



Effect of *Zingiber officinale* on Spasm

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Abstract – Zingiberaceae is one of the largest plant families consisting of rhizomes that are commonly used as spice in soups and curries as well as alternative medications in folklore medicine. *Zingiber officinale* or commonly known as ginger is extensively employed in Asian, Ayurvedic, Chinese, and Arabian folklore medicine for the treatment of pain, inflammation and various spasm-associated gastric ailments. The past few decades saw rapid advancements in the extraction process of ginger bioactive constituents and validation of their corresponding pharmacodynamic and pharmacotherapeutic activities, and biological properties *in vivo* and *in vitro*. Results reported from several biological studies on ginger showed that extracts and compounds from this tuberous rhizome exhibit antiemetic, anticancer, antipyretic, antispasmodic and antimicrobial activities. This article reviews the effect of *Zingiber officinale* and its bioactive constituents on isolated organ preparations from several species of animals in view of its potential use as an alternative treatment for muscle spasms and common gastric ailments.

Keywords: bioactive constituents, spasm, *Zingiber officinale*

Introduction

Zingiberaceae is a monocotyledonous family in the order of Zingiberales. As a member of the plant family, it is most notably identified by the diverse colours and shapes of its flowers. Furthermore, this tuberous rhizome comprises of 52 genera which accounts for a total of 1100 species (Wohlmuth, 2008) which can be found mostly in tropical and subtropical regions of Southeast Asia (Sirirugsa, 1999), where they are commonly used as spice or to enhance the flavour of soups, curries or fried dishes. In addition, several of the species belonging to this family exhibit many pharmacological characteristics which include antispasms or the inhibition of muscle spasms in isolated organs.

Muscle spasm is a sudden involuntary muscular contraction that causes several non-gastrointestinal as well as gastrointestinal problems such as abdominal pain, bowel syndromes and diarrhoea (Saini & Singh, 2015). However, spasms may affect many different types of muscles in the body leading to various symptoms and external presentations. According to Lloyd (2016), skeletal muscle spasms usually involve muscles that are used for strenuous and excessive work. Spasms of this nature are usually short-lived and can be relieved by muscle stretching, whereas smooth muscle spasms will cause colic pain and the symptoms are usually dependent upon the organ involved.

There are three types of spasms, which consists of tics, cramps, and convulsions. Among the three, a tic is the most benign of all types of spasmodic activities and often affects the eyelids or face (Janelle,

2015). However, it can also occur anywhere in the body such as in shoulder or leg muscles. Usually, twitching occurs when the individual is fatigued or under a great deal of stress.

Contrary to tics, a cramp can be characterized by an unusually prolonged and strong muscular contraction followed by a slow relaxation phase. These contractions can affect different muscle groups and it can also be very painful. Commonly affected muscles include those located at the back and front of the thigh, and at the back of the lower leg. However, some people also experience muscle cramps in the abdominal wall, arms, hands and feet (Kargus, 2009). Often, the situation is caused by lower levels of potassium in the body, thus causing the muscles to contract and lead to muscle cramps (Benjamin, 2015).

The third type of spasm is the convulsion which is considered the most serious among all three spasms. According to Malcolm (2016), convulsions can be extremely painful and intense where some susceptible individuals may even suffer seizures. Additionally, a spasm of the oesophagus may induce a detrimental effect by cutting off the air supply of these individuals and consequently causing breathing difficulties, similar to a heart attack (Thompson & Kahrilas, 2014). Unfortunately, people who are diagnosed with diabetes are more prone to this condition compared to other diseases (Ippoliti, 1983).

In contrast to the other forms of spasms, gastrointestinal muscle spasm and its mechanism(s) of action have long been the focus of researchers who have been interested in finding new drugs or relaxing agents to treat undesirable symptoms that arise from this condition. Furthermore, in the enteric nervous system, the innervations, neurotransmitter production and release, transduction and transmission of impulses, and the pathways involved in the induction of pain serve as potential loci for pain therapy and modulation for novel drugs.

Enteric nervous system (ENS)

The enteric nervous system comprises of the oesophagus, stomach, and intestines. The ENS is also known as the second brain as it has the ability to function independently of the central nervous system (CNS) (Kaufmann, 2008). Serio, Zizzo and Mastropaolo (2011) stated that ENS and CNS share similar origin whereby ENS is derived from the neural crest that migrates to the cranial portion of the gut which is then moved caudally to reach the entire gastrointestinal tract. These two systems are also similar in terms of their functional and chemical properties. The ENS consists of supporting cells (glia) that is similar to the astroglia found in the brain, possessing a diffusion barrier around the capillaries near the ganglia which is likened to the blood-brain barrier of cerebral blood vessels. Additionally, the number of neurons in ENS is similar to those found in the spinal cord which accounts for approximately 80–100 million neurons. Moreover, ENS expresses more than 30 neurotransmitters including those that are found in the CNS such as acetylcholine, serotonin, and dopamine. According to Kurt, Göy, Gülşah, Barutçu, and Bozer (2015), this system can affect human behaviour by sending signals to be processed and interpreted via the vagus nerve to the higher centres in the brain.

Anatomically, ENS is embedded within all the layers of the gut wall. The system comprises of the submucosal and the myenteric plexuses. The submucosal plexus which is also known as Meissner plexus is located under the submucosal layer while the myenteric or Auerbach plexus exist in between the circular muscle layer and the outer longitudinal muscle layer (Sayegh & Washington, 2012). The submucosal plexus is involved in sensing the environment in the gut, coordinating muscle movements, blood flow regulation in the gastrointestinal system as well as controlling the epithelial function (Serio et al., 2011). On the other hand, the myenteric plexus is responsible for regulating the relaxation and contraction of the intestinal walls (Nezami & Srinivasan, 2013), which comprises of non-striated muscles. Upon receiving electrical signals from various parts of the body, the actin and myosin found in the muscle slides over one another in a series of repetitive events referred to as the sliding filament mechanism. The calcium-regulated phosphorylation of myosin initiates this process, instead of calcium-activated troponin system in the cardiac and skeletal muscles (Moyes & Schulte, 2014).

According to Nezami and Srinivasan (2013), the neurons that produce acetylcholine are excitatory and are involved in the contraction of smooth muscles, release of enteric hormones, increase of intestinal secretions, as well as vasodilation. Additionally, according to Unno et al. (2005), contraction of the smooth muscles by acetylcholine and its related stimulants are achieved through the activation of muscarinic receptors. A comprehensive description of the mechanisms involved in smooth muscle contraction, maintenance and cessation are available elsewhere.

Failure or slight alterations to any of the processes or pathways involved in muscle contraction and relaxation may be dangerous or even fatal to the individual affected. At present, researchers are looking at novel compounds, naturally derived or synthetic, as a substitute to the commercially available drugs for spasms, with lesser side effects and toxicity. These drugs, compounds or agents may exert an antispasmodic, antispasmodogenic or spasmolytic activity or any of these combinations in the ENS.

Antispasmodic Drugs-Mechanism of action

Currently, muscle spasm can be treated with commercially available synthetic antispasmodic drugs. These drugs relax the smooth muscle of the gut and are frequently used to relieve muscle spasms or cramps of the stomach, intestine and bladder (Kulkarni, 2001). According to Nedelcu and Balescu (2010), antispasmodic drugs can be classified into three main classes which include anticholinergic/anti-muscarinic agents (e.g. atropine, hyoscine), smooth muscle relaxants (e.g. mebeverine, alverine) and calcium channel blockers (e.g. pinaverium bromide).

An anti-cholinergic / anti-muscarinic drug such as atropine and hyoscine exerts antispasmodic action by inhibiting the acetylcholine effect on muscles. These anticholinergic drugs prevent the chemicals from ‘docking’ and cause muscle contraction by binding to the muscarinic receptors (Colin, 2013). Generally, these drugs inhibit the propagation of parasympathetic nerve impulses from the nerve cells (Jacquelyn, 2013). On the other hand, smooth muscle relaxants work directly on the smooth muscle in the gut wall in order to relax and relieve the pain associated with the gut contraction (Colin, 2013). For example, pinaverium bromide which is a prototype of a calcium channel blocker, acts as a locally-acting antispasmodic agent in the gut. This drug produces the calcium-antagonistic effect by inhibiting the calcium ion influx into the smooth muscle (Guslandi, 1994). According to Zheng et al. (2015), pinaverium bromide is effective in improving symptoms of irritable bowel syndrome (i.e. abdominal pain, gas, diarrhoea or constipation) and can be considered as a first-line treatment for this syndrome.

Generally all of these drugs produce similar effect by inhibiting the spontaneous contraction of the gut. Nevertheless, the effects of these drugs on reducing muscle spasm differ according to the physiological mechanisms involved. Besides, the benefits of using these drugs present equally undesirable side effects. The most common side effect of anti-muscarinic drugs is dry mouth due to the reduced production of saliva in the mouth (Colin, 2013). In addition, Kathee (2016) reported that direct smooth-muscle relaxants can cause headaches, nausea, blurred vision, and also urinary retention. Moreover, calcium-channel blockers such as pinaverium bromide have been shown to produce common side effects such as nausea, dizziness, abdominal discomfort and increased blood pressure (Zheng et al., 2015).

Therefore, in conjunction with the public’s current preference of replacing conventional medicine with dietary herbs and medicinal plants as an alternative management for these conditions, the effects of several types of rhizomes such as *Zingiber officinale*, *Zingiber zerumbet*, *Kaempferia galanga*, *Curcuma aeruginosa* and *Curcuma longa* as potential antispasmodic agents were explored. However, this review focuses mainly on the medicinal properties of *Zingiber officinale* in treating spasm. The reviews for *Zingiber zerumbet*, *Kaempferia galanga*, *Curcuma aeruginosa* and *Curcuma longa* are available elsewhere.

***Zingiber officinale* in folklore medicine**

Zingiber officinale (*Z. officinale*) or internationally known as ginger, locally as 'halia' in Malay, 'jahe' in Indonesia or 'sunthi' in Ayurveda, is one of the largest group of rhizomes belonging to the flowering plants of the Zingiberaceae family. This rhizome has been widely used as a spice or condiment around the world for centuries (Ali, Blunden, Tanira, & Nemmar, 2008; Malhotra & Singh, 2003). Traditionally, ginger is used in Asian folklore medicine for the treatment of nausea, headaches, and gastrointestinal disorders such as diarrhoea and constipation (Iwami et al., 2011). Ginger has been used in Chinese traditional medicine for the past 2500 years as a digestion aid and is also a remedy for toothache, snakebites and respiratory problems. Practitioners of traditional Chinese medicine believe that ginger can be used to cure diseases triggered by cold weather (Kemper, 1999). Moreover, ginger root tea is commonly drunk by Chinese women to treat menstrual cramps or delayed menstruation. In Ayurveda, ginger is extensively used to block excessive blood clotting, reduce cholesterol levels and treat arthritis (Kemper, 1999). In addition, ginger has been used as a healing agent for joint pain, motion and air sickness (Palatty, Haniadka, Valder, Arora, & Baliga, 2013; Mindell, 2005). Ayurveda practitioners also believe that ginger can promote better absorption of nutrients and better elimination of wastes by clearing the microcirculatory channels. In Malaysia and Indonesia, ginger soup is given to the new mothers post-delivery to help warm their body (Sharma, Sinh, & Thakur, 2015). In Arabian medicine, ginger has been used as an aphrodisiac and recently has been shown scientifically to possess this property (Qureshi, Shah, Tariq, & Ageel, 1989). Additionally, ginger has been reported to exhibit anti-inflammatory, antiemetic, anticancer, analgesic, antipyretic, and antimicrobial activities (Iwami et al., 2011; Mascolo, Jain, Jain, & Capasso, 1989).

Bioactive constituents of *Zingiber officinale*

The phytochemical constituents *Z. officinale* has been extensively investigated. A GC-MS analysis of the un-derivatized active fractions conducted by Jolad et al. (2004) showed excellent resolution of the sixty three (1-63) components. From this total, 31 had been previously reported as ginger constituents, 20 were novel compounds and the remaining 12 components were artefacts that were isolated through thermal degradation process of the gingerols. Moreover, some of the active fractions contained gingerol derivatives or little to no gingerols at all. The active constituents and derivatives of *Z. officinale* are shown in Table 1.

Jolad, Lantz, Guan, Bates, and Timmermann (2005), conducted another study on commercially processed dry ginger. A total of 115 compounds were identified, where 88 compounds showed a retention time (Rt) of more than 21 minutes and 27 compounds showed an Rt of less than 21 minutes. Out of the 88 compounds, 45 compounds had been previously recorded for fresh ginger (Jolad et al., 2005) while 31 compounds including [6]-isoshogaol methyl, methyl [6]-isogingerol and [8]-paradol were relatively new. The remaining 12 compounds had been previously isolated by other researchers. Five of the 27 compounds with an Rt of < 21 min, were isolated from fresh ginger, 20 others were described in an earlier study while 5-(40-hydroxy-30-methoxyphenyl)-pent-2-en-1-al and 5-(40-hydroxy-30-methoxyphenyl)-3-hydroxy-1-pentanal, were new isolates. Gingerdiones in particular, was not found in either fresh white or yellow ginger but was detected in dry ginger in the form of [6]-, [8]-, [10]- and [12]-gingerdiones. The study also found that the concentration of gingerols was lower in dry ginger compared to fresh ginger while the concentration of shogaols was higher.

Table 1: Active constituents and derivatives of fresh ginger (Jolad et al., 2004)

Constituents
<i>gingerols</i>
acetyl derivatives of gingerols
[4]-, [6]-, [7]-, [8]-, [10]-gingerol
methyl [4]-gingerol and methyl [8]-gingerol
<i>shogaols</i>
3-dihydroshogaols
[4]-, [6]-, [8]-, [10]-, [12]-shogaol
methyl [4]-, methyl [6]-, and methyl [8]-shogaol
<i>paradols</i>
dihydroparadols
5-deoxygingerols
methyl [6]-paradol
[6]-, [7]-, [8]-, [9]-, [10]-, [11]-, and [13]-paradols
<i>gingerdiols</i>
1 dehydrogingerdiones
diarylheptanoids
methyl ether derivatives
mono- and di-acetyl derivatives of gingerdiols

According to Bode and Dong (2011), ginger rhizomes are made up of 60-70% carbohydrates, 9% protein, 8% ash, 3-6 % fatty oil, 3-8% crude fibre, and 2-3% volatile oils. The flavour of ginger and the warm pungent sensation in the mouth produced during and after ingestion of this rhizome in particular, are due to the presence of non-volatile pungent phytochemicals of ginger such as gingerols, shogaols, paradols and zingerone (Figure 1) (Srinivasan, 2017; Vasala, 2004; Govindarajan & Cornell, 1983), while the odour emitted by this rhizome is due to its volatile oil content (Ali et al., 2008). In total, this rhizome contains over 70 constituents which are present in the oil that gives ginger a pleasant aroma. The constituents comprise of monoterpenoids such as β -phellandrene, (+)-camphene, cineole, geraniol, curcumene, citral, terpineol and bomeol; sesquiterpenoids such as α -zingiberene (30-70%), β -sesquiphellandrene (15-20%), β -bisabolene (10-15%), (E-E)- α -farnesene, ar-curcumene, zingiberol, diterpenes and glycolipids (Govindarajan & Connell, 1983).

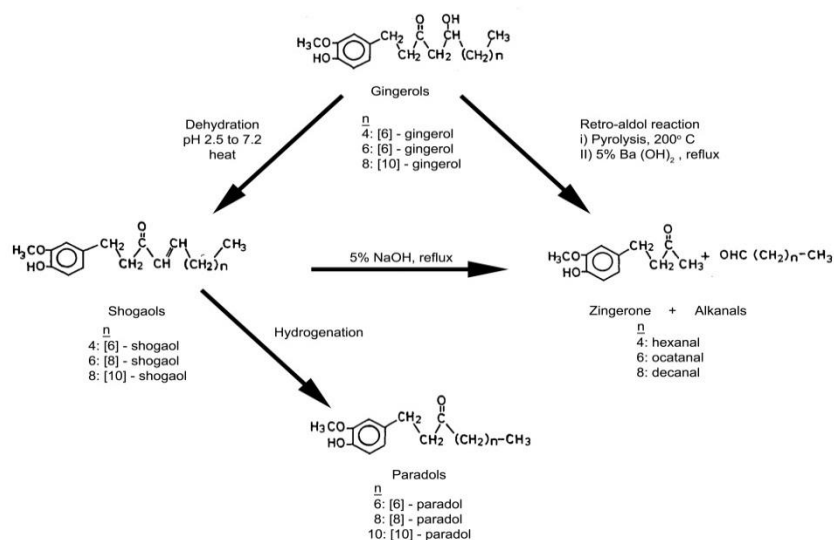


Figure 1: Active constituents of *Z. officinale* (Adapted from Govindarajan & Connell, 1983)

Recently, the nutritional contents of ginger rhizome were identified via proximate analysis and high performance liquid chromatography (HPLC) and verified using aluminium chloride calorimetric assay and Folin–Ciocalteu reagent, respectively (Table 2) (Mojani, Ghasemzadeh, Rahmat, Loh, & Ramasamy, 2014). The results obtained suggested that the medicinal effect produced by *Z. officinale* maybe at least, in part, attributed to the synergistic activity of its bioactive compounds with flavonoids and the functional phenolic group.

Table 2: Total phenolic and flavonoid contents of the methanolic extract of ginger rhizome
(Adapted from Mojani et al., 2014)

Rhizome extract	
Total Flavonoids ^a	3.66±0.45
Total Phenolics ^b	10.22±0.87

All analyses are the mean of triplicate measurements ± standard deviation

^a: Expressed as mg quercetin/g of dry plant material

^b: Expressed as mg gallic acid/g of dry plant material

***Zingiber Officinale* as a Potential Antispasmodic, Spasmogenic and Spasmolytic Agent**

Ginger is usually taken orally, applied to the skin, and injected into the muscle for different purposes. This rhizome has long been used as an antispasmodic agent in folklore medicine based on the trial and error method, without scientific validity on its effectiveness in combating this condition. According to Langner, Greifenberg, and Gruenwald (1998), ginger has been recorded in the “Generally Recognized as Safe” (GRAS) by the US FDA as it does not produce any adverse effect after it is consumed 2-3 times in a period of 3 months to 2.5 years at 0.5 – 1.0 g, in powder form. Despite the benefits and scientific validity of its effects, a standardised dose that can be used to treat spasms in the GIT or elsewhere in the body has not been specified.

Effect of Zingiber Officinale Extract on Rat Ileum and Jejunum Muscle Contraction

Borrelli, Capasso, Pinto, and Izzo (2004), studied the effects of ginger extract on muscle contraction induced by electrical field stimulation (EFS) and exogenous acetylcholine on the rat ileum preparation. In this study, the addition of ginger extract at 0.01-1000 µg/ml demonstrated a concentration-dependent inhibition on EFS and acetylcholine-stimulated ileum preparations. The EFS and acetylcholine-induced ileal contraction were significantly inhibited by the extract at 1 and 300 µg/ml, respectively. In addition, the extract reduced the KCl-induced ileal contractions, indicating the involvement of a direct antispasmodic effect.

Yassin, ElRokh, El-Shenawy, and Ibrahim (2012), adopted a similar procedure to the rat jejunum preparation. Data from the experiment showed that a lower volume of ginger extract 0.2 ml (20µg of ginger / tissue bath) induced a spasmogenic effect on the acetylcholine-induced jejunum contraction concurrent with an increase in the magnitude of the contraction. However, the extract at a slightly higher volume 0.4 ml (40 µg of ginger/tissue bath) induced a spasmolytic effect with a decrease in the magnitude of contractions produced which was similar to the results obtained by Borrelli et al. (2004), where a higher volume 0.8 ml (80 µg of ginger / tissue bath) of extract induced a relaxant effect on the jejunal contractions.

Effect of Zingiber Officinale Extract on Muscle Contraction Induced by High K⁺ Solution on Isolated Gastrointestinal Preparations in Rodents

Ghayur & Gilani (2005) studied the prokinetic action of ginger extract and its possible mechanism of action. Ginger extract was applied on the rat and mouse fundus preparations, rabbit jejunum, and also ileum preparations of the rat, mouse and guinea pig. In the *in vivo* test, the intestinal travel of charcoal meal in mice was enhanced, thus validating the prokinetic properties in ginger extract. Results showed that the propulsive effect of the extract was comparable to carbachol (CCh) which was blocked in mice treated with atropine, a cholinergic antagonist (Ghayur & Gilani, 2005). Similarly, ginger extract

also demonstrated an atropine-sensitive dose-dependent spasmogenic effect *in vitro* as well as in isolated mouse and rat stomach fundus tissues.

Gilani et al. (2000) reported that the relaxant effect produced by most plants is usually mediated through the blockade of calcium ion channels. Based on this theory, Ghayur & Gilani (2005) exposed ileum tissues which have been pre-incubated in high concentration of K^+ (80 mM) to increasing concentrations of the ginger extract. It is known that exposure of tissues to high concentrations of K^+ causes the calcium channels to open and allow the influx of Ca^{2+} from the extracellular fluid, thus depolarizing the tissues to produce sustained muscle contractions. The addition of the extract successfully relaxed the contraction of the tissues, showing a calcium channel blocker (CCB)-like activity. The same CCB-like effect was seen not only on the mouse and rat stomach fundus, but also on other tissues. Cumulatively, results showed that ginger extract exhibited prokinetic action, possessing both spasmogenic and spasmolytic activity which were mediated through the cholinergic and calcium antagonistic activities, respectively.

Effect of Zingiber officinale extract on smooth muscle contraction in the reticulum and rumen of sheep

Mamaghani, Maham, and Dalir-Naghadeh (2013), added *Z. officinale* aqueous extract to the tissue preparations from the reticulum and rumen of sheep. The extract showed an increase in the basal tone of the smooth muscles of both resting and acetylcholine-induced contractions at concentrations of 10.0 and 100 mg/L, respectively. However, the addition of 1000 mg/L of the extract to the tissue strips showed a relaxation effect.

Effect of Bioactive Constituents of Zingiber Officinale on Colonic Motility in Rats

The addition of zingerone at 0, 3, 10, 30, and 50 mM to the rat colon produced contradicting effects on colonic motility. For example, a high concentration of zingerone (30 and 50 mM) significantly inhibited colonic motility compared to lower concentrations (Iwami et al., 2011). Similarly, gingerol was able to inhibit the spontaneous contraction of rat colon smooth muscle at 100 μ mol/L (Cai et al., 2015).

Zingiber Officinale and Muscle Spasm: Mechanism of Action

Ginger and its bioactive constituents had been reported to exert a spasmolytic effect through anti-cholinergic, anti-histaminergic or anti-serotonergic activities (Qian & Liu, 1992). In addition, distal colon tissues treated with capsazepine (100 μ M) did not affect the spontaneous activity of the muscle indicating that the spasmolytic effect was not mediated by the transient receptor potential vanilloid 1 (TRPV1). However, zingerone failed to inhibit the contraction of tissues incubated with Tetrodotoxin (1 μ M), indicating that this bioactive constituent did not alter the activity of the voltage-dependent sodium channels (Iwami et al., 2011). On the other hand, an intravenous administration of [6]-shogaol inhibited gastric contraction in rats *in situ* much better than [6]-gingerol. Additionally, gingerol may inhibit or enhance muscle contraction by non-competitive antagonisms to acetylcholine but the effect was dose-dependent (Chrubasik, Pittler, & Roufogalis, 2005).

Despite these findings, the contraction of the smooth muscle are still dependent on the dose of the extract given, the frequency of extract administration, as well as the stimulant used in the study, which was previously suggested by Suekawa et al. (1984).

Conclusion

Although the use of this plant for various ailments has been scientifically proven, the standard concentration used in every experiment varies. Thus, more studies are recommended to standardize the dose or concentrations that produce repeatable biological effects, and elucidate the rhizome's mechanism of action for the development of *Z. officinale*-based products for the treatment of muscle spasm, constipation as well as post-natal tonic for women in the future.

Acknowledgements

The authors thank the Ministry of Higher Education for the MyMaster scholarship and Universiti Putra Malaysia for the Graduate Research Fellowship (GRF) awarded to the MS candidate Miss Nadia Hisamuddin and Miss Nadhirah Kamarudin.

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