**Review Article**

**Natural Antispasmodics: Source, Stereochemical Configuration, and Biological Activity**

**Edith Fabiola Martínez-Pérez,**¹ ² **Zaida N. Juárez,**³ **Luis R. Hernández** ² and **Horacio Bach** ¹

¹Department of Medicine, Division of Infectious Diseases, University of British Columbia, 2660 Oak Street, Vancouver, BC, Canada V6H 3Z6
²Departamento de Ciencias Químico-Biológicas, Universidad de las Américas Puebla, Ex Hacienda Sta. Catarina Mártir S/N, 72810 San Andrés Cholula, PUE, Mexico
³Ingeniería en Biotecnología, Facultad de Biotecnología, Decanato de Ciencias Biológicas, Universidad Popular Autónoma del Estado de Puebla, 21 Sur No. 1103, Barrio Santiago, 72410 Puebla, PUE, Mexico

Correspondence should be addressed to Luis R. Hernández; luisr.hernandez@udlap.mx and Horacio Bach; hbach@mail.ubc.ca

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Natural products with antispasmodic activity have been used in traditional medicine to alleviate different illnesses since the remote past. We searched the literature and compiled the antispasmodic activity of 248 natural compounds isolated from terrestrial plants. In this review, we summarized all the natural products reported with antispasmodic activity until the end of 2017. We also provided chemical information about their extraction as well as the model used to test their activities. Results showed that members of the Lamiaceae and Asteraceae families had the highest number of isolated compounds with antispasmodic activity. Moreover, monoterpenoids, flavonoids, triterpenes, and alkaloids were the chemical groups with the highest number of antispasmodic compounds. Lastly, a structural comparison of natural versus synthetic compounds was discussed.

## 1. Introduction

Antispasmodic compounds are currently used to reduce anxiety, emotional and musculoskeletal tension, and irritability. Although most of the available antispasmodic compounds are synthetic or semisynthetic, traditional uses of this group of compounds are still popular.

We collected information about natural compounds with antispasmodic activity isolated from terrestrial plants. We searched the databases of Google Scholar, PubMed, and SciFinder and compiled the information about 248 compounds published until December 2017. This review focuses on the antispasmodic activity of isolated compounds and activities from extracts without further purification are not discussed.

## 2. The Neurons

Nerve cells or neurons are responsible for receiving, conducting, and transmitting signals. A neuron consists of a nucleated body, a long thin extension called an axon, and several dendrites or prolongations extended from the cell body. Axons conduct signals from the nucleated body towards distant targets, while dendrites provide an enlarged surface area to receive signals from the axons of other neurons.

Signal transmission through axons is driven by a change in the electrical potential across the plasma membrane of neurons. This plasma membrane contains voltage-gated cation channels, which are responsible for generation of action potentials. An action potential is triggered by a depolarization of the plasma membrane or a shift to a less negative value.

In nerve and skeletal muscle cells, a stimulus can cause sufficient depolarization to open voltage-gated Na⁺ channels allowing the entrance of Na⁺ into the cell. This influx of Na⁺ depolarizes the membrane further causing the opening of more Na⁺ channels. To avoid a permanent influx, Na⁺ channels are able to reclose rapidly even when the membrane...
is still depolarized. This function is based on the presence of voltage-gated K⁺ channels, which are responsible for K⁺ efflux equilibrating the membrane potential even before the total inactivation of Na⁺ channels. In some cases, the action potential in some muscles depends on voltage-gated Ca²⁺ channels.

2. Transmission of Signals. The transmission of signals occurs mainly between neurons or from neurons to skeletal muscles, which are the final acceptors of electrical signals, causing a muscular contraction.

2.1. Signal Transmission between Neurons. Neuronal signals are transmitted between neurons at specialized sites of contact known as synapses. Neurons are separated by a synaptic cleft where a release of a neurotransmitter occurs. This neurotransmitter is stored in vesicles and is released by exocytosis. Upon triggering, the neurotransmitter is released into the cleft provoking an electrical change in the postsynaptic cell by binding to the transmitter-gated ion channels. To avoid a continuous electrical change and to ensure both spatial and temporal precision of signal transmission, the neurotransmitter is rapidly removed from the cleft either by specific enzymes in the synaptic cleft or by reuptake mediated by neurotransmitter carrier proteins [1].

Neurotransmitters can also open cation channels causing an influx of Na⁺ and then called excitatory neurotransmitters (e.g., acetylcholine, glutamate, and serotonin) or produce an opening of Cl⁻ channels and then inhibiting the signal transmission by maintaining the postsynaptic membrane polarization [e.g., γ-aminobutyric acid (GABA) and glycine].

2.1.2. Neuromuscular Signal Transmission. The transmission of electrical signals to muscles involves five sequential and orchestrated steps: (i) nerve electric signal reaches the nerve terminal, (ii) it depolarizes the plasma membrane of the terminal, (iii) voltage-gated Ca²⁺ channels opens causing an increase in Ca²⁺ concentration in the neuron cytosol, and (iv) release of acetylcholine into the synaptic cleft is triggered. Acetylcholine binds to acetylcholine receptors in the muscle plasma membrane opening Na⁺ channels and provoking a membrane depolarization. This depolarization enhances the opening of more Na⁺ channels causing a self-propagating depolarization. The generalized depolarization of the muscle plasma membrane activates Ca²⁺ channels in specialized regions on the membrane causing Ca²⁺ release from the sarcoplasmic reticulum (Ca²⁺ storage) into the cytosol.

As a consequence of an increase in the Ca²⁺ concentration, myofibrils in the muscle cell contract. The increase of Ca²⁺ in the cytosol is transient because Ca²⁺ is rapidly pumped back into the sarcoplasmic reticulum causing a relaxation of the myofibrils. This process is very fast and Ca²⁺ concentration at resting levels is restored within 30 milliseconds [2].

3. Receptors

The autonomic nerve system controls and monitors the internal environment of the body. The input of its activity is provided by neurons that are associated with specific sensory receptors located in the blood vessels, muscles, and visceral organs (Table 1). According to the neurotransmitter secreted, these neurons are classified as adrenergic or cholinergic. The adrenergic neurons secrete the neurotransmitter noradrenalin termed also norepinephrine. Adrenergic receptors include the types α and β, which are further categorized as α₁, α₂, β₁, β₂, and β₃. On the other hand, cholinergic neurons secrete acetylcholine, which induces a postsynaptic event. There are two types of cholinergic receptors, the nicotinic receptor (abundant at the neuromuscular junction) and the muscarinic receptor (abundant on smooth and cardiac muscles and glands).

There are several agonists (neurotransmitters, hormones, and others) able to bind to specific receptors and activate the contraction of smooth muscle. Upon binding the agonist to the receptor, the mechanism of contraction is based on an increase of phospholipase C. This enzyme hydrolyzes phosphatidylinositol 4,5-bisphosphate located on the membrane, producing two powerful secondary messengers termed diacylglycerol (DG) and inositol 1,4,5 triphosphate (IP3). IP3 binds to specific receptors in the sarcoplasmic reticulum, causing release of Ca²⁺ within the muscle. DG together with Ca²⁺ activates the protein kinase C (PKC), which phosphorylates specific proteins. In most smooth muscles, the contraction process commences when PKC phosphorylates Ca²⁺ channels or other proteins that regulate the cyclic process. For instance, Ca²⁺ binds to calmodulin (a multifunctional intermediate calcium-binding messenger protein), triggering the activation of the myosin light chain (MLC) kinase, which phosphorylates the light chain of myosin and together with actin carries out the process of initiating the shortening of the smooth muscle cell [147]. However, the elevation of the intracellular concentration of Ca²⁺ is transient, and the contractile response is maintained by a mechanism sensitized by Ca²⁺ modulated by the inhibition of myosin phosphatase activity by Rho kinase. This mechanism sensitized to Ca²⁺ is initiated at the same time that phospholipase C is activated and involves the activation of the small RhoA protein bound to guanosine triphosphatase (GTP). Above activation, RhoA increases the activity of Rho kinase, leading to the inhibition of myosin phosphatase. This promotes the contractile state, since the myosin light chain cannot be dephosphorylated [147].

Relaxation of smooth muscle occurs as a result of either removing the contractile stimuli or by the direct action of a substance that stimulates the inhibition of the contractile mechanism. In any circumstance, the relaxation process requires a decrease in the intracellular Ca²⁺ concentration and an increase in the activity of the MLC phosphatase. The sarcoplasmic reticulum and plasma membrane remove Ca²⁺ from the cytosol. Na⁺/Ca²⁺ channels are located on the plasma membrane and help to reduce the intracellular concentration of Ca²⁺. During relaxation, other contributors that restrict the Ca²⁺ entry into the cell are the voltage-operated channels and Ca²⁺ receptors in the plasma membrane, which remain closed [147].
| Receptor     | Targeted by                  |
|--------------|------------------------------|
| Adrenergic   | Epinephrine (adrenaline)     |
|              | Norepinephrine (noradrenaline)|
| Dopaminergic | Dopamine                     |
| Cholinergic  | Acetylcholine                |
| GABAergic    | GABA                         |
| Glutaminergic| Glutamate                    |
| Histaminergic| Histamine                    |
| Serotonergic | Serotonin                    |
| Glycinergic  | Glycine                      |
| Opioid       | Dynorphin                    |
| Receptor  | Targeted by |
|-----------|-------------|
| Enkephalin | ![Enkephalin structure](image) |
| Endorphin | ![Endorphin structure](image) |
| Endomorphin | ![Endomorphin structure](image) |
| Nociceptin | ![Nociceptin structure](image) |
4. Spasmodic Compounds

The historical antecedents date from the year 1504 when South American natives inhabiting the basins of the high Amazon and the Orinoco prepared a mixture of alkaloids termed curare. This substance was placed in the tips of arrows in order to hunt (prey paralyzing) and fight in wars. Curare produces muscle weakness, paralysis, respiratory failure, and death [148]. In 1800, Alexander von Humboldt, identified that curare was made from the extracts of the species Chondrodendron tomentosum and Strychnos toxifera.

In 1935, the French physiologist Claude Bernard managed to isolate the alkaloid d-tubocurarine from the curare [149]; and one year later, it was elucidated that this compound had the ability to inhibit acetylcholine, blocking the transmission of nerve impulses to the muscles [150]. Lastly, new benzylisoquinoline alkaloids were isolated from curare by Galeffi et al. in 1977 [151, 152].

In 1822, the pharmacist Rudolph Brandes obtained an impure alkaloid from Atropa belladonna (Solanaceae), which after purification was named atropine. Interestingly, atropine was not produced as a natural compound from the plant and it was a derivative generated from the alkaloid hyoscyamine during the process of purification [153]. It is important to note that atropine has been naturally found in small quantities in other members of the Solanaceae family such as Datura stramonium, Duboisia myoporoides, and Scopolia japonica [154–156].

The use of the plant Papaver somniferum (opium poppy) (Papaveraceae) dates back to about 4000 BC. At present the plant is only used to extract a base material for the manufacture of other alkaloids, such as noscapine and codeine, both discovered by the French pharmacist Pierre-Jean Robiquet in 1831 and 1832, respectively [157]. In 1848, papaverine was another substance extracted from the same plant by the German chemist Georg Merck [158], which is rarely used today because of the high doses needed (approximately 6 to 12 mg). However, it is still used as a control in experimental models with the purpose of studying antispasmodic activity of plant extracts.

In the 20th century, extracts and powders derived from A. belladonna were widely used as antispasmodics, but from the 1950s these preparations were displaced by synthetic and semisynthetic anticholinergic compounds in order to obtain a better response [159], such as the case of methocarbamol and guaifenesin. On the other hand, a series of compounds such as dantrolene, glutethimide, methaqualone, chloromezanone, metiprilone, and ethchlorvynol were introduced to replace the meprobamate, which had to be withdrawn from the market in 1960 due to problems resulting from use such as abstinence, addictions, and overdoses.

In 1962, the Swiss chemist Heinrich Keberle synthesized baclofen, which can be obtained by reacting glutarimide with an alkaline solution [160]. Glutarimide can also be found in plants such as Croton cuneatus and C. membranaceus (Euphorbiaceae) [161, 162].

The arrival of the quaternary compounds of nitrogen reinforce their peripheral anticholinergic activity offering also the advantages of being poorly absorbed in the gastrointestinal tract, producing a more powerful and longer lasting sedative effect unlike atropine [1]. For example, ipratropium bromide was developed by the German company Boehringer Ingelheim in 1976 and used to treat asthma. This compound was obtained by reacting atropine with isopropyl bromide [163]. Another quaternary compound was the n-butylyhydroxycine bromide, which is possible to obtain by the organic synthesis of scopalamine and the cimetropium bromide found in the A. belladonna [164]. Although at present the preparations of plant mixtures are no longer used for therapeutic purposes, these compounds formed a part of and served as the basis for modern pharmacology for their applicability as antispasmodics and anesthetics.

Spasms are involuntary contractions of the muscles, which are normally accompanied by pain and interfere with the free and effective muscular voluntary activity. Muscle spasm can originate from multiple medical conditions and is often associated with spinal injury, multiple sclerosis, and stroke.

Spasticity and rigidity are caused by a disinhibition of spinal motor mechanisms. There are several scenarios where a muscle can produce a spasm: (i) unstable depolarization of motor axons; (ii) muscular contractions persist even if the innervation of muscle is normal and despite attempts of relaxation (myotonia); (iii) after one or a series of contractions, the muscle can decontract slowly, as occurring in hypothyroidism; and (iv) muscles lack the energy to relax.

4.1. Distribution of Spasmodic Compound in Nature. Spasmodic compounds are widely distributed in nature (Table 2). Frequently, these compounds are found in animals that paralyze their preys or used for defense. Some examples include the venom of the black widow and tarantula spiders [11, 165] and the venom of snakes [166]. Plants also produce spasmodic metabolites, such as strychnine, an alkaloid obtained from the tree Strychnos nux-vomica (Loganiaceae). Furthermore, microorganisms synthesize spasmodic compounds such as the neurotoxins tetanospasmin and botulinum toxin from the Gram-positive bacteria Clostridium tetani and C. botulinum, respectively. These toxins produce a toxic disorder, which is characterized by persistent spasms of skeletal muscles on spinal neurons similar to strychnine.

4.2. Mechanisms of Antispasmodic Activity of Natural Products. Antispasmodic compounds exert their activity in different ways, such as antispasmodic activity through inhibition of the response to the neurotransmitters 5-hydroxytryptamine (5-HT) or serotonin and acetylcholine. However, other authors attribute the antispasmodic effect to (i) capsacin-sensitive neurons, (ii) the participation of vanilloid receptors [167], (iii) the activation of K+ ATP channels, (iv) the blockade of Na+ channels and muscarinic receptors, (v) the reduction of extracellular Ca2+, or (vi) the blockade of Ca2+ channels [22, 168, 169]. The above is merely a reflection of the ambiguity of the studies showing the mechanisms of action of the antispasmodic compounds [36]. For example, the hydroalcoholic extract of Marrubimum vulgare showed antispasmodic effect, having the ability to inhibit the
Table 2: Representative organisms producing spasmodic compounds.

| Compound       | Organism                                | Symptoms                                      | Mechanism                                                                 | Reference |
|----------------|-----------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------|-----------|
| **Bacterial**  |                                         |                                               |                                                                           |           |
| Botulinum toxin| *Clostridium botulinum*                  | Muscular relaxation                           | Secretion of acetylcholine into synapses is blocked                       | [3]       |
| Tetanospasmin  | *Clostridium tetani*                    | Muscular spasm                                | Inhibits the binding of GABA and glycine                                  | [4]       |
| **Marine**     |                                         |                                               |                                                                           |           |
| Nematocyst venom extract | Sea anemones                        | Nausea, vomiting, muscle cramp, severe pain, paralysis | Delay in the voltage-dependent Na\(^+\) channels inactivation                | [5]       |
| Nematocyst venom extract | *Chironex fleckeri* (Cnidaria)      | Contraction of arterial smooth muscle         | Increase of cytosolic Ca\(^{2+}\) concentration                           | [6]       |
| Ciguatoxin     | *Gambierdiscus toxicus* (Dinoflagellate) | Nausea, vomiting, abdominal pain, intestinal spasm | Interact with voltage-gated increasing the Na\(^+\) permeability and Ca\(^{2+}\) homeostasis | [7]       |
| Chordata       | *Plotosus lineatus* (Catfish)            | Violent pain, shock, spasm                    | Increase of the vascular permeability in peritoneum                       | [8]       |
| **Terrestrial**|                                         |                                               |                                                                           |           |
| Ergotamine     | *Claviceps purpurea* (fungus)            | Seizure, spasms psychosis, nausea, vomiting  | Agonist of several neurotransmitter receptors                              | [9]       |
| α-Latrotoxin   | *Latrodectus tredecimguttatus* (black widow spider) | Facial flushing, hypertension, muscle spasm, tachycardia | Causes Ca\(^{2+}\)-dependent and -independent release of neurotransmitters | [10]      |
| Vanillo-toxin, hanatoxin, huwentoxin | Tarantula species                     | Severe pain, cramps, erythema, swelling, tachycardia | Unrevealed                                                                 | [11–14]  |
| β-Neurotoxin   | *Mesobuthus martensi* (scorpion)         | Increases muscular contraction, spasm, convulsion | Modulates Ca\(^{2+}\) channels                                            | [15]      |
| Crototoxin     | *Crotalus durissus terrificus* (rattlesnake) | Severe pain, drooping eyelids, low blood pressure, muscle weakness | Blocks the cholinergic post-synaptic response                               | [16]      |

neurotransmitters acetylcholine, bradykinin, prostaglandin E2, histamine, and oxytocin [170], whereas a dual effect of antidiarrheal and laxative activities was reported in *Fumaria parviflora* [171].

5. Methods Used to Evaluate Antispasmodic Compounds

5.1. Gastrointestinal Model. The small intestine is characterized by its large surface area as a result of its circular folds, villi, and microvilli. It is the longest part of the GI system (approximately 5 meters) and comprises about 5% of its initial length, which corresponds to the duodenum (characterized by the absence of the mesentery) and then the jejunum (around 40% of the intestinal length), ending with the ileum. It is the organ of absorption of nutrients and digestion in organisms. These functions are carried out mainly in the duodenum and jejunum.

The main types of bowel movement are the segmentation and peristalsim. The segmentation is most frequent in the small intestine and consists of contractions of the circular muscle layer in very close areas. Contractions last for 11-12 and 8-9 contractions per min in the duodenum and ileum, respectively. When this segmentation is rhythmic, the contractions are alternated with relaxation. This type of movement results in a mixed effect of the chyme (acidic fluid that passes from the stomach to the small intestine) with the digestive secretions, allowing an optimal contact with the intestinal mucosa. In the case of peristalsis, contractions of successive sections of the circular smooth muscle cause the movement of the intestinal contents in anterograde form. The short peristaltic movement also takes place in the small intestine, but less frequently than the segmentation movements. Peristaltic waves rarely cross more than 10 cm of intestine and, due to the low frequency of propulsion of the chyme, it is in this zone where digestion and absorption are preferably carried out.
Peristalsis is regulated mainly by the nervous action of the myenteric plexus (major nerve supply to the gastrointestinal tract that controls GI tract motility) in the intestinal wall.

The diversity of experimental models used for the testing of antispasmodic compounds is large. These models mainly use isolated organs or live animals. Once the organ is extracted from the animal, the intestinal motility is assessed with the administration of a substance. The use of extracted organs can be sustained for hours when placed in a physiological solution, such as Ringer, Jalon, Tyrode, and Krebs [172].

The most used organs to perform the studies are guinea pig ileum, duodenum, heart, trachea, and jejunum. The same organs can be also extracted from rabbit, mouse, rat, and hamster (Table 3). The preparation of ileum is preferred because it evaluates the spasmolytic activity. However, although the jejunum contracts spontaneously, it allows evaluating the spasmolytic activity directly and without the use of an agonist [173].

Some advantages of performing ex vivo experiments are as follows: (i) different substances can be evaluated in fresh tissues without absorption factors, metabolic excretion or interference due to nerve reflexes; (ii) it is possible to quantify the effect produced by a precisely determined drug; and (iii) it is easier to obtain dose-effect curves, such as the smooth muscle where the contraction obtained under the influence of a spasm or in tissue homogenates is measured by determination of the enzyme activities [172, 174].

5.2. Guinea Pig Ileum and Rat Stomach. The ileum is removed and cut in strips of approximately 2 cm long and then placed in a bath filled with an isotonic solution as mentioned earlier. Electrophysiological studies are performed by graphically recording the contractions with the aid of a transducer, which is calibrated 30 min before the treatment begins. A range of 0.01 to 0.03 μM is generally used to determine dose response curves of the antispasmodic substance [175].

In rats, the stomach is removed and the corpus and fundus are cut in strips of approximately 5 mm x 15 mm and placed on a prewarmed warm solution as mentioned before.

5.3. Compounds Used to Elicit a Spasmodic Activity. The main compounds used are acetylcholine, atropine, BaCl₂, carbachol, histamine, KCl, and serotonin.

Acetylcholine is a postganglionic neurotransmitter in the parasympathetic neurons that innervate the intestine. The response to acetylcholine is regulated by activation of the two types of muscarinic receptors: M2 and M3 [176]. The activation of these receptors causes contractions by increasing the intracellular concentration of Ca²⁺ via IP3 [176]. Atropine is a competitive reversible antagonist of muscarinic acetylcholine receptors M1, M2, M3, M4, and M5.

Different substances are used to produce contractions. For example, BaCl₂ induces contractions by mobilizing membrane-bound Ca²⁺ [177], carbachol is a cholinomimetic drug (cholinergic agonist) that binds and activates acetylcholine receptors [178], histamine acts by either accelerating the release of acetylcholine or interacting supra-additively with the acetylcholine at the smooth muscle [179], whereas KCl increases the voltage-operated Ca²⁺ channel activity by increasing intracellular free Ca²⁺ in smooth muscle [180]. Serotonin is also an important neurotransmitter mainly stored in the digestive tract, affecting the secretory and motor activities. At high concentrations, it acts as a vasoconstrictor by contracting endothelial smooth muscle directly or by potentiating the effects of other vasoconstrictors [181, 182].

6. Antispasmodic Activity of Natural Compounds

Compounds isolated from terrestrial plants have shown the ability to function as antispasmodic compounds. The chemical group with the highest number of members of antispasmodic compounds is the monoterpenoid group (41 compounds) followed by flavonoids (35 compounds), alkaloids (with 33 compounds), and triterpenes with 31 (Figure 1). Although we summarize in Table 3 248 compounds, in most of the cases the mechanism behind their activity has not been elucidated.

7. Mutagenicity

Studies related to the mutagenicity of antispasmodics are very scarce. This topic has been underestimated when testing the bioactivities of ethnomedicinal plants. Probably the most useful method to determine the mutagenicity of natural products or plant extracts is the Ames method [183]. This test is based on the rate of mutations detected in genetically modified strains of Salmonella typhimurium. Moreover, this test has also been developed to detect mutagenicity of metabolized compounds in the liver. In this situation, a mixture of liver
Table 3: Natural products with antispasmodic activity isolated from terrestrial plants.

| Compound name                  | Species (Family)                        | Preparation (Solvent)       | Model tested                                      | Source | Reference |
|--------------------------------|----------------------------------------|----------------------------|---------------------------------------------------|--------|-----------|
| **Monoterpenoids**             |                                        |                            |                                                   |        |           |
| 1 Myrcene, β-myrcene           | *Plectranthus barbatus* (Lamiaceae)     | Leaf (MeOH)                | ACh, BaCl\(_2\), KCl in guinea pig ileum         | EO     | [17]      |
| 2 Citral B, β-citral, Neral    | *Aloysia triphylla* (Verbenaceae)       | Leaf (Hexane)              | Carbachol, KCl, O, PGF (2α) in rat uterus          | IC     | [18]      |
| 3 Geranyl formate              | *Cymbopogon citratus* (Poaceae)         | Leaf (MeOH 70%)            | ACh, KCl in rabbit ileum                          | IC     | [19]      |
| 4 Geranyl acetate              | *Melissa officinalis* (Lamiaceae)       | Aerial part (EtOH 70%)     | ACh, KCl in rat ileum                             | EO     | [20]      |
| 5 Geraniol                     | *Athyris mauritiana* (Compositae)       | Flower (Distillation)      | Ca\(^{2+}\), carbachol, KCl in rabbit and jejenum | EO     | [21]      |
| 6 Citronellol                  | *Nepeta cataria* (Lamiaceae)            | Leaf (Aqueous)             | Carbachol, KCl in guinea pig trachea and jejenum  | EO     | [22]      |
| 7 (+)-α-Phellandrene           | *Rosa damascene* (Rosaceae)             | Flower (hydrodistillation) | ACh, KCl, electrical field stimulation in rat ileum| IC     | [23]      |
| 8 (+)-β-Phellandrene           | *Zingiber officinalis* (Zingiberaceae)  | Leaf (Distillation)        | ACh, KCl in rat tracheal smooth muscle             | EO     | [25]      |
| 9 Terpinolene                  | *Zingiber officinalis* (Zingiberaceae)  | Rhizome (MeOH)             | Serotonin in rat ileum                            | EO     | [24]      |
| 10 D-(+)-Limonene              | *Zingiber officinalis* (Zingiberaceae)  | Rhizome (MeOH)             | Serotonin in rat ileum                            | EO     | [24]      |
| 11 γ-Terpinene                 | *Rosmarinus officinalis* (Lamiaceae)    | Leaf infusion (MeOH)       | Carbachol, KCl in rat duodenal smooth muscle       | EO     | [26]      |
| 12 Thymoquinone                | *Acalypha phleioides* (Euphorbiaceae)   | Aerial part (Hydrodistillation) | KCl in guinea pig ileum                           | IC     | [27]      |
| 13 (R)-(+)-Pulegone             | *Calamintha glandulosa* (Lamiaceae)     | Aerial part infusion (EtOH) | ACh, BaCl\(_2\), H, S in guinea pig ileum and jejenum | IC     | [29]      |
| 14 (-)-Menthol                  | *Rosa damascene* (Rosaceae)             | Leaf and flower infusion (EtOH) | KCl in guinea pig ileum                          | IC     | [27]      |
|                                | *Dracocephalum kotschyi* (Lamiaceae)    | Aerial part (EtOH)         | S in rat ileum                                    | IC     | [27]      |
| Compound name          | Species (Family)                  | Preparation (Solvent)                                      | Model tested                                     | Source | Reference |
|------------------------|-----------------------------------|-----------------------------------------------------------|--------------------------------------------------|--------|-----------|
| dl-α-Terpineol         | *Casimiroa pringlei* (Rutaceae)   | Aerial part infusion (Ethyl ether)                         | KCl in rat uterine smooth muscle                | IC     | [33]      |
| Zingiber roseum       | **Zingiberaceae**                  | Fresh seeds (Hydrodistilled with diethyl ether)            | Carbachol, KCl in rat duodenal smooth muscle     | EO     | [26]      |
| Dracocephalum kotschyi| (Lamiaceae)                       | Aerial part (Hydrodistillation)                            | ACh, electrical field stimulation, KCl in rat ileum | EO     | [28]      |
| (-)-Piperitone         | *Casimiroa pringlei* (Rutaceae)   | Aerial part infusion (Ethyl ether)                         | KCl in rat uterine smooth muscle                | IC     | [33]      |
| (+)-Rotundifolone      | *Mentha x villosa* (Lamiaceae)     | Leaf infusion (MeOH)                                       | KCl in guinea pig ileum                         | IC     | [27]      |
| (R)-(−)-Carvone        | *Mentha x villosa* (Lamiaceae)     | Leaf infusion (MeOH)                                       | KCl in guinea pig ileum                         | IC     | [27]      |
| (R,R,R)-Carvone-1,2-oxide| *Mentha x villosa* (Lamiaceae)     | Leaf infusion (MeOH)                                       | KCl in guinea pig ileum                         | IC     | [27]      |
| (S)-(−)-Carvone        | *Mentha x villosa* (Lamiaceae)     | Leaf infusion (MeOH)                                       | KCl in guinea pig ileum                         | IC     | [27]      |
| Ocimum gratissimum     | (Lamiaceae)                       | Leaf infusion (MeOH)                                       | ACh, KCl in guinea pig ileum                    | IC     | [34]      |
| Nepeta cataria         | (Lamiaceae)                       | Leaf infusion (Aqueous)                                    | Carbachol, KCl in guinea pig trachea and rabbit jejunum | EO     | [22]      |
| *Casimiroa pringlei*   | (Rutaceae)                        | Aerial part infusion (Ethyl ether)                         | KCl in rat uterine smooth muscle                | IC     | [33]      |
| Lippia graveolens      | (Verbenaceae)                     | Leaf infusion (Distillation)                               | Carbachol, H in guinea pig ileum                | IC     | [35]      |
| Zingiber roseum       | **Zingiberaceae**                  | Fresh seeds (Hydrodistilled with diethyl ether)            | Carbachol, KCl in rat duodenal smooth muscle     | EO     | [26]      |
| Polimomtha longiflora | (Lamiaceae)                       | Leaves stem infusion (Distillation)                        | Carbachol, H in guinea pig ileum                | IC     | [35]      |
| Thymus vulgaris        | (Lamiaceae)                       | Leaf, stem and flower infusion (MeOH)                     | Spontaneous contraction in rat ileum            | EO     | [36]      |
| Acalypha phleoides     | (Euphorbiaceae)                   | Aerial part infusion [MeOH·CHCl₃ (1:1)]                    | ACh, BaCl₂, KCl in rat trachea and ileum        | IC     | [37]      |
| Thymus vulgaris        | (Lamiaceae)                       | Whole plants (Ethanol)                                    | ACh, BaCl₂, KCl in rat trachea and ileum        | IC     | [29]      |
| Anthemis mauritiana    | (Asteraceae)                      | Flower infusion (Aqueous)                                  | Carbachol, KCl in rabbit jejunal smooth muscle   | EO     | [21]      |
| Compound name      | Species (Family)               | Preparation (Solvent)                          | Model tested                                    | Source | Reference |
|--------------------|--------------------------------|------------------------------------------------|-------------------------------------------------|--------|-----------|
| 26 (±)-Camphor     | *Acalypha phleoides* (Euphorbiaceae) | Aerial part infusion [MeOH-CHCl₃ (1:1)] | ACh, BaCl₂, H, KCl, S in guinea pig ileum and rabbit jejunum | IC     | [29]      |
|                    | *Lippia dulcis* (Verbenaceae)   | Leaf infusion (Steam distillation)            | Carbachol, H in porcine bronchi                 | EO     | [38]      |
|                    | *Anthemis mauritiana* (Asteraceae) | Flower infusion (Aqueous)                    | Carbachol, KCl in rabbit jejunal smooth muscle  | EO     | [21]      |
| 27 (+)-α-Pinene    | *Nepeta cataria* (Lamiaceae)    | Leaf infusion (Aqueous)                      | Carbachol, KCl in guinea pig trachea and rabbit jejunum | EO     | [22]      |
|                    | *Plectranthus barbatus* (Lamiaceae) | Leaf infusion (MeOH)                          | ACh, BaCl₂, H, KCl in guinea pig ileum         | EO     | [17]      |
|                    | *Dissotis rotundifolia* (Melastomataceae) | Leaf infusion (EtOH)                          | Carbachol in mouse intestinal motility          | E      | [39]      |
| 28 (-)-α-Pinene    | *Eucalyptus tereticornis* (Myrtaceae) | Commercial                                  | ACh, KCl in rat trachea                         | EO     | [40]      |
|                    | *Zingiber roseum* (Zingiberaceae) | Fresh seeds (Hydrodistilled with diethyl ether) | Carbachol, KCl in rat duodenal smooth muscle    | EO     | [26]      |
|                    | *Ferula gummosa* (Apioaceae)     | Resin infusion (Hydroalcoholic, ether, MeOH) | ACh, KCl in rat ileum                          | IC     | [41]      |
| 29 (+)-β-Pinene    | *Zingiber officinale* (Zingiberaceae) | Rhizome infusion (MeOH)                      | S in rat ileum                                  | EO     | [24]      |
|                    | *Zingiber roseum* (Zingiberaceae) | Fresh seeds (Hydrodistilled with diethyl ether) | Carbachol, KCl in rat duodenal smooth muscle    | EO     | [26]      |
| 30 Cantleyine      | *Styrchnos trineris* (Loganiaceae) | Root bark (EtOAc)                            | Carbachol, H, KCl in guinea pig trachea         | IC     | [42]      |
| 31 Penstemonoside  | *Parentucellia latifolia* (Scrophulariaceae) | Whole plant infusion (Butanol)               | ACh, CaCl₂, KCl in rat uterus                  | IC     | [43]      |
| 32 Aucubine or aucuboside |
|                    | *Parentucellia latifolia* (Scrophulariaceae) | Whole plant infusion (Butanol)               | ACh, CaCl₂, KCl in rat uterus                  | IC     | [43]      |
| 33 2'-O-Acetylhydrogensteine | *Viburnum prunifolium* (Caprifoliaceae) | Root and stem bark infusion (MeOH)          | Carbachol in rabbit jejenum and guinea pig trachea | E      | [44]      |
| 34 2'-O-trans-p-Coumaroyldihydrogensteine | *Viburnum prunifolium* (Caprifoliaceae) | Root and stem bark infusion (MeOH)          | Carbachol in rabbit jejenum and guinea pig trachea | E      | [44]      |
| 35 2'-O-Acetylpatrinoside | *Viburnum prunifolium* (Caprifoliaceae) | Root and stem bark infusion (MeOH)          | Carbachol in rabbit jejenum and guinea pig trachea | E      | [44]      |
| 36 Patrinoside     | *Viburnum prunifolium* (Caprifoliaceae) | Root and stem bark infusion (MeOH)          | Carbachol in rabbit jejenum and guinea pig trachea | E      | [44]      |
| 37 Valtriate or Valepotriate |
|                    | *Valeriana proceran* (Valerianaceae) | Root infusion (EtOH)                         | BaCl₂, carbachol, KCl in guinea pig ileum and stomach | IC     | [45]      |
| Compound name                  | Species (Family)              | Preparation (Solvent) | Model tested                                                                 | Source | Reference |
|--------------------------------|-------------------------------|-----------------------|-----------------------------------------------------------------------------|--------|-----------|
| Isovaltrate or Isovaltratum     | Valeriana procera (Valerianaceae) | Root infusion (EtOH)  | BaCl₂, carbachol, KCl in guinea pig ileum and stomach                      | IC     | [45]      |
| Epoxygaertneroside             | Morinda morindoides (Rubiaceae) | Leaf infusion (Aqueous) | ACh, KCl in guinea pig ileum                                               | IC     | [46]      |
| Gaertneroside                  | Morinda morindoides (Rubiaceae) | Leaf infusion (Aqueous) | ACh, KCl in guinea pig ileum                                               | IC     | [46]      |
| Catalpinoside or Catapol        | Parentucellia latifolia (Scrophulariaceae) | Whole plant infusion (Butanol) | ACh, CaCl₂, KCl in rat uterus                                              | IC     | [43]      |

**Sesquiterpenes**

| Compound name                  | Species (Family)              | Preparation (Solvent) | Model tested                                                                 | Source | Reference |
|--------------------------------|-------------------------------|-----------------------|-----------------------------------------------------------------------------|--------|-----------|
| 43 (±)-Hernandulcin            | Lippia dulcis (Verbenaceae)   | Leaf infusion (Steam distillation) | Carbachol, H in porcine bronchi                                            | EO     | [38]      |
| 43 Humulene or α-Caryophyllene | Nepeta cataria (Lamiaceae)    | Leaf infusion (Aqueous) | Carbachol, KCl in guinea pig trachea and rabbit jejunum                    | EO     | [22]      |
| 44 β-Caryophyllene epoxide     | Conyza filaginoides (Asteraceae) | Leaf infusion [CHCl₃:MeOH (1:1)] | ACh, KCl in rat tracheal smooth muscle                                      | EO     | [25]      |
|                                | Croton sonderianus (Euphorbiaceae) | Leaf infusion (Steam distillation) | ACh, KCl in rat tracheal smooth muscle                                      | EO     | [25]      |
|                                | Croton sonderianus (Euphorbiaceae) | Leaf infusion (Steam distillation) | ACh, KCl in rat tracheal smooth muscle                                      | EO     | [25]      |
| 45 β-Caryophyllene             | Conyza filaginoides (Asteraceae) | Leaf infusion [CHCl₃:MeOH (1:1)] | Spontaneous contraction in rat ileum                                        | IC     | [47]      |
|                                | Plectranthus barbatus (Lamiaceae) | Leaf infusion (MeOH)   | Spontaneous contraction in rat ileum                                        | IC     | [47]      |
|                                | Pterodon polygalaeiflorus (Fabaceae) | Seed (Steam distillation) | ACh, KCl in rat ileum smooth muscle                                         | IC     | [48]      |
| 46 Bicyclogermacrene or Leptidozene | Croton sonderianus (Euphorbiaceae) | Leaf infusion (Steam distillation) | ACh, KCl in rat tracheal smooth muscle                                      | EO     | [25]      |
| 47 (+)-Capsidiol               | Nicotiana silvestri (Solanaceae) | Leaf infusion (EtOAc)  | ACh, BaCl₂, bradykinin, carbachol in guinea pig ileum and trachea           | IC     | [49]      |
| 48 S-Petasin                   | Petasites formosanus (Compositae) | Aerial parts (EtOH)   | CaCl₂, carbachol, H, KCl in guinea pig trachea                             | IC     | [50]      |
| 49 (+)-Isopetasin              | Petasites formosanus (Compositae) | Aerial parts (EtOH)   | CaCl₂, carbachol, H, KCl in guinea pig trachea                             | IC     | [50]      |
| 50 Valeranone o Jatamansone    | Valeriana procera (Valerianaceae) | Root infusion (EtOH)  | BaCl₂, carbachol, KCl in guinea pig ileum and stomach                      | IC     | [45]      |
| 51 Chamazulene                 | Matricaria recutita (Asteraceae) | Plant infusion (Aqueous) | Human platelet                                                               | E      | [51]      |
| 52 Spathulenol                 | Croton sonderianus (Euphorbiaceae) | Leaf infusion (Steam distillation) | ACh, KCl in rat tracheal smooth muscle                                      | EO     | [25]      |
|                                | Lepechiniaca caulescens (Lamiaceae) | Leaf infusion (Hexane) | KCl in rat uterus                                                           | IC     | [52]      |
| Compound name | Species (Family) | Preparation (Solvent) | Model tested | Source | Reference |
|---------------|------------------|-----------------------|--------------|--------|-----------|
| 53 Cynaropicrin | *Cynara scolymus* (Asteraceae) | Leaf and flower infusion (MeOH 70%) | ACh in guinea pig ileum | IC | [53] |
| 54 Cedrenol | *Anthemis mauritiana* (Asteraceae) | Flower infusion (Aqueous) | Carbachol, KCl in rabbit jejunal smooth muscle | EO | [21] |
| 55 (+)-Bakkenolide A | *Hertia cheirifolia* (Asteraceae) | Aerial parts (MeOH) | ACh, BaCl₂ in rat duodenum | IC | [54] |
| 56 Himachalol | *Cedrus deodara* (Pinaceae) | Wood infusion | ACh, BaCl₂, H, nicotine, S in guinea pig ileum and seminal vesicle, rabbit jejunum and rat uterus | IC | [55] |
| 57 (E)-Damascenone | *Ipomoea pes-caprae* (Convolvulaceae) | Leaf infusion (Aqueous) | H in guinea pig ileal smooth muscle | IC | [56] |
| 58 (-)-Isogermacrene D | *Artemisia vulgaris* (Compositae) | Stem and leaf infusion (Aqueous) | guinea pig ileum | | [57] |
| 59 Ezoalantonin | *Artemisia vulgaris* (Compositae) | Leaf (CHCl₃) | H, PMA, S in guinea pig ileum and trachea | IC | [57] |
| 60 Costunolide | *Radix aucklandiae* (Asteraceae) | Rhizome (MeOH) | ACh, KCl, S in rat jejunum | IC | [58] |
| 61 Dehydrocostus lactone | *Radix aucklandiae* (Asteraceae) | Rhizome (MeOH) | ACh, KCl, S in rat jejunum | IC | [58] |
| **Diterpenes** | | | | | |
| 62 E-Phytol | *Ipomoea pes-caprae* (Convolvulaceae) | Leaf infusion (Aqueous) | H in guinea pig ileal smooth muscle | IC | [56] |
| 63 3α-Angelloyloxy-2α-hydroxy-13,14Z-dehydrocativic acid | *Brickellia paniculata* (Compositae) | Leaf infusion (MeOH) | KCl in rat myometrial tissue | IC | [59] |
| 64 15-Epicyllenin A | *Marrubium globosum* ssp. *libanoticum* (Lamiaceae) | Aerial part infusion (MeOH) | ACh in mouse ileum | IC | [60] |
| 65 Cyllenin A | *Marrubium globosum* ssp. *libanoticum* (Lamiaceae) | Aerial part infusion (MeOH) | ACh in mouse ileum | IC | [60] |
| 66 Marrulibacetal | *Marrubium globosum* ssp. *libanoticum* (Lamiaceae) | Aerial part infusion (MeOH) | ACh in mouse ileum | IC | [60] |
| 67 (13R)-9α,13α-epoxylabda-6β(9(16(15)-diol dilactone | *Marrubium globosum* ssp. *libanoticum* (Lamiaceae) | Aerial part infusion (MeOH) | ACh in mouse ileum | IC | [60] |
| 68 Marrubin | *Marrubium vulgare* (Lamiaceae) | Aerial parts (Aqueous) | KCl in rat aorta | IC | [61] |
| 69 Marrubenol or Marrubiol | *Marrubium vulgare* (Lamiaceae) | Aerial parts (Aqueous) | KCl in rat aorta | IC | [61] |
| Compound name | Species (Family) | Preparation (Solvent) | Model tested | Source | Reference |
|---------------|------------------|-----------------------|--------------|--------|-----------|
| Marrulanic acid | Marrubium globosum ssp. libanoticum (Lamiaceae) | Aerial part infusion (MeOH) | ACh in mouse ileum | KC | [60] |
| Marrulactone | Marrubium globosum ssp. libanoticum (Lamiaceae) | Aerial part infusion (MeOH) | ACh in mouse ileum | KC | [60] |
| (+)-Dehydroabietic acid | Lepechinia acaulescens (Lamiaceae) | Leaf infusion (Hexane) | KC | in rat uterus | IC | [52] |
| 9\(\beta\)-Hydroxydehydroabietyl alcohol | Lepechinia acaulescens (Lamiaceae) | Leaf infusion (Hexane) | KC | in rat uterus | IC | [52] |
| 9\(\alpha\),13\(\alpha\)-Epidioxyabiet-8(14)-en-18-oic acid methyl ester | Lepechinia acaulescens (Lamiaceae) | Leaf infusion (Hexane) | KC | in rat uterus | IC | [52] |
| 4-epi-Hyalic acid | Croton argyrophylloides (Euphorbiaceae) | Bark infusion (MeOH) | ACh, KCl in guinea pig ileum | IC | [62] |
| Pimaradienoic acid or Continentalic acid | Viguiera arenaria (Asteraceae) | Root infusion (CH\(_2\)Cl\(_2\)) | ACh, KCl in rat carotid artery | KC | IC | [63] |
| 8(14),15-Sandaracopimaradiene-7\(\alpha\),18-diol | Tetradenia riparia (Lamiaceae) | Leaf infusion (CHCl\(_3\)) | BaCl\(_2\), HCl, guinea pig ileum | IC | [64] |
| 3,4-Secoisopimara-4(18),7,15-triene-3-oic acid | Salvia cinnabarina (Lamiaceae) | Aerial parts (EtOH) | ACh, BaCl\(_2\), HCl in guinea pig ileum | IC | [65] |
| ent-Kaurenoic acid | Viguiera hypargyrea (Asteraceae) | Root infusion (Hexane) | Spontaneous contraction in guinea pig ileum | IC | [66] |
| | Viguiera hypargyrea (Asteraceae) | Root infusion (Hexane) | Spontaneous contraction in guinea pig ileum | IC | [66] |
| Beyerenic acid or Monogynoic acid | Viguiera hypargyrea (Asteraceae) | Root infusion (Hexane) | Spontaneous contraction in guinea pig ileum | IC | [66] |
| ent-7\(\alpha\)-Acetoxytrachyloban-18-oic acid | Xylopia langsdorfiana (Annonaceae) | Stem infusion (EtOH 95%) | BaCl\(_2\), HCl in guinea pig ileum | IC | [67] |
| ent-7\(\alpha\)-hydroxytrachyloban-18-oic acid | Xylopia langsdorfiana (Annonaceae) | Stem infusion (EtOH 95%) | BaCl\(_2\), HCl in guinea pig ileum | IC | [67] |
| Phorbol 12-acetate-13-tiglate | Croton tiglium (Euphorbiaceae) | Fruit (MeOH) | Spontaneous contraction in rabbit jejunum | E | [68] |
| 3,7,10,14,15-pentaacetyl-5-butanoyl-13,17-epoxy-8-myrsinene | Pycnocyclaspinosa (Umbelliferae) | Aerial parts (MeOH) | KCl in rat ileum | IC | [69] |
| Agapanthagenin 3-O-\(\beta\)-D-glucopyranoside | Allium elburzense (Alliaceae) | Flower and bulb infusion (Hexane) | H in guinea pig ileum | E | [70] |
| Agapanthagenin | Allium elburzense (Alliaceae) | Flower and bulb infusion (Hexane) | H in guinea pig ileum | IC | [70] |
| \(\beta\)-Sisosterol | Eucalyptus camaldulensis (Myrtaceae) | Leaf infusion (EtOAc) | Spontaneous contraction in rabbit jejunum | IC | [71] |
Table 3: Continued.

| Compound name                      | Species (Family)                  | Preparation (Solvent)          | Model tested                                                | Source | Reference |
|------------------------------------|-----------------------------------|--------------------------------|-------------------------------------------------------------|--------|-----------|
| 88 β-sitosterol 3-O-β-D-glucopyranoside | *Eucalyptus camaldulensis* (Myrtaceae) | Leaf infusion (EtOAc)          | KCl, spontaneous contraction in rabbit jejunum              | IC     | [71]      |
| 89 α-Spinastyeryl β-D-glucoside    | *Conyza filaginoides* (Asteraceae) | Leaf infusion [CHCl₃:MeOH (1:1)] | Spontaneous contraction in rat ileum                        | IC     | [47]      |
| 90 Tropeoside B1 and B2            | *Allium cepa* (Alliaceae)         | Bulbs [CHCl₃:MeOH (9:1)]       | ACh, H in guinea pig ileum                                 | IC     | [72]      |
| 91 Tropeoside A1 and A2            | *Allium cepa* (Alliaceae)         | Bulbs [CHCl₃:MeOH (9:1)]       | ACh, H in guinea pig ileum                                 | IC     | [72]      |
| 92 Elburzensoside A1 and A2        | *Allium elburzense* (Alliaceae)   | Flower and bulb infusion (Hexane) | H in guinea pig ileum                                     | IC     | [70]      |
| 93 Elburzensoside C1 and C2        | *Allium elburzense* (Alliaceae)   | Flower and bulb infusion (Hexane) | H in guinea pig ileum                                     | IC     | [70]      |
| 94 Galphimin A                      | *Galphimia glauca* (Malpighiaceae) | Leaf infusion (MeOH)           | Electrical-induced contraction in guinea pig ileum         | IC     | [73]      |
| 95 Galphimin B                      | *Galphimia glauca* (Malpighiaceae) | Leaf infusion (MeOH)           | Electrical-induced contraction in guinea pig ileum         | IC     | [73]      |
| 96 Galphimin C                      | *Galphimia glauca* (Malpighiaceae) | Leaf infusion (MeOH)           | Electrical-induced contraction in guinea pig ileum         | IC     | [73]      |
| 97 Galphimin E                      | *Galphimia glauca* (Malpighiaceae) | Leaf infusion (MeOH)           | Electrical-induced contraction in guinea pig ileum         | IC     | [73]      |
| 98 Galphimin F                      | *Galphimia glauca* (Malpighiaceae) | Leaf infusion (MeOH)           | Electrical-induced contraction in guinea pig ileum         | IC     | [73]      |
| 99 Handianol                        | *Herissanthia tiubae* (Malvaceae)  | Leaf infusion (EtOH)           | Carbachol, H, KCl in guinea pig ileum and trachea, and rat aorta | IC     | [74]      |
| 100 Cycloartanol                    | *Herissanthia tiubae* (Malvaceae)  | Leaf infusion (EtOH)           | Carbachol, H, KCl in guinea pig ileum and trachea, and rat aorta | IC     | [74]      |
| 101 Taraxasteryl acetate            | *Brickellia veronicaefolia* (Malvaceae) | Aerial parts [CH₂Cl₂:MeOH (1:1)] | Gastrointestinal motility test in mouse                     | E      | [75]      |
| 102 Pomolic acid or Benthamic acid or Randialic acid A | *Licania pittieri* (Rosaceae) | Leaf infusion (EtOH)           | Carbachol, KCl in rat aorta                                | IC     | [76]      |
| 103 Ursolic acid                    | *Agastache mexicana* (Lamiaceae)   | Aerial part (MeOH)             | ACh, KCl in guinea pig ileum                               | IC     | [77]      |
| 104 Ehretiolide                     | *Eucalyptus camaldulensis* (Myrtaceae) | Leaf infusion (EtOAc)          | KCl, spontaneous contraction in rabbit jejunum              | IC     | [78]      |
| 105 Ehretiolide acetate             | *Eucalyptus camaldulensis* (Myrtaceae) | Leaf infusion (EtOAc)          | KCl, spontaneous contraction in rabbit jejunum              | IC     | [78]      |
| 106 Camaldulin                      | *Eucalyptus camaldulensis* (Myrtaceae) | Leaf infusion (EtOAc)          | KCl, spontaneous contraction in rabbit jejunum              | IC     | [71]      |
| 107 Zygophyloside N                 | *Zygophyllum gaetulum* (Zygophyllaceae) | Root infusion (MeOH)           | Electrically-induced contractions of isolated guinea pig ileum | E      | [79]      |
| Compound name | Species (Family) | Preparation (Solvent) | Model tested | Source |
|---------------|-----------------|-----------------------|--------------|--------|
| 108 Erythrodiol | *Conyza filaginoides* (Asteraceae) | Leaf infusion [CHCl₃:MeOH (1:1)] | Spontaneous contraction in rat ileum | IC [47] |
| 109 3-β-tridecanoyloxy-28-hydroxyolean-12-ene | *Conyza filaginoides* (Asteraceae) | Leaf infusion [CHCl₃:MeOH (1:1)] | Spontaneous contraction in rat ileum | IC [47] |
| 110 3-β-Hydroxyolean-9(11),12-dien-28-oic acid | *Eucalyptus camaldulensis* (Myrtaceae) | Leaf infusion (EtOAc) | KCl, spontaneous contraction in rabbit ileum | IC [78] |
| 111 4-epi-Hederagenin | *Hedera helix* (Araliaceae) | Leaf infusion (EtOH) | ACh in guinea pig ileum | IC [80] |
| 112 Hederacoside C | *Hedera helix* (Araliaceae) | Leaf infusion (EtOH) | ACh in guinea pig ileum | IC [80] |
| 113 Betulinic acid | *Eucalyptus camaldulensis* (Myrtaceae) | Leaf infusion (EtOAc) | KCl, spontaneous contraction in rabbit ileum | IC [78] |
| 114 α-Amyrin acetate | *Tylophora hirsuta* (Asclepiadaceae) | Aerial parts (MeOH) | KCl in rabbit ileum | IC [81] |
| **Phloroglucinol derivatives** | | | | |
| 115 Hyperforin | *Hypericum perforatum* (Hypericaceae) | Aerial parts (EtOH 70%) | KCl in rabbit ileum | IC [82] |
| 116 Hypericin | *Hypericum perforatum* (Hypericaceae) | Aerial parts (EtOH 70%) | KCl in rabbit ileum | IC [82] |
| **Coumarins** | | | | |
| 117 Scopoletin | *Brunfelsia hopeana* (Solanaceae) | Root infusion (EtOH) | Phenylephrine, KCl, PGF2, serotonin in rat aorta | IC [83] |
| 118 Todannone | *Toddalia asiatica* var. floribunda (Rutaceae) | Aerial parts (EtOH 95%) | ACh, BaCl₂, H, nicotine in guinea pig ileum | IC [84] |
| 119 (2S,3R+)-2-([(3E)-4,8-dimethyl-7-hydroxy-2,3-dimethylfuro[3,2c]coumarin | *Ferula heuffelii* (Apiaceae) | Underground part (CHCl₃) | ACh, KCl in rat ileum | IC [85] |
| 120 Osthole | *Prangos ferulacea* (Apiaceae) | Root (Acetone) | ACh, KCl, electric field stimulation in rat ileum | IC [86] |
| 121 Angelicin | *Heracleum thomsoni* (Apiaceae) | Aerial part infusion (EtOH) | ACh, BaCl₂, H, S in cat ureter, guinea pig bile duct and trachea, monkey gall bladder, rabbit jejunum, and rat uterus | IC [87] |
| 122 Glycycoumarin | *Glycyrrhiza radix* (Leguminosae) | Root infusion (Aqueous) | A23187, BaCl₂, carbachol, KCl in mouse jejunum | IC [88] |
| | *Glycyrrhiza uralensis* (Leguminosae) | Root infusion (Aqueous) | Carbachol in mouse jejunum | E [89] |
| Compound name | Species (Family) | Preparation (Solvent) | Model tested | Source | Reference |
|---------------|------------------|-----------------------|--------------|--------|-----------|
| Chalcones     |                  |                       |              |        |           |
| 123 Davidigenin | *Mascarenhasia arborescens* (Apocynaceae) | Leaf and stem infusion (MeOH) | ACh, H in guinea pig and rat duodenum | IC | [90] |
| 124 Isoliquiritigenin | *Glycyrrhiza glabra* (Leguminosae) | Root infusion (Aqueous) | ACh, KCl, O, spontaneous contraction in rat uterus | IC | [91] |
|               | *Glycyrrhiza ularensis* (Leguminosae) | Root infusion (Aqueous) | BaCl₂, carbachol, KCl in mouse jejunum, ileum and rectum | IC | [92] |
| 125 Licochalcone A | *Glycyrrhiza inflata* (Leguminosae) | Root infusion (Aqueous) | ACh, KCl, BaCl₂, carbachol, KCl in mouse jejunum | IC | [93] |
| Flavonoids    |                  |                       |              |        |           |
| 126 (-)-Pinostrobin | *Conyza filaginoides* (Asteraceae) | Leaf infusion [CHCl₃:MeOH (1:1)] | Spontaneous contraction in rat ileum | IC | [47] |
| 127 (-)-(S)-Sakuranetin | *Dodonaeaviscosa* (Sapindaceae) | Leaf infusion [CHCl₃:MeOH (1:1)] | ACh, BaCl₂, H in rat uterus | IC | [94] |
| 128 (±)-Sternbin | *Artemisia monosperma* (Compositae) | Aerial part (EtOH) | ACh, O in rat ileum, pulmonary artery, urinary bladder, trachea, and uterus | IC | [95] |
| 129 Ouratea catechin | *Maytenus rigida* (Celastraceae) | Stem bark (EtOH) | BaCl₂, carbachol, KCl, H in guinea pig ileum | IC | [96] |
| 130 Apegenin | *Achillea millefolium* (Asteraceae) | Whole plant infusion (MeOH 40%) | ACh, CaCl₂, H, PE, S in rat ileum | IC | [97] |
| 131 Buddleolavonol or Linarinigenin | *Achillea millefolium* (Asteraceae) | Aerial part (MeOH 40%) | ACh, KCl in guinea pig ileum | IC | [97] |
| 132 Luteolin | *Achillea millefolium* (Asteraceae) | Aerial parts (Aqueous) | KCl, PE, S in rat aorta | E | [98] |
|               | *Artemisia copa* (Compositae) | Aerial part (EtOH) | ACh, BaCl₂, H, KCl in guinea pig ileum and trachea | IC | [99] |
|               | *Plantago lanceolata* (Plantaginaceae) | Leaf and flower (EtOH) | ACh, BaCl₂, carbachol, KCl in guinea pig ileum and trachea, and rat vas deferens | IC | [100] |
| 133 Scutellarein 6-β-D-glucoside (isovitexin) | *Aloysia citridora* (Verbenaceae) | Leaf infusion (Aqueous) | ACh, CaCl₂, KCl in rat duodenum | IC | [101] |
| Compound name | Species (Family) | Preparation (Solvent) | Model tested | Source | Reference |
|---------------|-----------------|-----------------------|--------------|--------|-----------|
| 134 Vitexin   | Aloysia citridora (Verbenaceae) | Leaf infusion (Aqueous) | ACh, CaCl₂, KCl in rat duodenum | IC | [101] |
| 135 Xanthomyrcrol | Brickellia paniculata (Compositae) | Leaf infusion (MeOH) | KCl, O in rat uterus | IC | [59] |
| 136 Demethoxycentaureidin | Piptadenia stipulacea (Leguminosae) | Aerial parts, (CHCl₃) | Carbachol, H, O, in guinea pig ileum and trachea, rat aorta and uterus | IC | [103] |
| 137 Gnaphaliin B | Gnaphalium liebmannii (Asteraceae) | Aerial parts (Hexane) | ACh, carbachol in guinea pig trachea | IC | [104] |
| 138 Kaempferol or Kaempherol | Hedera helix (Araliaceae) | Aerial parts (EtOH 30%) | ACh in guinea pig ileum | IC | [80] |
| 139 Gnaphaliin A | Gnaphalium liebmannii (Asteraceae) | Aerial parts (Hexane) | ACh, carbachol in guinea pig ileum | IC | [104] |
| 140 Quercetin | Achillea millefolium (Asteraceae) | Whole plant infusion (MeOH 40%) | ACh, CaCl₂, H, PE, serotonin in rat ileum | IC | [97] |
| 141 3-O-Methylquercetin | Rhamnus nakaharai (Rhamnaceae) | Stem bark (not reported) | Carbachol, H, KCl in guinea pig trachea | IC | [108] |
| 142 3,4′-Dimethylquercetin | Artemisia abrotanum (Asteraceae) | Aerial part (MeOH 67%) | Carbachol in guinea pig trachea | IC | [109] |
| 143 3,7-Dimethylquercetin | Artemisia abrotanum (Asteraceae) | Aerial part (MeOH 67%) | Carbachol in guinea pig trachea | IC | [109] |
| 144 Isoquercetin | Conyza ficaginoides (Asteraceae) | Leaf infusion [CHCl₃:MeOH (1:1)] | Spontaneous contraction in rat ileum | IC | [47] |
|               | Hedera helix (Araliaceae) | Aerial parts (EtOH 30%) | ACh in guinea pig ileum | IC | [80] |
|               | Drosera rotundifolia (Droseraceae) | Aerial parts (EtOH 70%) | Carbachol in guinea pig ileum | IC | [107] |
|               | Drosera rotundifolia (Droseraceae) | Aerial parts (EtOH 70%) | Carbachol in guinea pig ileum | IC | [107] |
|               | Drosera rotundifolia (Droseraceae) | Leaf extract (EtOH 70%) | Carbachol, H, PGF₂ in guinea pig ileum and trachea | IC | [106] |
|               | Drosera rotundifolia (Droseraceae) | Leaf extract (MeOH) | Peristalsis in guinea pig ileum | IC | [105] |
| Compound name | Species (Family) | Preparation (Solvent) | Model tested | Source | Reference |
|---------------|-----------------|-----------------------|--------------|--------|-----------|
| 145 Quercetin 3-α-rhamnoside or Quercitroside | *Psidium guajava* (Myrtaceae) | Leaf extract (MeOH) | Peristalsis in guinea pig ileum | IC | [105] |
| | *Morinda morindoides* (Rubiaceae) | Leaf extract (Aqueous) | ACh, KCl in guinea pig ileum | IC | [46] |
| 146 Quercetin 3-O-β-L-arabinoside | *Psidium guajava* (Myrtaceae) | Leaf extract (MeOH) | Peristalsis in guinea pig ileum | IC | [105] |
| 147 Quercetin 3-O-β-D-galactoside | *Psidium guajava* (Myrtaceae) | Leaf extract (MeOH) | Peristalsis in guinea pig ileum | IC | [105] |
| 148 Quercetin 3-O-β-gentiobioside | *Morinda morindoides* (Rubiaceae) | Leaf extract (Aqueous) | ACh, KCl in guinea pig ileum | IC | [46] |
| | *Drosera madaseriensis* (Droseraceae) | Leaf extract (EtOH 70%) | Carbachol, H, PGE2 in guinea pig ileum and trachea | IC | [106] |
| 149 Centaureidin | *Artemisia abrotanum* (Asteraceae) | Aerial part (MeOH 67%) | Carbachol in guinea pig ileum | IC | [109] |
| 150 Casticin or Vitexicarpin | *Artemisia abrotanum* (Asteraceae) | Aerial part (MeOH 67%) | Carbachol in guinea pig trachea | IC | [109] |
| 151 Prunetol or Sophoricol | *Genista tridentata* (Papilionaceae) | Not reported | AC, electric field stimulation, 6-oxo PGE1 in guinea pig ileum | IC | [110] |
| 152 Boeravinone E | *Boerhaavia diffusa* (Nyctaginaceae) | Root infusion (MeOH) | ACh in guinea pig ileum | IC | [111] |
| 153 4,6,11-trihydroxy-9-methoxy-10-methyl-6,12-dihydro-5,7-dioxatetraphen-12-one | *Boerhaavia diffusa* (Nyctaginaceae) | Root infusion (MeOH) | ACh in guinea pig ileum | IC | [111] |
| 154 Boeravinone G | *Garcinia buchananii* (Clusiaceae) | Stem bark (EtOH 70%) | Bay K 8644 in mouse ileum | IC | [112] |
| 155 (2R,3S,2"R,3"R)-Manniflavonone | *Hypericum perforatum* (Hypericaceae) | Aerial parts (EtOH 70%) | KCl in rabbit jejunum | IC | [82] |
| 156 Hyperoside | *Artemisia capa* (Compositae) | Aerial parts (Aqueous) | KCl, PE, S in rat aorta | E | [98] |
| 157 Chrysoeriol | *Aspalathus linearis* (Fabaceae) | Commercial (Aqueous) | KCl in rabbit jejunum | IC | [102] |
| 158 Spinacetin | *Artemisia capa* (Compositae) | Aerial parts (Aqueous) | KCl, PE, S in rat aorta | E | [98] |
| 159 Vicenin 2 | *Perilla frutescens* (Lamiaceae) | Commercial (Aqueous) | ACh, BaCl2 in rat ileum | IC | [113] |
| 160 Orientin | *Aspalathus linearis* (Fabaceae) | Commercial (Aqueous) | KCl in rabbit jejunum | IC | [102] |
### Table 3: Continued.

| Compound name                          | Species (Family)                      | Preparation (Solvent)           | Model tested                  | Source | Reference |
|----------------------------------------|---------------------------------------|---------------------------------|-------------------------------|--------|-----------|
| Phenylmetanoids                        |                                       |                                 |                               |        |           |
| Phenylmetanoids                         |                                       |                                 |                               |        |           |
| 161 Salicylic acid methyl ether        | Brickellia veronicaefolia (Asteraceae) | Aerial parts [CH$_2$Cl$_2$:MeOH (1:1)] | Gastrointestinal motility test in mouse | E      | [75]      |
| 162 O-Anisic acid or 6-Methoxysalicylic acid | Brickellia veronicaefolia (Asteraceae) | Aerial parts [CH$_2$Cl$_2$:MeOH (1:1)] | Gastrointestinal motility test in mouse | E      | [75]      |
| 163 Protocatechuc acid                  | Heder a  helix (Araliaceae)            | Aerial parts (EtOH 30%)         | ACh in guinea pig ileum       | IC     | [80]      |
| 164 Benzyl 2,5-dimethoxybenzoate       | Brickellia veronicaefolia (Asteraceae) | Aerial parts [CH$_2$Cl$_2$:MeOH (1:1)] | Gastrointestinal motility test in mouse | E      | [75]      |
| Phenylethanoids                        |                                       |                                 |                               |        |           |
| Phenylethanoids                        |                                       |                                 |                               |        |           |
| 165 O-Methylbalsamide                  | Zanthoxylum hyemale (Rutaceae)         | Stem bark infusion (EtOH)       | ACh, BaCl$_2$ in rat ileum    | IC     | [114]     |
| 166 (-)-Tembamide                      | Zanthoxylum hyemale (Rutaceae)         | Stem bark infusion (EtOH)       | ACh, BaCl$_2$ in rat ileum    | IC     | [114]     |
| 167 O-Methyltembamide                  | Zanthoxylum hyemale (Rutaceae)         | Steam bark infusion (EtOH)      | ACh, BaCl$_2$ in rat ileum    | IC     | [114]     |
| Phenylpropanoids                       |                                       |                                 |                               |        |           |
| Phenylpropanoids                       |                                       |                                 |                               |        |           |
| 168 Eugenol                            | Ocimum gratissimum (Lamiaceae)         | Not reported                     | ACh, KCl in guinea pig ileum  | EO     | [34]      |
| 169 Rosemaric acid or Rosemary acid or trans-Rosmarinic acid | Thymus vulgaris (Lamiaceae) | Commercial                      | KCl in rat trachea            | IC     | [100]     |
|                          | Hedera helix (Araliaceae)              |                                 |                               |        |           |
|                          | Hedera helix (Araliaceae)              |                                 |                               |        |           |
|                          | Hedera helix (Araliaceae)              |                                 |                               |        |           |
| 170 trans-Chlorogenic acid             | Hedera helix (Araliaceae)              | Aerial parts (EtOH 30%)         | ACh in guinea pig ileum       | IC     | [80]      |
| 171 cis-Chlorogenic acid               | Hedera helix (Araliaceae)              | Aerial parts (EtOH 30%)         | ACh in guinea pig ileum       | IC     | [80]      |
| 172 3,5-Dicaffeoylquininic acid        | Hedera helix (Araliaceae)              | Aerial parts (EtOH 30%)         | ACh in guinea pig ileum       | IC     | [80]      |
| 173 Verbascoside                       | Plantago lanceolata (Plantaginaceae)   | Aerial part infusion (EtOH 20%) | ACh, BaCl$_2$, H, KCl in guinea pig ileum and trachea | E      | [99]      |
| 174 Isoacteoside or Isoverbascoside    | Plantago lanceolata (Plantaginaceae)   | Aerial part infusion (EtOH 20%) | ACh, BaCl$_2$, H, KCl in guinea pig ileum and trachea | E      | [99]      |
| 175 Plantamajoside or Plantamoside or Purpureaside A | Plantago lanceolata (Plantaginaceae) | Aerial part infusion (EtOH 20%) | ACh, BaCl$_2$, H, KCl in guinea pig ileum and trachea | E      | [99]      |
| 176 Lavandulifolioside                 | Plantago lanceolata (Plantaginaceae)   | Aerial part infusion (EtOH 20%) | ACh, BaCl$_2$, H, KCl in guinea pig ileum and trachea | E      | [99]      |
| 177 Echinacoside                       | Cistanche tubulosa (Orobanchaceae)     | No reported (EtOH)              | KCl, PE in rat aorta          | IC     | [115]     |
| 178 Schisandrin A or Wuweizisu A       | Schisandra chinensis (Schisandraceae)  | Academic                        | Spontaneous contractions in rat colon | IC     | [116]     |
| Compound name | Species (Family) | Preparation (Solvent) | Model tested | Source | Reference |
|---------------|-----------------|-----------------------|--------------|--------|-----------|
| Schisandrin B or Wuweizisu B | *Schisandra chinensis* (Schisandraceae) | Fruit decoction (Aqueous) | ACh, KCl, S in guinea pig ileum | IC | [117] |
| Schisandrol B | *Schisandra chinensis* (Schisandraceae) | Fruit decoction (Aqueous) | ACh, KCl, S in guinea pig ileum | IC | [117] |
| Stilbenoids | | | | |
| Aloifol II or Dendrophenol or Moscatilin | *Nidema boothii* (Orchidaceae) | Whole plant infusion | Spontaneous contraction in guinea pig ileum | IC | [118] |
| Batatasin III | *Scaphyglottis livida* (Orchidaceae) | Whole plant infusion | ACh, BaCl$_2$, H in rat ileum | IC | [119] |
| 4-[2-(3-hydroxy-5-methoxyphenyl)ethyl]-2-methoxyphenol | *Scaphyglottis livida* (Orchidaceae) | Whole plant infusion | ACh, BaCl$_2$, H in rat ileum | IC | [119] |
| Gigantol | *Nidema boothii* (Orchidaceae) | Whole plant infusion | Spontaneous contraction in guinea pig ileum | IC | [118] |
| Coelonin | *Scaphyglottis livida* (Orchidaceae) | Whole plant infusion | ACh, BaCl$_2$, H in rat ileum | IC | [119] |
| Erianthridin | *Maxillaria densa* (Orchidaceae) | Whole plant infusion | ACh, BaCl$_2$, H in rat ileum | IC | [120] |
| Ephemeranthoquinone | *Nidema boothii* (Orchidaceae) | Whole plant infusion | Spontaneous contraction in guinea pig ileum | IC | [118] |
| Nudol | *Scaphyglottis livida* (Orchidaceae) | Whole plant infusion | ACh, BaCl$_2$, H in rat ileum | IC | [120] |
| 3,4- dimethoxyphenanthrene-2,5-diol | *Maxillaria densa* (Orchidaceae) | Whole plant infusion | ACh, BaCl$_2$, H in rat ileum | IC | [120] |
| 3,4- dimethoxyphenanthrene-2,5-diol | *Maxillaria densa* (Orchidaceae) | Whole plant infusion | ACh, BaCl$_2$, H in rat ileum | IC | [120] |
| 3,4- dimethoxyphenanthrene-2,5-diol | *Scaphyglottis livida* (Orchidaceae) | Whole plant infusion | ACh, BaCl$_2$, H in rat ileum | IC | [120] |
| Gymnopusin | *Maxillaria densa* (Orchidaceae) | Whole plant infusion | ACh, BaCl$_2$, H in rat ileum | IC | [120] |
| Fimbriol A | *Maxillaria densa* (Orchidaceae) | Whole plant infusion | ACh, BaCl$_2$, H in rat ileum | IC | [120] |
| Curcumoid | | | | |
| Curcuminoid | | | | |
| Benzofurans and Related | | | | |
| Compound name | Species (Family) | Preparation (Solvent) | Model tested | Source | Reference |
|---------------|------------------|-----------------------|--------------|--------|-----------|
| 197 Ligustilide A or cis-Ligustilide | *Ligusticum wallichii* (Umbelliferae) | Rhizome (hydrodistillation) | CaCl<sub>2</sub>, KCl in rat aorta | EO | [123] |
| 198 12-acetoxytremetone | *Helichrysum italicum* ssp. *italicum* (Asteraceae) | Flowers (EtOH) | ACh, BaCl<sub>2</sub> in mouse ileum | IC | [124] |
| 199 1-[(2R)-2-(3-hydroxyprop-1-en-2-yl)-2,3-dihydro-1-benzofuran-5-yl]ethan-1-one | *Helichrysum italicum* ssp. *italicum* (Asteraceae) | Flowers (EtOH) | ACh, BaCl<sub>2</sub> in mouse ileum | IC | [124] |
| Alkaloids | | | | | |
| 200 Indicaxanthin | *Opuntia ficus indica* (Cactaceae) | Fruit pulp infusion (Aqueous) | Carbachol, KCl in mouse ileum | IC | [125] |
| 201 Papaverine | *Daucus carota* (Apiaceae) | Seed infusion (MeOH 90%) | ACh, BaCl<sub>2</sub>, H, KCl, S, O in dog trachea, guinea pig, rabbit, rat ilea, rat uterus | IC | [126] |
| 202 Higenamine | *Nandina domestica* (Berberidaceae) | Fruit (Aqueous) | ACh, H, KCl in guinea pig trachea | IC | [127] |
| 203 Atherospermine | *Fissistigma glaucescens* (Annonaceae) | Bark (MeOH) | Carbachol, KCl, LTC4, PGF2α, U46619 in guinea pig trachea | IC | [128] |
| 204 (+)-Domestine or (+)-Nantenine | *Platyacanthus spicata* (Pumariaceae) | Academic supplier | BaCl<sub>2</sub>, CaCl<sub>2</sub>, KCl, PE, S in rat aorta and atria | IC | [129] |
| 205 10-Methylacridone | *Citrus deliciosa* (Rutaceae) | Root juice (MeOH) | Rabbit ileum | IC | [130] |
| 206 Spermatheridine or liriodenin | *Fissistigma glaucescens* (Annonaceae) | Leaf infusion (MeOH) | Carbachol in canine trachea | IC | [131] |
| 207 Citpressine I | *Citrus deliciosa* (Rutaceae) | Root juice (MeOH) | Rabbit ileum | IC | [130] |
| 208 Jatrorhizine or Neprotine | *Berberis aristata* (Berberidaceae) | Institutional supplier | ACh, S, spontaneous contractions in rat ileum | IC | [132] |
| 209 Coptisine | *Coptis chinensis* (Ranunculaceae) | Rhizoma (EtOH 70%) | ACh in guinea pig ileum | IC | [133] |
| 210 Escholine or Thalictrine | *Mahonia aquifolium* (Berberidaceae) | Cortex and fruit infusion | KCl, PE in rat aorta | IC | [134] |
| 211 (+)-Isothebaine | *Mahonia aquifolium* (Berberidaceae) | Cortex and fruit infusion | KCl, PE in rat aorta | IC | [134] |
| 212 (+)-Corytuberine | *Mahonia aquifolium* (Berberidaceae) | Cortex and fruit infusion | KCl, PE in rat aorta | IC | [134] |
| 213 (+)-Isocorydine or Luteanine | *Mahonia aquifolium* (Berberidaceae) | Cortex and fruit infusion | KCl, PE in rat aorta | IC | [134] |
| 214 (+)-Chelidonine or Stylphorine | *Chelidonium majus* (Papaveraceae) | Commercial supplier | BaCl<sub>2</sub>, carbachol in guinea pig ileum | IC | [135] |
| Compound name                                      | Species (Family)                      | Preparation (Solvent)               | Model tested                     | Source | Reference |
|----------------------------------------------------|--------------------------------------|------------------------------------|-----------------------------------|--------|-----------|
| 215 (-)-8beta-(4'-hydroxybenzyl)-2,3-dimethoxyberbin-10-ol | *Aristolochia constricta* (Aristolochiaceae) | Aerial part infusion (MeOH)         | ACh, electrical contraction, H in guinea pig ileum | IC     | [136]     |
| 216 3-O-methylconstrictosine                       | *Aristolochia constricta* (Aristolochiaceae) | Aerial part infusion (MeOH)         | ACh, electrical contraction, H in guinea pig ileum | IC     | [136]     |
| 217 3,5-di-O-methylconstrictosine                  | *Aristolochia constricta* (Aristolochiaceae) | Aerial part infusion (MeOH)         | ACh, electrical contraction, H in guinea pig ileum | IC     | [136]     |
| 218 5,6-dihydro-3,5-di-O-methylconstrictosine      | *Aristolochia constricta* (Aristolochiaceae) | Aerial part infusion (MeOH)         | ACh, electrical contraction, H in guinea pig ileum | IC     | [136]     |
| 219 5,6-dihydroconstrictosine                      | *Aristolochia constricta* (Aristolochiaceae) | Aerial part infusion (MeOH)         | ACh, electrical contraction, H in guinea pig ileum | IC     | [136]     |
| 220 Constrictosine                                 | *Aristolochia constricta* (Aristolochiaceae) | Aerial part infusion (MeOH)         | ACh, electrical contraction, H in guinea pig ileum | IC     | [136]     |
| 221 Isojuripidine                                  | *Solanum asterophorum* (Solanaceae)    | Leaf infusion (MeOH)                | ACh, CaCl₂, H in guinea pig ileum | IC     | [137]     |
| 222 Sarcodine                                      | *Sarcococca saligna* (Buxaceae)        | Whole plant (MeOH)                 | ACh, KCl in guinea pig ileum, rat stomach fundus, rabbit jejunum | IC     | [138]     |
| 223 Saracorine or Sarcorine                        | *Sarcococca saligna* (Buxaceae)        | Whole plant infusion (MeOH)         | ACh, KCl in rabbit jejunum         | IC     | [139]     |
| 224 Saracocine                                     | *Sarcococca saligna* (Buxaceae)        | Whole plant (MeOH)                 | ACh, KCl in guinea pig ileum, rat stomach fundus, rabbit jejunum | IC     | [138]     |
| 225 Alkaloid C                                     | *Sarcococca saligna* (Buxaceae)        | Whole plant (MeOH)                 | ACh, KCl in guinea pig ileum, rat stomach fundus, rabbit jejunum | IC     | [138]     |
| 226 (-)-Pachyaximine A                             | *Sarcococca saligna* (Buxaceae)        | Whole plant infusion (MeOH)         | ACh, KCl in rabbit jejunum, KCl    | IC     | [139]     |
| 227 (-)-(R)-Geibalansine or (-)-R-Geibalansine     | *Zanthoxylum hyemale* (Rutaceae)       | Stem bark infusion (EtOH)           | ACh, BaCl₂ in rat ileum            | IC     | [114]     |
| 228 Hyemaline                                      | *Zanthoxylum hyemale* (Rutaceae)       | Stem bark infusion (EtOH)           | ACh, BaCl₂ in rat ileum            | IC     | [114]     |
| 229 Theophylline                                   | *Fisistigma glaucescens* (Annonaceae)  | Leaf infusion (MeOH)                | Carbachol in canine trachea        | IC     | [131]     |
| 230 Carboxyscotangamine A                          | *Scopolia tanguatica* (Solanaceae)     | Root (95% EtOH)                    | Carbachol in Chinese hamster ovarian cell | IC     | [140]     |
| 231 Scotanamine A                                  | *Scopolia tanguatica* (Solanaceae)     | Root (95% EtOH)                    | Carbachol in Chinese hamster ovarian cell | IC     | [140]     |
| 232 Piperine                                       | *Piper nigrum* (Piperaceae)            | Fruit (EtOH)                       | Ileum loop in mice                 | IC     | [141]     |
| Amines                                             | *Scopolia tanguatica* (Solanaceae)     | Root (95% EtOH)                    | Carbachol in Chinese hamster ovarian cell | IC     | [123]     |
### Table 3: Continued.

| Compound name                      | Species (Family)                             | Preparation (Solvent)               | Model tested                                | Source | Reference |
|------------------------------------|----------------------------------------------|-------------------------------------|---------------------------------------------|--------|-----------|
| 234 Scotanamine C                  | *Scopolia tanguica* (Solanaceae)            | Root (95% EtOH)                    | Carbachol in Chinese hamster ovarian cell   | IC     | [140]     |
| 235 Scotanamine D                  | *Scopolia tanguica* (Solanaceae)            | Root (95% EtOH)                    | Carbachol in Chinese hamster ovarian cell   | IC     | [140]     |
| 236 N\(^1\)-Caffeoyl-N\(^3\)-dihydrocaffeoylspermidine | *Scopolia tanguica* (Solanaceae) | Root (95% EtOH)                    | Carbachol in Chinese hamster ovarian cell   | IC     | [140]     |
| 237 N\(^1\), N\(^{10}\)-Bis(dihydrocaffeoyl)spermidine | *Scopolia tanguica* (Solanaceae) | Root (95% EtOH)                    | Carbachol in Chinese hamster ovarian cell   | IC     | [140]     |
| 238 Caffeoylputrescine              | *Scopolia tanguica* (Solanaceae)            | Root (95% EtOH)                    | Carbachol in Chinese hamster ovarian cell   | IC     | [140]     |
|                                    | *Cruciferous vegetables* (Brassicaceae)     | Commercial source                  | ACh, electrical contraction in mouse ileum | IC     | [142]     |
| 240 (3E)-4-(3,4-dimethoxyphenyl)but-3-en-1-ol | *Zingiber cassumunar* (Zingiberaceae)       | Chemically synthesized             | O in rat uterus                             | IC     | [143]     |
|                                    | *Ruta chalepensis* (Rutaceae)               | Leaf (EtOH 70%)                    | KCl in rat ileum                           | E      | [144]     |
| 243 2-Tridecanone                  | *Ruta chalepensis* (Rutaceae)               | Leaf (EtOH 70%)                    | KCl in rat ileum                           | E      | [144]     |
| 244 Latifolone                     | *Ferula heuffelii* (Apiaceae)               | Underground part (CHCl\(_3\))     | ACh, KCl in rat ileum                      | IC     | [85]      |
| 245 Dshamirone                     | *Ferula heuffelii* (Apiaceae)               | Underground part (CHCl\(_3\))     | ACh, KCl in rat ileum                      | IC     | [85]      |
| 246 6-(4-hydroxy-3-methoxyphenyl)hexanonic acid (HMPHA) | *Pycnophylla spinosa* (Umbelliferae)  | Aerial parts (MeOH)                | KCl in rat ileum                           | IC     | [145]     |
| 247 Isovanillin                    | *Pycnophylla spinosa* (Umbelliferae)        | Aerial parts (MeOH)                | KCl in rat ileum                           | IC     | [146]     |
| 248 Iso-acetovanillon              | *Pycnophylla spinosa* (Umbelliferae)        | Aerial parts (MeOH)                | KCl in rat ileum                           | IC     | [146]     |

IC = isolated compound, E = extract, EO = essential oil, ACh = acetylcholine, O = oxytocin, PMA = β-Phenylethyl amine, PGF = Prostaglandin F2α, H = histamine, S = serotonin.
Table 4: Synthetic antispasmodic compounds used in medicine.

| Synthetic compound | Receptor targeted | Main use |
|--------------------|-------------------|----------|
| **Alkaloids**       |                   |          |
| Chlorzoxazone       | Prevents release of histamine | Muscular spasm |
| Pancuronium         | Nicotinic acetylcholine | Muscle relaxant |
| Riluzole            | Sodium channels    | Amyotrophic lateral sclerosis |
| Rocuronium          | Antagonist of neuromuscular junction | Muscle relaxant and anaesthesia |
| Tizanidine          | α₃ adrenergic agonist | Muscle relaxant |
| Vecuronium          | Nicotinic acetylcholine | Muscle relaxant and anaesthesia |
| **Curcuminoïds**    |                   |          |
| Atracurium          | Nicotinic acetylcholine | Muscle relaxant and anaesthesia |
| Cisatracurium       | Nicotinic acetylcholine | Muscle relaxant and anaesthesia |
| Mivacurium          | Nicotinic acetylcholine | Muscle relaxant and anaesthesia |
| **Methylpropanoid** |                   |          |
| Diazepam            | GABA_A            | Anxiety, alcohol withdrawal syndrome, muscle spasms, seizures, and restless legs syndrome |
| Prograbide          | GABA_A+B          | Epilepsy |
| Orphenadrine        |                   | Skeletal muscle relaxant that is used for the treatment of acute muscle aches, pain, or spasms. |
| **Phenylpropanoids**|                   |          |
| Baclofen            | GABA_B            | Spinal cord injury, cerebral palsy, and multiple sclerosis |
| Idrocilamide        | Prevents release of intracellular Ca²⁺ | Skeletal muscle relaxant and muscular pain |

enzymes (S9 microsomal fraction) is used to mimic the metabolites that will be produced in the liver [184]. Few studies have been performed to determine the mutagenicity of natural products with antispasmodic activity. For example, the flavonoids quercetin and luteolin were tested using the Ames method and the appearance of point mutations in four of the tested bacterial strains was shown [185]. In another study, the extracts of the plants *Brickellia veronicaefolia*, *Gnaphalium* sp., *Poliomintha longiflora*, and *Valeriana procera* were studied. Compounds isolated from these plants are listed as antispasmodic compounds (Table 3). Results of the mutagenicity test indicated that *Gnaphalium* sp., *Poliomintha longiflora* (used in the Mexican cuisine and as a traditional medicine), and *Valeriana procera* induced mutagenesis in the tested bacterial strain [186].

8. Chemical Similarities between Natural and Synthetic Antispasmodic Compounds

To determine whether or not there is an analogy between synthetic (Table 4) and natural antispasmodic compounds, the structures of both groups were compared. Results showed that no similarities were found except for alkaloids, amines, and amino acids.

One of the main differences is that commercial alkaloids are methylated in their nitrogen to make them positive, increasing their solubilities because of salt formation. In contrast, natural products have no positive nitrogen, rendering the molecule neutral and pH dependent. Thus, the compound may or may not be protonated, resulting in a change in its solubility and consequently a change on the targeting tissues.

The comparison can perhaps be focused on the distribution of charges rather than by functional groups or families of compounds, emphasizing the electron distribution. For example, a physical characterization such as the heat of formation, the surface electrostatic potential, the molecular weight, the surface tension, the refractive index, the lipophilicity, and others has been used to characterize the structure-activity relationship of alkaloids extracted from the Amaryllidaceae family [187]. These alkaloids were selected because of their ability to inhibit the effect of the acetylcholinesterase enzyme.

Of special interest is the natural compound salvinorin A isolated from the Mexican hallucinogenic *Salvia divinorum* (Lamiaceae) used in the traditional medicine as an antidiarrheal. It has been reported that this compound inhibited the intestinal motility through the activation of other receptors such as κ-opioid receptors (KORs). Upon inflammation of the gut, the cannabinoid C, B₁, and KOR receptors are upregulated. It appears that salvinorin A interacts in the cross-talk between these receptors with a reduction of the inflammation as demonstrated in murine and guinea pig models [188, 189].

Analysis of the similarities between synthetic and natural antispasmodic structures is depicted in Table 5.

9. Conclusions

A large number of natural products with antispasmodic activities have been reported. Although the use of plants in traditional medicine is still relevant, it is necessary to perform new studies to elucidate the mechanism of action.
| Synthetic          | Natural          |
|--------------------|------------------|
| Chlorzoxazone      | Theophylline     |
| Cl                 |                 |
|                    |                 |
| Riluzole           | Butylphthalide   |
| F                  |                 |
| O                  |                 |
| S                  | cis-Butylidenephthalide |
| NH₂                |                 |
|                    |                 |
| Pancuronium        | Isojuripidine    |
|                    |                 |
| Rocuronium         | Sarcodine        |
|                    |                 |
of antispasmodics. Moreover, more information about cytotoxicity and mutagenesis should be explored to ensure that these compounds are safe for consumption. The findings of this study corroborated the need for safety studies on plants extensively used for primary health care in countries such as Mexico. Such studies must be carried out before continuing with the widespread use of some species, which may provoke long-term and irreversible damage.

**Conflicts of Interest**

The authors declare no conflicts of interest.

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**Supplementary Materials**

This file contains the structures of the compounds described in the main text. (Supplementary Materials)

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