spasms, gallbladder hyperactivity and uterine cramps [6]. In the large category of medicinal plants, aromatic plants rich in essential oils are considered a valuable and easily accessible natural resource for the development of new molecules capable of becoming drug candidates. Essential oils are complex mixtures containing mainly aromatic terpenes classified in monoterpenes and sesquiterpenes according to the number of isoprene units but also phenylpropanoid compounds. These compounds are secondary metabolites formed by isoprenoid pathways in specialized secretory tissues of aromatic plants and diffused at the surface of their flowers or leaves [7]. The biological effects of essential oils have been extensively researched, as they can easily pass through cellular membranes and influence a variety of molecular targets from ion channels to intracellular enzymes [8]. Multiple in vitro and in vivo studies have confirmed the anti-oxidant, antimicrobial, antifungal, antiparasitary, anti-inflammatory, antinociceptive or antitumoral effects of essential oils [7], but the antispasmodic effect has been less studied experimentally, despite being mentioned in traditional medicine sources. Hence, this review was aimed at the investigation of the antispasmodic effect of essential oils, presenting the experimental models used for pharmacological testing with the subsequent mechanistic explanations, but also the chemical composition of the studied essential oils.

2. Methodology

A search was performed in Web of Science, PubMed and Scopus scientific databases, including the last 20 years (1998–2018). The search terms “essential oils” and “antispasmodic” (“spasmolytic”) were used for data selection. Only articles in English were included in this work. Our study investigated the antispasmodic effect of the essential oils and was not focused on the bronchodilator and vasodilator effects, presented by other reviews.

3. Results and Discussion

3.1. Preclinical Studies Investigating Antispasmodic Effect of Essential Oils

This review showed that essential oils from thirty-nine plant species belonging to twelve families presented antispasmodic properties demonstrated by specific animal models. The plants were organized alphabetically by family and botanical name, the proposed antispasmodic mechanism being also presented, where available. The families with the highest proportion of plant species showing antispasmodic effects due to essential oils (EO) were Lamiaceae (13 species), Apiaceae (6 species), and Asteraceae (5 species). Other identified families were Annonaceae and Poaceae (3 species), Rutaceae and Verbenaceae (2 species) while Anacardiaceae, Araeaceae, Geraniaceae, Rosaceae and Zingiberaceae families each presented only one plant species with antispasmodic essential oil (Table 1).
Table 1. Plant species containing essential oils with antispasmodic activity demonstrated in preclinical studies.

| No. | Plant Species with Essential Oils | Experimental Model/Concentration of EO in Organ Bath | Mechanism of Antispasmodic Effect | Reference |
|-----|----------------------------------|------------------------------------------------------|-----------------------------------|-----------|
| 1.  | *Pistacia integerrima*—zebrawood | Isolated guinea pig ileum/50 µg/mL | Inhibition of Ca\(^{2+}\) channels | Shirole et al., 2015 [9] |
| 2.  | *Cananga odorata var. genuina*—ylang ylang | Isolated guinea pig ileum/5–729 µg/mL; Isolated rat bladder in vivo/0.01–0.05 mL/rabbit | Increase of cAMP* | Kim et al., 2003 [10] |
| 3.  | *Xylopia frutescens* | Isolated guinea pig ileum/243–729 µg/mL | Inhibition of Ca\(^{2+}\) channels; antagonism of histaminergic receptors | Souza et al., 2015 [11] |
| 4.  | *Xylopia langsdorffiana* | Isolated guinea pig ileum; isolated rat uterus/243–729 µg/mL | Decrease in cytosolic calcium concentration | Correia et al., 2015 [12] |
| 5.  | *Anethum graveolens*—dill | Isolated guinea pig ileum/0.5–2 mg/mL | Inhibition of Ca\(^{2+}\) channels | Gharib Naseri et al., 2007 [13] |
| 6.  | *Carum carvi*—caraway | Isolated guinea pig ileum/2.20–6.63 mg/mL; Dispersed smooth muscle cells of guinea pigs/2.5 mg/mL | Not available | Heinle et al., 2006 [14]; Al-Essa et al., 2010 [15] |
| 7.  | *Coriandrum sativum*—coriander | Isolated guinea pig ileum/0.3–1 mg/mL | Inhibition of Ca\(^{2+}\) channels | Gilani et al., 2006 [20] |
| 8.  | *Ferula heuffeli* Griseb. | Isolated guinea pig ileum/1–30 mg/mL; | Not available | Pavlovic et al., 2012 [17] |
| 9.  | *Foeniculum vulgare*—fennel | Isolated guinea pig ileum/243–729 µg/mL | Not available | Ostad et al., 2001 [18] |
| 10. | *Pimpinella anisum*—aniseed | Isolated guinea pig ileum/0.3–1 mg/mL | Activation of NO-cGMP pathway | Tirapelli et al., 2007 [19] |
| 11. | *Acorus calamus*—sweet flag, calamus | Isolated guinea pig ileum/0.3–1 mg/mL | Inhibition of Ca\(^{2+}\) channels | Gilani et al., 2006 [20] |
| 12. | *Artemisia dracunculus*—tarragon | Isolated sheep ruminal and abomasal smooth muscles/0.1–100 µg/mL | Not available | Jalilzadeh-Amin et al., 2012 [21] |
| 13. | *Chamaemelum nobile*—roman chamomile | Isolated guinea pig ileum/60 µg/mL | Direct smooth muscle relaxation | Sandor et al., 2018 [22] |
| 14. | *Chrysactinia mexicana*—damianna daisy | Isolated rabbit ileum/30 µg/mL | Inhibition of Ca\(^{2+}\) channels; increase of cAMP | Zavala-Mendoza et al., 2016 [23] |
| 15. | *Hofmeisteria schaffneri* | Gastrointestinal transit test in mouse (in vivo)/316 mg/kg | Not available | Perez-Vasquez et al., 2017 [24] |
| 16. | *Matricaria recutita* (chamomilla)—German chamomile | Isolated rabbit ileum/0.3–3 mg/mL | K\(^{+}\) channels activation | Mehmood et al., 2015 [25] |
| 17. | *Pelargonium graveolens*—geranium | Isolated guinea pig ileum/4.8–6 µg/mL | Reduction of calcium flux into the intestinal smooth muscles | Lis-Balchin et al., 1997 [26] |
Table 1. Cont.

| No. | Plant Species with Essential Oils | Experimental Model/Concentration of EO in Organ Bath | Mechanism of Antispasmodic Effect | Reference |
|-----|----------------------------------|----------------------------------------------------|----------------------------------|-----------|
| 18. | *Lavandula angustifolia*—true lavender | Isolated guinea pig ileum, isolated rat uterus/6 µg/mL | Increase of cAMP | Lis-Balchin and Hart, 1999 [27] |
| 19. | *Melissa officinalis*—melissa | Isolated rat ileum/20 µg/mL; isolated mouse jejenum/1–50 mg/mL | Inhibition of Ca<sup>2+</sup> channels; Not available | Sadraei et al., 2003 [28]; Aubert et al., 2016 [29] |
| 20. | *Mentha x piperita*—peppermint | Isolated guinea pig ileum/10–320 µL/mL | Inhibition of Ca<sup>2+</sup> channels; Inhibition of 5HT3 receptor channels | Grigoleit et al., 2005 [30]; Heimes et al., 2011 [31] |
| 21. | *Mentha spicata*—spearmint | Isolated guinea pig ileum | Inhibition of Ca<sup>2+</sup> channels; Inhibition of 5HT3 receptor channels | Grigoleit et al., 2005 [30]; Heimes et al., 2011 [31] |
| 22. | *Mentha x villosa*—mojito mint | Isolated guinea pig ileum/250 µg/mL–1 mg/mL | Inhibition of Ca<sup>2+</sup> channels | Souza et al., 2008 [33] |
| 23. | *Ocimum basilicum*—basil | Isolated guinea pig ileum | Inhibition of Ca<sup>2+</sup> channels | Janbaz et al., 2014 [34] |
| 24. | *Ocimum selloi*—green pepperbasil | Isolated guinea pig ileum | Inhibition of Ca<sup>2+</sup> channels | Souza et al., 2015 [35] |
| 25. | *Ocimum gratissimum*—African basil | Isolated guinea pig ileum/0.1 nM–10 µM | Inhibition of Ca<sup>2+</sup> channels | Janbaz et al., 2014 [34] |
| 26. | *Origanum majorana*—sweet marjoram | Isolated rabbit jejunum, isolated rat jejunum/0.01–0.3 mg/mL | Inhibition of Ca<sup>2+</sup> channels | Madeira et al., 2002 [36] |
| 27. | *Plectranthus barbatus* synonym *Coleus forskohlii*—Indian coleus | Isolated guinea pig ileum/1–300 µg/mL | Direct smooth muscle relaxation | Camara et al., 2003 [38] |
| 28. | *Rosmarinus officinalis*—rosemary | Isolated guinea pig ileum/150–1200 µg/mL | Inhibition of Ca<sup>2+</sup> channels | Ventura-Martinez et al., 2011 [39] |
| 29. | *Salvia officinalis*—sage | Isolated rabbit jejunum/0.1–3 mg/mL | K<sup>+</sup> channels activation | Khan et al., 2011 [40] |
| 30. | *Satureja hortensis*—summer savory | Isolated rat ileum/1.55 µg/mL | Not available | Hajhashemi et al., 2000 [41] |
| 31. | *Cymbopogon citratus*—lemongrass | Isolated rabbit ileum/0.001–1 mg/mL | Inhibition of Ca<sup>2+</sup> channels | Devi et al., 2011 [42] |
| 32. | *Cymbopogon schoenanthus* (L.) Spreng.—cabelgrass | Isolated rat ileum/30–120 µg/mL | Not available | Pavlovic et al., 2017 [43] |
| 33. | *Cymbopogon martinii*—palmarosa | Isolated rabbit jejunum/0.01–3 mg/mL | Inhibition of Ca<sup>2+</sup> channels | Janbaz et al., 2014 [44] |
| 34. | *Rosa indica* (L.) | Isolated rabbit jejunum/0.01–1 mg/mL | Inhibition of Ca<sup>2+</sup> channels | Rasheed et al., 2015 [45] |
| 35. | *Citrus aurantifolia* var. acidae—lime | Isolated rabbit jejunum/Not available | Not available | Spadaro et al., 2012 [46] |
| 36. | *Citrus aurantium* var. sinensis—sweet orange | Isolated rat ileum/9.7–1000 µg/mL | Not available | Sanchez-Reccillas et al., 2017 [47] |
| 37. | *Lippia alba* | Isolated rat ileum/7–37 mg/mL | Reduction of calcium influx, stimulation of NO production | Blanco et al., 2013 [48] |
| 38. | *Lippia thyroidea* | Isolated guinea pig ileum/11.56–48.83 µg/mL | Not available | Menezes et al., 2018 [49] |
| 39. | *Elettaria cardamomum*—cardamom | Isolated rabbit jejunum/3–10 mg/mL | Inhibition of Ca<sup>2+</sup> channels | Gilani et al., 2008 [50] |

* For the in vivo experimental models dose of essentials oils (EO) was expressed in mL/animal or mg/kg.
The majority of the presented preclinical studies used whole essential oils, the antispasmodic effect of individual chemical constituents of essential oils being rarely investigated. Sadraei et al. [28] demonstrated antispasmodic effects not only for the essential oil from Melissa officinalis but also for citral, one of its main components. Heimes et al. [31] investigated the spasmylytic effects of menthol, a major constituent in the essential oil from Mentha piperita. De Souza et al. [33] tested the antispasmodic effect of several monoterpenes from Mentha x villosa essential oil, carvone and rotundifolone being the most active compounds.

While several studies confirmed the antispasmodic effect of essential oils extracted from common vegetal species extensively used in Asia or Europe like Cananga odorata [10], Foeniculum vulgare [18] or Artemisia dracunculus [21], other studies showed significant spasmylytic effects of essential oils from less-known plant species like Xylopia langsdorffiana [12], Ferula heuffelii [17] or Hofmeisteria schaffneri [24], proving that new natural sources of bioactive molecules are constantly being discovered.

The collected data from this review confirmed other studies investigating biological effects of essential oils. Martinez-Perez et al. [51] showed that monoterpenes frequently found in essential oils are the leading class of natural molecules responsible for the antispasmodic effect, followed by flavonoids and alkaloids. De Almeida et al. [52] and Sarmento-Neto et al. [53] also showed in their studies that aromatic plants from the Lamiaceae, Apiaceae and Asteraceae families are a rich source of essential oils, highly valuable for medicinal or industrial purposes.

Also, analysis of the included studies showed that, generally, the experimental models used for the assessment of essential oil antispasmodic activity were represented by ex vivo techniques. Among these, the isolated guinea pig ileum method was preferred, being considered a precise pharmacological tool capable of investigating the antispasmodic effect of natural or synthetic compounds [54]. Other isolated organs used for the evaluation of antispasmodic effect were rabbit jejunum, rat ileum, bladder or uterus and sheep ruminal and abomasal muscles. An experimental model used in vitro cell cultures [15] and only two experiments used in vivo techniques: rabbit bladder in vivo and gastrointestinal transit test in mouse [10,24]. The ex vivo techniques are predominant due to their use without the limitations of drug bioavailability which may be a problematic issue for the in vivo models. Ex vivo methods are also well suited for mechanistic studies due to the diversity of contractile agents which could be used experimentally [55].

3.2. Clinical Studies Evaluating Antispasmodic Potential of Essential Oils

Antispasmodic effect of essential oils was investigated in several clinical studies for different situations: functional dyspepsia, irritable bowel syndrome, discomfort produced by endoscopic procedures, infantile colic or dysmenorrhea (Table 2).
Table 2. Clinical studies evaluating antispasmodic potential of essential oils.

| Area of Interest         | Authors                                | Type of Clinical Study          | Number of Patients | Treatment                                      | Results                                                                 |
|--------------------------|----------------------------------------|----------------------------------|--------------------|------------------------------------------------|------------------------------------------------------------------------|
| Functional dyspepsia     | Papathanasopoulos et al., 2013 [56]    | Randomized, crossover study      | 13 healthy volunteers | Peppermint oil 182 mg p.o., single dose       | Decreased intragastric pressure and gastric motility                   |
| Functional dyspepsia     | Inamori et al., 2007 [57]              | Randomized control study         | 10 healthy volunteers | Peppermint oil 6.4 mL p.o., single dose       | Enhancement of gastric emptying without altering gastric emptying coefficient |
| Functional dyspepsia     | May et al., 2000 [58]                  | Randomized control study         | 96 patients with functional dyspepsia | Peppermint oil and caraway oil combination 90 mg + 50 mg p.o., 4 weeks | Reduction of symptoms (pain, fullness, heaviness)                      |
| Functional dyspepsia     | Madisch et al., 1999 [59]              | Randomized control study         | 118 patients with functional dyspepsia | Peppermint oil and caraway oil combination 90 mg + 50 mg p.o., 4 weeks | Reduction of dyspeptic symptoms                                       |
| Irritable bowel syndrome (IBS) | Cash et al., 2016 [60]               | Randomized control study         | 72 patients with IBS | Peppermint oil 180 mg p.o., 4 weeks          | Reduction of symptoms                                                  |
| IBS                      | Khanna et al., 2014 [61]               | Meta-analysis                     | 9 studies with 726 patients with IBS | Peppermint oil 200 mg                        | Global improvement of IBS symptoms (RR 2.23, 95% CI 1.78–2.81)          |
| IBS                      | Merat et al., 2010 [62]                | Randomized control study         | 90 patients with IBS | Peppermint oil 187 mg p.o., 8 weeks          | Reduction of abdominal pain and discomfort                             |
| IBS                      | Cappello et al., 2007 [63]             | Randomized control study         | 57 patients with IBS | Peppermint oil 225 mg p.o., 4 weeks          | Reduction of total IBS symptoms                                        |
| IBS                      | Pittler and Ernst 1998 [64]            | Meta-analysis                     | 8 randomized control studies | Peppermint oil                                | Reduction of IBS symptoms not established beyond reasonable doubt Improvement of pain and other IBS symptoms |
| IBS                      | Liu et al., 1997 [65]                  | Randomized control study         | 110 patients with IBS | Peppermint oil 187 mg p.o., 4 weeks          | Non-significant reduction of duodenal contractions                      |
| Endoscopic procedures    | Inoue et al., 2014 [66]                | Randomized control study         | 226 patients with colonoscopy | L-menthol applied on the mucosa               | Decreased frequency and duration of infantile colic                     |
| Endoscopic procedures    | Hiki et al., 2012 [67]                 | Randomized control study         | 131 patients with gastric endoscopy | L-menthol applied on the mucosa               |                                                                       |
| Endoscopic procedures    | Yamamoto et al., 2006 [68]             | Randomized, control study        | 40 patients with endoscopic cholangiopancreatography | Peppermint oil applied to papilla         |                                                                       |
| Infantile colic          | Bezerra Alves et al., 2012 [69]        | Randomized crossover study       | 30 infants           | *Mentha piperita* liquid drops, 1 drop/kg    | Reduction of dysmenorrhea symptoms                                     |
| Primary dysmenorrhea     | Ghodsi and Asltoghiri, 2014 [70]       | Randomized control study         | 80 female students   | Fennel capsules 180 mg/day, 3 months         |                                                                       |
The analysis of data resulted from the presented clinical studies show that peppermint oil was the predominant essential oil used for symptomatic treatment of various conditions, the strongest evidence being available for irritable bowel syndrome (IBS). The randomized controlled studies of Cash et al. [60], Merat et al. [62] and Capello et al. [63] enrolled patients with IBS diagnosed according to Rome II or III criteria, showing that peppermint oil was superior to placebo in reducing the symptom score of irritable bowel syndrome (IBS) after oral administration for one or two months. According to other studies [58,59], peppermint and caraway essential oils are a possible treatment option for patients with functional dyspepsia, reducing epigastric discomfort and abdominal bloating over four weeks of treatment. Also, L-menthol and peppermint oil were tested for the reduction of discomfort caused by endoscopic procedures being used with good results in upper GI endoscopies, colonoscopies [66,67] but also in cholangiopancreatographies [68]. The study of Bezerra Alves et al. [69] found that *Mentha piperita* essential oil reduced the frequency of infantile colic. In addition, Ghodsi and Asltoighiri [70] found that fennel essential oil reduced primary dysmenorrhea symptoms after a prolonged oral administration [70].

The systematic reviews of Chumpitazi et al. [71] and Shams et al. [72] pointed out that peppermint oil was safe and well-tolerated by the patients, with a minimal side effect profile. Nevertheless, clinical studies evaluating the antispasmodic potential of essential oils have some limitations. They were represented mainly by randomized crossover or control studies using small numbers of patients with an insufficient statistical significance. Only the studies of Khanna et al. [61] and Pittler and Ernst [64] were metaanalysis with superior statistical power. Therefore, additional clinical studies are necessary to ascertain the therapeutic value of antispasmodic essential oils.

3.3. Mechanisms of Antispasmodic Effect of Essential Oils and Their Constituents

Smooth muscles are a key element present in the internal structure of multiple abdominal organs including stomach, intestine, bladder or uterus, receiving innervation from the autonomic nervous system but also autocrine or paracrine stimuli [73]. Recently, considerable progress was made to understand in great molecular detail the complex physiology of smooth muscle contraction. Excitation-contraction coupling occurs when Ca$^{2+}$ ions enter from the extracellular side into the smooth muscle cells through sarcolemma voltage-dependent calcium channels, being also released from intracellular stores via inositol 1,4,5-triphosphate receptor (IP3R) situated on endoplasmic reticulum (ER) [74]. The calcium release from ER is triggered by the binding of agonists like acetylcholine or histamine on specific G-protein coupled receptors (GPCRs) from the membrane of smooth muscle cells, which activate phospholipase-C (PLC) to generate IP3. After the intracellular concentration of calcium has increased, Ca$^{2+}$ ions bind to calmodulin (CaM) and phosphorylate the myosin light-chain kinase (MLCK) with the subsequent activation of the contractile apparatus [75].

Thus, the identification and characterization of multiple molecular targets involved in smooth muscle contraction has led to the development of a variety of drugs able to reduce excessive contractility responsible for cramps and colics of the abdominal organs. Among potential new drug candidates, essential oils have become increasingly attractive due to their complex chemical composition and multiple pharmacological mechanisms: inhibition of voltage-dependent calcium channels, modulation of potassium channels, antagonism of cholinergic receptors, and modulation of intracellular cyclic adenosine monophosphate (cAMP) (Figure 1). Although some details of the antispasmodic effect of essential oils and their constituents have been explained, further research is needed to better understand their mechanism of action at cellular and molecular levels.
3.3.1. Inhibition of Voltage-Dependent Calcium Channels

The opening of voltage-dependent calcium channels (VDCCs) is directly responsible for Ca$^{2+}$ influx into the smooth muscle cells, partially triggering the contractile mechanism. Thus, inhibition of VDCCs has a good potential of relaxing smooth muscles, already used by several antispasmodic drugs like pinaverium [76]. Essential oils have been studied for their antispasmodic effect, the inhibitory effect on voltage-dependent calcium channels being the most commonly reported mechanism of action in the studies mentioned in our review (19 studies from 39). Some of these studies presented detailed mechanistic explanations of the antispasmodic effect for the non-fractioned essential oils. Makrane et al. [37] showed that organic fractions rich in essential oils from *Origanum majorana* showed a consistent spasmolytic effect on isolated rat and rabbit ileum not altered by atropine, L-NAME or methylene blue, and shifted to the right the concentrations-response curves for CaCl$_2$, suggesting a calcium channel blocking effect. Rasheed et al. [45] showed in an experiment on isolated rabbit jejunum that essential oil from *Rosa indica* relaxed the organ, shifting the calcium curves to the right, showing a similar effect to verapamil, a phenylalkylamine derivative from the calcium channel blocker class. The study of Souza et al. [35] identified the same mechanism for the essential oil from *Ocimum seloii* which reduced the contraction of isolated guinea pig ileum induced by carbachol, BaCl$_2$ and K$^+$ and shifted calcium concentration-response curves to the right.
Other studies were focused on the individual components of the essential oils. Amato et al. showed that menthol (0.1 mM–30 mM) reduced in a concentration-dependent manner the contractility of human colon circular muscle, acting by an antagonistic effect on L-type Ca\(^{2+}\) channels [77]. The study of Ramos-Filho et al. [78] showed that menthol markedly inhibited contractions of wild and TRPM8 knockout mice bladder strips evoked by carbachol, CaCl\(_2\) or electric field stimulation. The effects of menthol were not influenced by previous incubation with sodium or potassium channel inhibitors or by the removal of urothelium, suggesting a blockade of calcium channels. Electrophysiological studies have shown that menthol was able to inhibit the calcium influx through the low-voltage activated Ca\(^{2+}\) channels but also to enhance the inactivation of high-voltage activated Ca\(^{2+}\) channels [79]. Another monoterpene, (-)-carvone was tested by Souza et al. [32] on guinea pig ileum in order to ascertain the mechanism of its spasmolytic effect, proving to be almost 100 times more potent than verapamil, a well-known calcium channel blocker (CCB) with a similar mode of action. Devi et al. [42] studied the antispasmodic effect of another terpene, citral, the major component of *Cymbopogon citratus* essential oil on rabbit ileum, the results showing a marked reduction of contractions evoked by CaCl\(_2\), similarly to verapamil.

3.3.2. Modulation of Potassium Channels

Potassium channels are largely distributed in human and animal tissues, having important physiological roles such as the regulation of smooth muscle tone [80]. Generally, the activation of voltage-gated potassium channels induces a hyperpolarisation of cell membrane with a subsequent de-activation of calcium channels leading to smooth muscle relaxation. Only a few studies investigated the effect of essential oils on potassium channels situated on smooth muscles of internal organs. Mehmood et al. [25] showed that a crude extract from *Matricaria chamomilla* L. containing sesquiterpenes (bisabolol) and flavonoids produced a significant antispasmodic effect on isolated rabbit jejenum. The effect on low K\(^+\) induced contractions was completely blocked by 4-aminopyridine, suggesting that the activation of potassium channels was responsible for smooth muscle relaxation. Khan et al. [40] showed that a crude extract from *Salvia officinalis* rich in essential oils (thujone, 1,8-cineole, camphor, linalool) caused a dose-dependent relaxation of isolated rabbit jejunum by an activation of K\(^+\) channels.

Silva et al. [81] investigated the mechanism of smooth muscle relaxation of rotundifolone, the major constituent of *Mentha x villosa* essential oil. Patch-clamp recordings made in mesenteric smooth muscle cells showed that rotundifolone significantly increased K\(^+\) currents, effect blocked by charybdotoxin which suggested the participation of big potassium (BK) channels.

3.3.3. Antagonism of Cholinergic Receptors

The parasympathetic nervous system has an important role in the regulation of gastrointestinal motility. Muscarinic receptors located directly on smooth muscle cells can trigger their contraction in response to acetylcholine, but nicotinic receptors have also been identified on the nerve cells from the enteric nervous system. Research on the effect of essential oils on cholinergic receptors from smooth muscles is extremely rare, only a few studies being published to date. Amato et al. [82] found that menthol induced relaxation of isolated mouse stomach by inhibiting nicotinic receptors from the enteric nervous system, reducing the release of acetylcholine from enteric nerves. The study of Lozon et al. [83] investigated the effects of vanilin, pulegone, eugenole, carvone, carvacrol, carveol, thymol, thymoquinone, menthone, and limonene on human nicotinic cholinergic receptors expressed in *Xenopus* oocytes. Carveol showed the most potent inhibition at the \(\alpha 7\) subunit of the nicotinic receptor. The molecular interactions between terpenic compounds from essential oils and nicotinic cholinergic receptors were investigated by electrophysiological studies which showed that menthol caused a shortening of channel open time and a prolongation of channel closed time of human \(\alpha 4\beta 2\) nicotinic receptors [83].
3.3.4. Modulation of Intracellular Cyclic Adenosine Monophosphate (cAMP)

The main intracellular second messengers cAMP and cGMP are directly involved in smooth muscle relaxation. cAMP is generated by adenylyl cyclase mainly as a result of beta-adrenergic receptor activation. cGMP is produced by soluble guanylyl cyclase activated by nitric oxide or other mediators. Both cAMP and cGMP activate protein kinases PKA and PKG which may relax smooth muscles either by increasing the expulsion of calcium from the cell or by activation of MLC phosphatase which inhibits MLCK. The levels of cAMP and cGMP are severely reduced by the intervention of phosphodiesterases (PDE) involved in their degradation to inactive metabolites [73]. Multiple studies have investigated the effects of essential oils on the intracellular mechanisms of smooth muscle relaxation. In a study from 2018, Sandor et al. [22] studied the effects of the essential oil and extract from *Chamaemelum nobile* L. (roman chamomile) on isolated guinea pig ileum and rat gastrointestinal preparations. The essential oil significantly relaxed the isolated organs contracted with histamine, without any influence of a pretreatment with atropine, tetrodotoxin, propranolol or NG–nitro-L-arginine, thus suggesting an intracellular mechanism of the antispasmodic effect. Zavala-Mendoza et al. [23] investigated the antispasmodic mechanism of the essential oil from *Chrysactinia mexicana* on isolated rabbit ileum. The effect was reduced by the preincubation with dibutyryl-cAMP but increased by forskolin, whereas chelerytrine or L-NNa did not modify the response, suggesting an involvement of cAMP in the antispasmodic mechanism of the essential oil. The study of Kim et al. [10] showed that essential oil from *Cananga odorata* (ylang-ylang) relaxed the isolated rat bladder muscle, the effect being reduced by N-ethylmaleimide but not by inhibitors of NO pathway, demonstrating the involvement of cAMP. Also, Lis-Balchin and Hart [27] found that essential oil from *Lavandula angustifolia* induced relaxation of isolated guinea-pig ileum through a rise in intracellular level of cAMP The effects of individual components from essential oils on intracellular mechanism of antispasmodic effect were less studied. Leal-Cardoso et al. [84] found that eugenol (1–2000 microM) relaxed the isolated rat ileum precontracted with KCl, without any influence from tetrodotoxin, L-NAME, hexamethonium or indomethacin, thus suggesting an intracellular mechanism.

3.4. Chemical Composition of the Essential Oils with Antispasmodic Activity

Essential oils are complex mixtures of volatile compounds with terpenoid or non-terpenoid structure that can be extracted from different parts of plants (flower, buds, seed, leaves, and fruits). Many of those compounds have been identified in essential oils and classified as functionalized derivatives of alcohols, ketones or aldehydes, esters, ethers, oxydes and phenols [85,86]. The composition of an essential oil may vary according to the plant’s environment and growing conditions, stage of development, methods of harvesting, extraction, and storage. The major constituents of an essential oil can also vary according to different chemotypes of the same plant species [85]. Although there is a tendency to correlate pharmacological properties with the presence of certain functional groups, this concept cannot be generalized. Thus, neurotoxicity cannot be reported for all ketones, even if it was reported in the case of thujone [86,87], as not all the alcohols have a sedative action, even if it was described for l-linalool [86,88,89].

Several molecules with a structure clearly linked to the antispasmodic effect have been identified by our review. According to the surveyed literature, they are classified as alcohols (menthol), phenols (eugenol) [84], esters (linalyl acetate, neryl acetate, geranyl acetate, iso-amyl angelate and tiglate), ethers (trans-anethole, methyl chavicol or estragole, methyleugenol) [90], oxides (1,8-cineole, piperitenone oxide) [86,91,92] (Figure 2). However, other constituents present in low concentrations could be important for the pharmacological activity.
Figure 2. Chemical structures of main constituents from antispasmodic essential oils.

Chemical composition of the antispasmodic essential oils included in our study is presented in Table 3.
| Plant Species | Part Use | Reference |
|---------------|----------|-----------|
| Pistacia integerrima, (Anacardiaceae)-zebrawood | Galls | [93–95] |
| Cananga odorata var. genuina, (Annonaceae)—ylang ylang | Flowers | [86,96–99] |
| Xylopia frutescens, (Annonaceae) | Leaves | [11] |
| Xylopia langsdorffiana, (Annonaceae) | Fruits | [100] |
| Anethum graveolens, (Apiaceae)—dill | Seeds | [86,101–108] |
| Carum carvi, (Apiaceae)—caraway | Fruits | [86,109–111] |

Table 3. Chemical composition of the studied antispasmodic essential oils.

- Hydrocarbons: **monoterpenes**: α-pinene 21.81%, β-pinene 16.18, α-terpinene 1.37%, carene 11.09%, limonene 6.35%, α-phellandrene 15.48%, β-phellandrene 5.72%, cis-β-ocimene 4.13%, trans-β-ocimene 4.25%; **sesquiterpenes**: β-caryophyllene 3.88–5.33%, β-farnesene 7.88%; **aromatic**: p-cymene 11.54%
- Alcohols: terpinen-4-ol 11.93–28.82%, 4-carvomenthenol 17.06%, p-meth-1-en-8-ol 43.38%, borneol 8.90%, spathulenol 6.35%
- Ketones: tetrahydrocarvone 10.27%
- Ethers: bornyl acetate 13.99%
- Major components differ significantly depending on the fraction of essential oil, origin of the plant material and harvesting time
- Hydrocarbons: **sesquiterpenes**: ß-caryophyllene 15–26.8%, germacrene D 8.1–25.13%, δ-cadinene 2–4.7%, α-humulene 0.9–7.1%, α-farnesene 0.3–23.75%
- Alcohols: linalool 8.7–30%, farnesol 5.6%
- Ethers: p-methyl anisole 0.39–16.5%
- Hydrocarbons: **monoterpenes**: α-pinene 2.30%, β-ocimene 8.19%; **sesquiterpenes**: caryophyllene 23.91%, γ-cadinene 12.48%, γ-elemene 4.55%, β-elemene 4.31%, α-selinene 4.29%, δ-cadinene 3.02%, α-humulene 2.48%, γ-muurolene 2.23%, β-selinene 2.11%
- Alcohols: cadin-4-en-10-ol 5.78%, viridiflorol 4.83%, sphatulenol 3.97%
- Oxides: 1,8-cineol 1.15%, caryophyllene oxide 3.79%
- Hydrocarbons: **monoterpenes**: α-pinene 37.73%, camphene 11.50%, β-pinene 4.04%, limonene 31.75%; **sesquiterpenes**: sclarene 10.38%
- Alcohols: α-terpineol 1.08%, spathulenol 1.74%
- Oxides: 1,8-cineol 1.15%, caryophyllene oxide 3.79%
- Hydrocarbons: **monoterpenes**: limonene 1.11–83%, α-phellandrene trace–25%, β-phellandrene 0–3.38%
- Phenols: carveol 2%, eugenol
- Ketones: carvone (28–62.48%), cis-dihydrocarvone 0–5.87%, trans-dihydrocarvone 0–11.7%, pipertione 0–8.2%
- Ethers: apiole 0–16.79%, dillapiole 0–26.8
- Hydrocarbons: **monoterpenes**: limonene 1.5–51.3%, carvone 30%
- Alcohols: cis-carveol 5.5%
- Ketones: carvone 44.5–95.9%
- Ethers: trans-anethole 0–2.2%, apiole 12.3%
| Plant Species | Part Use          | Representative Compounds                                                                 | Reference |
|---------------|------------------|-----------------------------------------------------------------------------------------|-----------|
| *Coriandrum sativum*, (Apiaceae)—coriander | Fruits | Hydrocarbons: monoterpenes: γ-terpinene 1–8%, limonene 0.1–4%, α-pinene 0–10.9%, β-myrcene 0.2–2%; aromatic p-cymene trace–8.1% | [86,89,112,113] |
|               |                  | Alcohols: linalool 60–87%, geraniol 1.2–3.6%, terpin-4-ol trace–3%                        |           |
|               |                  | Ketones: camphor 0.9–5.3%                                                                 |           |
|               |                  | Esters: geranyl acetate 0.1–5.4%, linalyl acetate 0–2.7%                                   |           |
|               |                  | Hydrocarbons: monoterpenes: α-pinene 4%, γ-terpinene 1.2%; sesquiterpenes: α-cadinene 3.4%, aromadendrene 1.8%, viridiflorene 2.1%, α-muurolene 1.7% |           |
| *Ferula houffelii* Griseb., (Apiaceae) |                  | Alcohols: viridoflorol 1.0%, cedrol 5.1%                                                | [17]     |
|               |                  | Ethers: myristicin 20.6%, elemicin 35.4%                                                 |           |
| *Foeniculum vulgare var. dulce*, (Apiaceae)—sweet fennel | Fruits | Hydrocarbons: monoterpenes: α-pinene 0.4–10%, limonene 1.4–26.4%, α-phellandrene 0.2–9.26%, β-myrcene 0.5–3%, β-phellandrene 0.4–2.6%, γ-terpinene 10.5%, cis-β-ocimene 1.6–12%, α-terpinolene trace–3.3%; aromatic: p-cymene 0.1–4.7% |           |
|               |                  | Alcohols: fenchol trace–4%                                                                | [86,114–118] |
|               |                  | Ketones: fenchone trace–22%                                                               |           |
|               |                  | Ethers: methyl chavicol trace–17%, cis-anethole trace–1.7%, trans-anethole 50–90%         |           |
|               |                  | Oxides: 1,8-cineole 1–6%                                                                 |           |
| *Pimpinella anisum*, (Apiaceae) - aniseed | Fruits | Hydrocarbons: sesquiterpenes: γ-himachalene 0.4–8.2%                                     | [86,119–121] |
|               |                  | Alcohols: anisol 0.5–4%                                                                  |           |
|               |                  | Ethers: cis-anethole 0–1%, trans-anethole 90–93.7%, methyl chavicol 0–2.3%                |           |
|               |                  | Aldehydes: anisaldehyde 0–5.4%                                                            |           |
|               |                  | Hydrocarbons: monoterpenes: α-pinene 2.96%, limonene 0.1–2.8%; sesquiterpenes: β-gurjunene 0.2–28.0%, calamene 0.1–9.75%, δ-cadinene 0.5–2.1%, α-cedrene 3.09% |           |
|               |                  | Alcohols: linalool 0.3–12%                                                                |           |
| *Acorus calamus*, (Araceae)—sweet flag, calamus | Rhizomes | Phenols: cis-isoeugenol 2.5–25%, trans-isoeugenol 0.5–2%                                   | [86,122–126] |
|               |                  | Aldehydes: asaronal 0.2–6%, citronellal 2.82%, neral 2.57%                                |           |
|               |                  | Ketones: shyobunone trace–13.3%, epishyobunone 0.1–4.8%, isoshyobunone 0.6–13.0%, camphor 2.42% |           |
|               |                  | Ethers: methyl eugenol trace–8.59%, cis-methyl isoeugenol 2.4–49%, trans-methyl isoeugenol 1.1–7.9%, α-asarone 1–50.09%, β-asarone 2.22–83.2% |           |
|               |                  | Major components differ significantly depending on the origin of the plant material and harvesting time |           |
| *Artemisia dracunculus*, (Asteraceae)—tarragon | Flowering tops and leaves | Hydrocarbons: monoterpenes: α-pinene 5.1%, limonene 2.40–12.4%, trans-ocimene 2.99–20.6%, α-terpinolene 0.5–25.4%, cis-ocimene 2.65–22.2%, sabine 14.28–39.44% | [127–132] |
|               |                  | Ethers: trans-anethole 10–21.2%, cis-anethole 53.37–81.0%, methyl eugenol 2.2–39.35%, methyl isoeugenol 1.8–35.8%, methyl chavicol 1.09–74.46% |           |
|               |                  | Others: asaron 21.69–40.36                                                                |           |
| Plant Species                     | Part Use          | Representative Compounds                                                                 | Reference          |
|----------------------------------|-------------------|------------------------------------------------------------------------------------------|-------------------|
| *Chamaemelum nobile* (Asteraceae) | Flowers           | Hydrocarbons: *monoterpenes*: $\alpha$-terpinene 0–10%, $\alpha$-pinene 0–10%, $\beta$-pinene 0–10%, sabinene 0–10%; *sesquiterpenes*: caryophyllene 0–10%  
|                                  |                   | Alcohols: *trans*-pinocarveol 5%  
|                                  |                   | Aldehydes: myrtenal 0–10%  
|                                  |                   | Ketones: pinocarvone 13%  
|                                  |                   | Oxides: 1,8-cineole 0–25%  
|                                  |                   | Ethers: methyl chavicol 5%  
|                                  |                   | Esters: 2-methylbutyl 2-methyl propionate 0.5–25%, 2-methylpropyl butanoate 0.5–10%, 2-methylbutyl 2-methylbutanoate 0.5–25%, 2-methylpropylangelate 0.5–25%, butylangelate 0.5–10%, 3-methylpentylangelate 0–10%, isobutylangelate 36–40%, isobutylisobutanoate 4%, 2-methylbutyl methyl-2-butanoate 3%, isoamyl methyl-2-butanoate 3%, hexylacetate 0.5–10%  
|                                  |                   | Hydrocarbons: *monoterpenes*: $\alpha$-myrcene 1.20%  
|                                  |                   | Alcohols: linalool 1.39%  
|                                  |                   | Ketones: $\alpha$-thujone 1.17%, piperitone 37.74%  
|                                  |                   | Oxides: 1,8-cineole 41.3%  
|                                  |                   | Esters: linalyl acetate 9.08%  
|                                  |                   | Major components differ depending on the harvesting time  
|                                  |                   | Alcohols: linalool 0.25–1.38%  
| *Chrysactinia mexicana*, (Asteraceae) | Leaves                    | Ketones: $\alpha$-thujone 1.17%, piperitone 37.74%  
|                                  |                   | Oxides: 1,8-cineole 41.3%  
|                                  |                   | Esters: linalyl acetate 9.08%  
| *Hofmeisteria schaffneri* (Asteraceae) | Aerial parts               | Esters: thymyl isobutyrate 1.54–3.41%, thymyl isovalerate 14.12–30.97%, 9-acetoxy-8,9-dehydrothymylangelate 2.36–5.23%, 8,9-epoxy-10-acetoxythymylangelate 0.41–15%  
|                                  |                   | Hydrocarbons: *sesquiterpenes* chamazulene 1–35%, *trans*-farnesene 2–13%,  
|                                  |                   | *trans*- $\alpha$-farnesene 27%, $\delta$-cadinene 5.2%, $\gamma$-muurolene 1.3%, $\alpha$-muurolene 3.4%  
|                                  |                   | Alcohols: *sesquiterpenes*: $\alpha$-bisabolol 2–67%  
|                                  |                   | Oxides: $\alpha$-bisabol oxide A 0–55%, $\alpha$-bisabol oxide B 4.3–19%, bisabolone oxide A 0–64%  
| *Matricaria recutita* (Asteraceae)—german chamomile | Flowers              | Hydrocarbons: *sesquiterpenes* chamazulene 1–35%, *trans*-farnesene 2–13%,  
|                                  |                   | *trans*- $\alpha$-farnesene 27%, $\delta$-cadinene 5.2%, $\gamma$-muurolene 1.3%, $\alpha$-muurolene 3.4%  
|                                  |                   | Alcohol: *sesquiterpenes*: $\alpha$-bisabolol 2–67%  
|                                  |                   | Oxides: $\alpha$-bisabol oxide A 0–55%, $\alpha$-bisabol oxide B 4.3–19%, bisabolone oxide A 0–64%  
|                                  |                   | Hydrocarbons: *monoterpenes*: $\alpha$-pinene 22.47%; *sesquiterpenes*: guai-6,9-diene 3.9–5.3%, $\beta$-bourbonene 2.7–3.14%, germacrene D 2.92–4.33%, $\gamma$-cadinene 2.38%  
|                                  |                   | Alcohol: citronellol 15.2–48.44%, geraniol 6–25%, linalool 1–13.79%, octen-1-ol 18.61%  
|                                  |                   | Aldehydes: geranial 0–9%  
|                                  |                   | Ketones: menthone 0.6–6.96%, isomenthone 4–8.4%  
|                                  |                   | Oxides: *cis*-rose oxide 0.69–25%, *trans*-rose oxide 0.31–2.01%, cariopyllene oxide 2.52–3.7%  
|                                  |                   | Esters: citronellyl formate 8–24.4%, geranyl formate 1–6.22%, citronellyl propionate 1–3%, geranylangelate 1–2%, citronellylbutanoate 1.3%, geranylbutanoate 1.3%  
| *Pelargonium graveolens*, (Geraniaceae)—geranium | Aerial parts              | Alcohol: $\alpha$-bisabol oxide A 0–55%, $\alpha$-bisabol oxide B 4.3–19%, bisabolone oxide A 0–64%  
|                                  |                   | Hydrocarbons: *sesquiterpenes* chamazulene 1–35%, *trans*-farnesene 2–13%,  
|                                  |                   | *trans*- $\alpha$-farnesene 27%, $\delta$-cadinene 5.2%, $\gamma$-muurolene 1.3%, $\alpha$-muurolene 3.4%  
|                                  |                   | Alcohol: *sesquiterpenes*: $\alpha$-bisabolol 2–67%  
|                                  |                   | Oxides: $\alpha$-bisabol oxide A 0–55%, $\alpha$-bisabol oxide B 4.3–19%, bisabolone oxide A 0–64%  
|                                  |                   | Hydrocarbons: *monoterpenes*: $\alpha$-pinene 22.47%; *sesquiterpenes*: guai-6,9-diene 3.9–5.3%, $\beta$-bourbonene 2.7–3.14%, germacrene D 2.92–4.33%, $\gamma$-cadinene 2.38%  
|                                  |                   | Alcohol: citronellol 15.2–48.44%, geraniol 6–25%, linalool 1–13.79%, octen-1-ol 18.61%  
|                                  |                   | Aldehydes: geranial 0–9%  
|                                  |                   | Ketones: menthone 0.6–6.96%, isomenthone 4–8.4%  
|                                  |                   | Oxides: *cis*-rose oxide 0.69–25%, *trans*-rose oxide 0.31–2.01%, cariopyllene oxide 2.52–3.7%  
|                                  |                   | Esters: citronellyl formate 8–24.4%, geranyl formate 1–6.22%, citronellyl propionate 1–3%, geranylangelate 1–2%, citronellylbutanoate 1.3%, geranylbutanoate 1.3%  

Table 3. Cont.
| Plant Species                        | Part Use         | Representative Compounds                                                                 | Reference         |
|-------------------------------------|------------------|------------------------------------------------------------------------------------------|-------------------|
| *Lavandula angustifolia* (Lamiaceae) | Flowers          | Hydrocarbons: *monoterpene*: cis-8-ocimene 1.3–10.9%, *trans*-8-ocimene 0.8–5.8%, limonene 0.2–7%; *sesquiterpenes*: β-caryophyllene 2.6–7.6% | [33,89,99,137,145–148] |
|                                     |                  | Alcohols: linalool 26–49%, terpinen-4-ol 0.03–6.4%, α-terpineol 0.1–1.4%, bornol 0.8–1.4%, *lavadulol* 0.5–1.5% |                   |
|                                     |                  | Oxides: 1,8-cineole 0.5–2.5%                                                            |                   |
|                                     |                  | Esters: linalyl acetate 35–55%, lavandulyl acetate 0.2–5.9%                             |                   |
|                                     |                  | Major components differ significantly depending on the origin of the plant material      |                   |
|                                     |                  | Hydrocarbons: *sesquiterpenes*: β-caryophyllene 8–10%, α-copaene 4–5%                    |                   |
| *Melissa officinalis* (Lamiaceae)   | Aerial parts     | Hydrocarbons: *monoterpene*: α-pinene 0.2–2%, β-pinene 0.3–4%, limonene 0.6–6%; *sesquiterpenes*: germacrene D 1.75–4.3% | [149–152]         |
|                                     |                  | Alcohols: linalool 0.4–2.74%, nerol 1.4%, geraniol 0.20–27.22%, citronelol 0.26–36.71%   |                   |
|                                     |                  | Aldehydes: neral 3.28–31.5%, geranial 0.38–31.1%, citronellal 1.48–39.6%                  |                   |
|                                     |                  | Oxides: caryophyllene oxide 0.2–10.26%                                                  |                   |
| *Mentha × piperita* (Lamiaceae)     | Aerial parts     | Hydrocarbons: *monoterpene*: α-pinene 0.2–2%, β-pinene 0.3–4%, limonene 0.6–6%; *sesquiterpenes*: germacrene D 1.75–4.3% | [153–156]         |
|                                     |                  | Alcohols: menthol 25.16–48%, neomenthol 2–7.7%, α-terpineol 0.1–1.9%, *cis*-carveol 3.86%, *terpinen* 0.4–2.4%, *cis*-thujan-4-ol trace 0.6–2.7% |                   |
|                                     |                  | Ketones: *menthone* 16–42.97%, *isomenthone* 4–10.4%, neomenthone 2–3%, *piperitone* 0.5–1.2%, *pulegone* 4.39% |                   |
|                                     |                  | Oxides: 1,8-cineole 2.15–7.4%, *transpiperitonoxide* 0.5–3.1%                           |                   |
|                                     |                  | Esters: menthyol acetate 1.6–10%                                                         |                   |
|                                     |                  | Benzofurans: menthofuran 0.1–5.7%                                                        |                   |
|                                     |                  | Hydrocarbons: *monoterpene*: β-pinene 0.3–2.3%, β-myrcene 1.2–5.5, limonene 2–25%; *sesquiterpenes*: β-caryophyllene 0.3–4.41%, γ-farnesene 1.71%, β-bourbonene trace 2.14%, germacrene D 0.1–3.14% |                   |
|                                     |                  | Alcohols: *cis*-carveol 5.30%, menthol 0.5–2%, *terpinen* 4-ol trace 6.1%, α-terpineol 0.2–2.7% |                   |
| *Mentha spicata* (Lamiaceae)         | Aerial parts     | Ketones: *carvone* 39–70%, *menthone* trace 5.2%, *cis*-dihydrocarveol 3.1–21.6%, *trans*-dihydrocarveol 0–21%, *isomenthone* 3.33% | [86,99,156–158]   |
|                                     |                  | Oxides: 1,8-cineole 0.5–17.0%, *piperetone* 20.0–79.2%                                   |                   |
|                                     |                  | Esters: dihydrocarvyl acetate 1.2–24.8%, *cis*-carvyl acetate 0.2–5.5%, *trans*-carvyl acetate 0.7–5.9%, *neoisodihydrocarveol* 0–21%, *menthol acetate* 2% |                   |
|                                     |                  | Benzofurans: menthofuran 2%                                                               |                   |
| *Mentha x vilosa* Huds. (Lamiaceae)  | Aerial parts     | Hydrocarbons: *monoterpene*: β-pinene 1.42–4.04%, myrcene 3.10–3.66%, limonene 2.38–8.75%; *sesquiterpenes*: β-caryophyllene 2.82–5.16%, δ-cardene 9.69%, γ-muurolene 2.18–16.02%, germacrene-D trace 3.81% | [33,91,159–161]   |
|                                     |                  | Oxides: 1,8-cineole 1.58–3.93%, *piperetone* oxide 58.74–79.03%, *caryophyllene oxide* 2.82% |                   |

**Table 3.**
| Plant Species                   | Part Use          | Representative Compounds                                                                 | Reference |
|--------------------------------|-------------------|------------------------------------------------------------------------------------------|-----------|
| **Ocimum basilicum** (Lamiaceae)—basil | Aerial parts      | Hydrocarbons: *sesquiterpenes*: β-caryophyllene 2–3%                                      | [86,162] |
|                                |                   | Alcohols: linalool 40–55%, α-fenchyl alcohol 3–12%, terpinen-4-ol 1.6%, α-terpineol 2%   |           |
|                                |                   | Ethers: methyl chavicol 3–31%, methyl eugenol 1–9%                                         |           |
|                                |                   | Oxides: 1.8-cineole 2–8%                                                                   |           |
| **Ocimum selloi** (Lamiaceae) —green pepper basil | Aerial parts      | Hydrocarbons: *sesquiterpenes*: β-caryophyllene 2.2–3%, germacrene D 0–3.14%              | [35,162–164] |
|                                |                   | Alcohols: linalool 20.6%, spathulenol 1.3%                                                |           |
|                                |                   | Ethers: *trans*-anethole 45.42%, *cis*-anethole 3.95%, methyl chavicol 24.14–93.2%,      |           |
|                                |                   | methyl eugenol 2.2–39.35%                                                                  |           |
| **Ocimum gratissimum** (Lamiaceae)—african basil | Aerial parts      | Hydrocarbons: *monoterpenes*: β-pinene 6.2%, *cis*-ocimene 13.9–23.97%, *trans*-ocimene    | [36,162,165,166] |
|                                |                   | 19.60–48.28%, γ-terpinene 0.20–28.10%, limonene 11.40%; *sesquiterpenes*: β-caryophyllene |           |
|                                |                   | 2.7–3.06%, β-phellandrene (21.10), germacrene D 7.30–10.36%, *α*-trans-bergamotene 4.1%    |           |
|                                |                   | *γ*-murolene 9.32–11.6%; *aromatic*: *p*-cymene 4.40–19.90%                               |           |
|                                |                   | Phoenols: eugenol 10.70–74.80%, thymol 13.10–46.60%                                       |           |
|                                |                   | Oxides: 1.8-cineole 0–54.94%                                                              |           |
| **Origanum majorana**, (Lamiaceae)—sweet marjoram | Aerial parts      | Major components differ significantly depending on chemotype and the origin of the plant material |           |
|                                |                   | Hydrocarbons: *monoterpenes*: sabinene 1.45–10%, β-myrcene 1–9%, *α*-terpinolene 1–7%,  |           |
|                                |                   | *α*-pinene 1–5%, *cis*-trans-*β*-ocimenes 6.4%, *3*-carene 6.2%, myrcene 1.12–4.7%,       |           |
|                                |                   | *α*-terpinene 3.9–8%, γ-terpinene 11.16–20%; *sesquiterpenes*: β-caryophyllene 2–7.44%,  |           |
|                                |                   | δ-cadinene 4.2%, *α*-farnesene 4.58%, germacrene D 9.2%; *aromatic*: *p*-cymene 7.0–12.05% |           |
|                                |                   | Phenols: eugenol 10.70–74.80%, thymol 13.10–46.60%                                       |           |
|                                |                   | Oxides: 1.8-cineole 0–54.94%                                                              |           |
|                                |                   | Alcohols: terpinen-4-ol 14–38.4%, *cis*-thujan-4-ol 0.11–44%, *trans*-thujan-4-ol 1–5%,  |           |
|                                |                   | linalool 2–31.68%, *α*-terpineol 7–27%                                                     |           |
|                                |                   | Phenols: carvacrol 0–83.47%                                                                |           |
|                                |                   | Esters: terpenyl acetate 0–3%, geranyl acetate 1–7.8%, linalyl acetate 2.41–17.4%          |           |
|                                |                   | Hydrocarbons: *monoterpenes*: *α*-pinene 12–67%, *β*-pinene 0.1–22%, *β*-myrcene 1.8%,   |           |
|                                |                   | *cis*-β-ocimene 1.9%, *trans*-β-ocimene 1.2%; *sesquiterpenes*: β-caryophyllene 7–12%,    |           |
|                                |                   | *α*-copaene 8.9%, *β*-cubebene 3.7%                                                       |           |
|                                |                   | Alcohols: oct-1-en-3-ol traces 28%                                                         |           |
|                                |                   | Phenols: thymol 15.3%, carvacrol 12.1%, eugenol 25.1%                                      |           |
| **Plectranthus barbatus** synonym Coleus forskohlii, (Lamiaceae)—Indian coleus | Aerial parts      | Hydrocarbons: *sesquiterpenes*: β-caryophyllene 2–3%                                      | [38,172–174] |
|                                |                   | Alcohols: linalool 40–55%, α-fenchyl alcohol 3–12%, terpinen-4-ol 1.6%, α-terpineol 2%   |           |
|                                |                   | Ethers: methyl chavicol 3–31%, methyl eugenol 1–9%                                         |           |
|                                |                   | Oxides: 1.8-cineole 2–8%                                                                   |           |
Table 3. Cont.

| Plant Species | Part Use | Representative Compounds | Reference |
|---------------|----------|---------------------------|-----------|
| *Rosmarinus officinalis* ct. verbenone, (Lamiaceae)—rosemary | Aerial parts | Hydrocarbons: monoterpenes: α-pinene 15–34%, Ketones: verbenone 15–37%, camphor 1–22.35% Oxides: 1,8-cineole trace–20% Esters: bornyl acetate 12% | [86,175–177] |
| *Salvia officinalis* (Lamiaceae)—sage | Aerial parts | Alcohol: linalool 0.4–12%, terpinen-4-ol 0.2–4%, α-terpineol trace–9%, bornol 1.5–14%, viridiflorol 0–10% Ketones: α-thujone 1.1–35.7%, β-thujone 1.71–33%, camphor 4.1–43.83% Oxides: 1,8-cineole 5–57.18%, caryophyllene oxide 0.4–2.1% Esters: bornyl acetate 0.1–5.59%, linalyl acetate 1–2% | [40,86,178,179] |
| *Satureja hortensis* (Lamiaceae)—summer savory | Aerial parts | Alcohol: linalool 9–54%, terpinen-4-ol trace–7%, α-terpineol 6–9% Phenols: carvacrol 59.70–67.00%, eugenol 1–1.7%, thymol 0–29.0% Oxides: 1,8-cineole 0–37.82% | [86,99,180,181] |
| *Cymbopogon citratus* Stapf (Poaceae)—West Indian lemongrass | Aerial parts | Alcohol: α-terpineol 0.2–2.3%, linalool 1.2–3.4%, geraniol 2.6–40%, nerol 0.8–4.5%, citronellol 0.1–8%, farnesol 12.8% Aldehydes: neral 3–43%, geranial 4.5–58%, citronellal 0.1–9% Esters: geranyl acetate 0.1–3.0% | [42,86,182–185] |
| *Cymbopogon schoenantus* (L.) Spreng (Poaceae)—camelgrass | Aerial parts | Alcohol: α-eudesmol 11.5%, elemol 10.8%, β-eudesmol 8.5%, γ-eudesmol 4.2%, intermedeol 6.1–17.3%, linalool 21.6% Aldehydes: neral 3.3%, geranial 2.4% Ketones: pipertone 47.7–71.5% | [43,185] |
| *Cymbopogon martini* (Poaceae)—palmarosa | Aerial parts | Alcohol: linalool 1.6–3.4%, geraniol 67.6–83.6%, citronellol 1.6–2.1% Aldehydes: geranial 1–8.8% Esters: geranyl acetate 2.2–24.6% | [185,186] |
| *Rosa indica* L. (Rosaceae) | Aerial parts | Alcohol: citronellol 11.7%, nerol 8.0%, geraniol 24.8%, farnesol 2.0% | [45,187] |
| Plant Species | Part Use | Representative Compounds | Reference |
|---------------|----------|--------------------------|-----------|
| Citrus aurantifolia/Citrus medica var. acida (Rutaceae)—lime | Pericarps | Hydrocarbons: monoterpenes: limonene 36–60%, γ-terpinene 6–17.6%, α-pinene 0.2–5.03%, 8-pinene 4.9–19.5%, β-myrcene 1–2.6%; sesquiterpenes: β-caryophyllene 1.3–3.4%, α-bisabolene 2.3%; aromatic p-cymene 0.1–6.8% <br> Alcohols: linalool 1.4–16.9%, α-terpineol 13–23% <br> Aldehydes: citronellal 0–5.3%, neral 0.7–4.7%, geranial 1.8–6.4% <br> Esters: linalyl acetate 26–27% | [46,86,99,188,189] |
| Citrus aurantium var. sinensis (Rutaceae)—sweet orange | Pericarps | Hydrocarbons: limonene 87.9–96.8%, β-myrcene 1.37–2.5%, β-phellandrene 0–1.5% <br> Alcohols: linalool 0.5–2.4% | [86,99,190,191] |
| Lippia alba, (Verbenaceae) | Leaves | Hydrocarbons: monoterpenes: limonene 8.2–15.7%, γ-terpinene 4.09%, myrcene 6.6–8.3%; sesquiterpenes: β-caryophyllene 2.7–3.07%, germacrene D 3.0–5.47% <br> Alcohols: β-elemol 5.37%, nerol 2.2%, geraniol 2.9%, linalool 0.8–64.2% <br> Aldehydes: geranial 6.5–50.94%, neral 11.5–33.32% <br> Ketones: carvone 16.7–33.7% <br> Oxides: caryophyllene oxide 0–2.64% | [48,192–195] |
| Lippia thymoides, (Verbenaceae) | Leaves | Hydrocarbons: monoterpenes: α-pinene 0.94–2.38%, camphene 2.64–5.66%, limonene 1.67–3.75%; sesquiterpenes: copaene 2.42–3.38%, β-caryophyllene 5.32–26.27%, α-caryophyllene 3.06–5.48%, germacrene D 4.72–6.18% <br> Alcohols: borneol 4.45–7.36% <br> Phenols: thymol trace–66.33% <br> Ketones: camphor 3.22–8.61% <br> Oxides: cariophyllene oxide 0.9–2.7% <br> Ethers: 1,8-cineole 1.86–4.5% <br> Esters: thymol acetate 0.7–9.49% | [49,196,197] |
| Elettaria cardamomum, (Zingiberaceae)—cardomom | Fruits | Hydrocarbons: monoterpenes: limonene 1.7–14%, sabine 1.3–5%, β-myrcene 0.2–2.2% <br> Alcohols: linalool 0.4–6.9%, terpinen-4-ol 0.1–3.2%, α-terpineol 0.8–5.25%, geraniol 0.2–1.6%, trans-nerolidol 0.1–2.7%, cis-nerolidol 0.2–1.6% <br> Oxides: 1,8-cineole 15.13–50% <br> Esters: α-terpinyl acetate 29–56.87%, linalyl acetate 0.2–7.7% | [86,198–202] |
4. Conclusions

This review identified 39 plant species bearing essential oils with antispasmodic effect demonstrated in preclinical studies. The main mechanisms of the antispasmodic effect were represented by inhibition of voltage-dependent calcium channels, modulation of potassium channels and modulation of intracellular cAMP. Certain individual components identified in the chemical composition of the essential oils studied could become promising new drug candidates but future clinical studies are needed in order to ascertain their therapeutical value.

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