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The Chemical Constituents and Pharmacological / Biofunctional Effects of Ginger

Hisashi MATSUDA*, Seikou NAKAMURA, Masayuki YOSHIKAWA

Department of Pharmacognosy, Kyoto Pharmaceutical University, Kyoto 607-8412, Japan matsuda@mb.kyoto-phu.ac.jp

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Mini Review

The Chemical Constituents and Pharmacological / Biofunctional Effects of Ginger

Hisashi MATSUDA*, Seikou NAKAMURA, Masayuki YOSHIKAWA

Department of Pharmacognosy, Kyoto Pharmaceutical University, Kyoto 607-8412, Japan (matsuda@mb.kyoto-phu.ac.jp)

Abstract

Zingiber officinale Roscoe, which belongs to the family of *Zingiberaceae*, has long been cultivated, and its rhizome 'ginger' has been used therapeutically in the world. Traditional medicinal systems have applied this herb to a wide range of illunesses and disorders, including nausea and intestinal disorders. In this review, we described the chemical constituents and their fluctuations during drying and/or heating processes. Furthermore, we summarized the important pharmacological/biofunctional effects of ginger and its pungent constituents (6, 8, 10-gingerols; 6, 8-shogals, *etc.*) such as antiserotonergic, activation of transient receptor potential vanilloid 1 (TRPV1), antitumor, and antiobesity effects *in vivo* and/or in *vitro*.

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1. Introduction

Zingiberaceae plant, *Zingiber officinale* Roscoe, originates from the topical areas of Asia, and is currently cultivated worldwide in places such as India, Southeast Asia, China, Africa, South America, Japan, *etc.* The rhizome of this plant is usually called 'ginger' and has been used as a spice and in folk medicines throughout the world.

In Indian cuisines, ginger is a key ingredient, especially in thick gravies, as well as in many other dishes. Ginger also has a role in traditional Ayurvedic medicine. It is an ingredient in traditional Indian drinks including spiced masala chai and other herbal beverages. Fresh ginger is one of the main spices used for making pulse and lentil curries and other vegetable preparations. Fresh or dried ginger is used to spice up tea and coffee, especially in winter. Ginger powder is also used in food preparations in-

tended primarily for pregnant or nursing women. Ginger is also consumed in the form of candy and pickled vegetables. In Western cuisines, ginger is traditionally and mainly used in sweet foods such as ginger ale, ginger bread and biscuits. Ginger wine is a ginger-flavored wine produced in the United Kingdom, traditionally sold in a green glass bottle. Ginger is also used as a spice added to hot coffee and tea. In Japan, ginger is pickled to make 'beni shoga' (紅生姜) and 'gari' (ガリ) or grated and used raw on bean curd/tofu (豆腐) or noodles. It is made into a confectionary product called 'shoga no sato zuke' (生姜の砂糖漬け).

In Japanese Pharmacopoeia XVII, ginger (生姜, shokyo) is listed as the dried rhizome of *Zingiber officinale*, and the steamed and dried rhizome is called processed ginger (乾姜, kankyo) and used in formulae separately from ginger (shokyo). In China, on the other hand, the fresh rhizome is called ginger (生姜, sheng jiang) and used as an antiemetic, expectorant, antitussive, detoxicant, antipyretic, digestive system stimulant, *etc.* The dried rhizome, which is equivalent to ginger (shokyo) in Japan, is called 'gan jiang' (乾姜) (or'bai jiang' (白姜), 'jun jiang' (均姜),'gan sheng jiang' (乾生姜), *etc.*) and present in various formulae to reduce cough and improve abdominal pain, stomachache, and gastrointestinal retention. In summary, the name, medicinal effects, and usage of medical *Zingiber officinale* in Japanese Kampo medicine are different from those in traditional Chinese medicine.[1,2]

Various reports and reviews about phytochemistry and pharmacology of this herb have been published to date. In this review, we summarize our previous studies of chemical constituents and pharmacological investigation of ginger (shokyo) together with important and intriguing reports by other research groups.

2. Principal bioactive constituents of ginger and fluctuation of constituents during the drying process

Pungent constituents such as gingerols (**6**–**8**) and shogalols (**9**, **10**), which are the principal ingredients of ginger (shokyo), have been characterized by many researchers.[1] Because of poor availabity in Japan, imported ginger (shokyo) originating in China and Taiwan have been widely used used for medicinal preparations in Japan.

During the course of our screening to find biologically active constituents contained in crude medicinal preparations using ginger, we have found certain bioactive compounds show anti-catalitic, antiserotonergic, and gastromucosal protecting effects.[3–6] From ginger (shokyo) originating from Taiwan, we have isolated and identified bisabolane-type sesquiterpenes (α-zingiberene (**1**), β-sesquiphellandrene (**2**), β-bisabolene (**3**), *ar*-curcumene (**4**)), a diterpene (galanolactone (**5**)), pungent constituents (6-gingerol (**6**), 8-gingerol (**7**), 10-gingerol (**8**), 6-shogaol (**9**), 8-shogaol (**10**), 6-dehydrogingerdione (**11**), 6-gingerdione (**12**), 6-gingediol (**13**), and 6-paradol (**14**)). In addition, we isolated and determined a new sufonic derivative (6-gingesulfonic acid (**16**)) with gastroprotective effects, and a new diarylheptanoid ((3*S*,5*S*)-dihydroxy-1-(4'-hydroxy-3',5'-dimethoxyphenyl)-7-(4''-hydroxy-3''-methoxyphenyl)heptane (**15**)) and three new monoacydigalactosylglyceros (gingerglycolipid A (**17**), B (**18**), C (**19**)), etc. (Fig. 1).[3–5,7]

It is well known that gingerols (**6**, **7**) in fresh rhizomes are converted to shogaols (**9**, **10**) during the drying and heating processes. We have reported a quantitative analysis by high performance liquid chromatography (HPLC) for gingerols (**6**–**8**), shogaols (**9**, **10**), 6-dehydrogingerdione (**11**), and galanolactone (**5**) in many kinds of ginger (shokyo) originating from China, Taiwan, Vietnam, and Japan (Shizuoka Prefecture), and a fresh ginger 'Kintoki' cultivated in Shizuoka Prefecture.[8,9] As a result, the fresh ginger 'Kintoki' contained high contents of 6-dehydrogingerdione (**11**) (0.770–1.690%; calculated as dried material), 6-gingerol (**6**) (0.999–1.510%), and galanolactone (**5**) (0.961–2.430%) as major constituents, with less shogalos (**9**: 0.010–0.027%, **10**: 0.034–0.050%). These constituents in the fresh ginger decreased remarkably in the dried ginger (shokyo) made from 'Kintoki' (**5**: 0.090–0.686%; **6**: 0.283–0.484%; **11**: 0.237–0.742%), although contents of **9** increased (0.052–0.085%). Interestingly, galanolactone (**5**) is found in the Japanese ginger only, but not detected in imported ginger from China, Taiwan, and Vietnam. In Chinese ginger (shokyo), the contents of **6**–**9** were 0.234–0.606%, 0.011–0.260%, 0.015–0.045%, and 0.042–0.214, repectively.

Furthermore, we tried to analyze four bisabolane-type sesquiterpenes (α-zingiberene (**1**), β-sesquiphellandrene (**2**), β-bisabolene (**3**), and *ar*-curcumene (**4**)) using a gas liquid chromatography

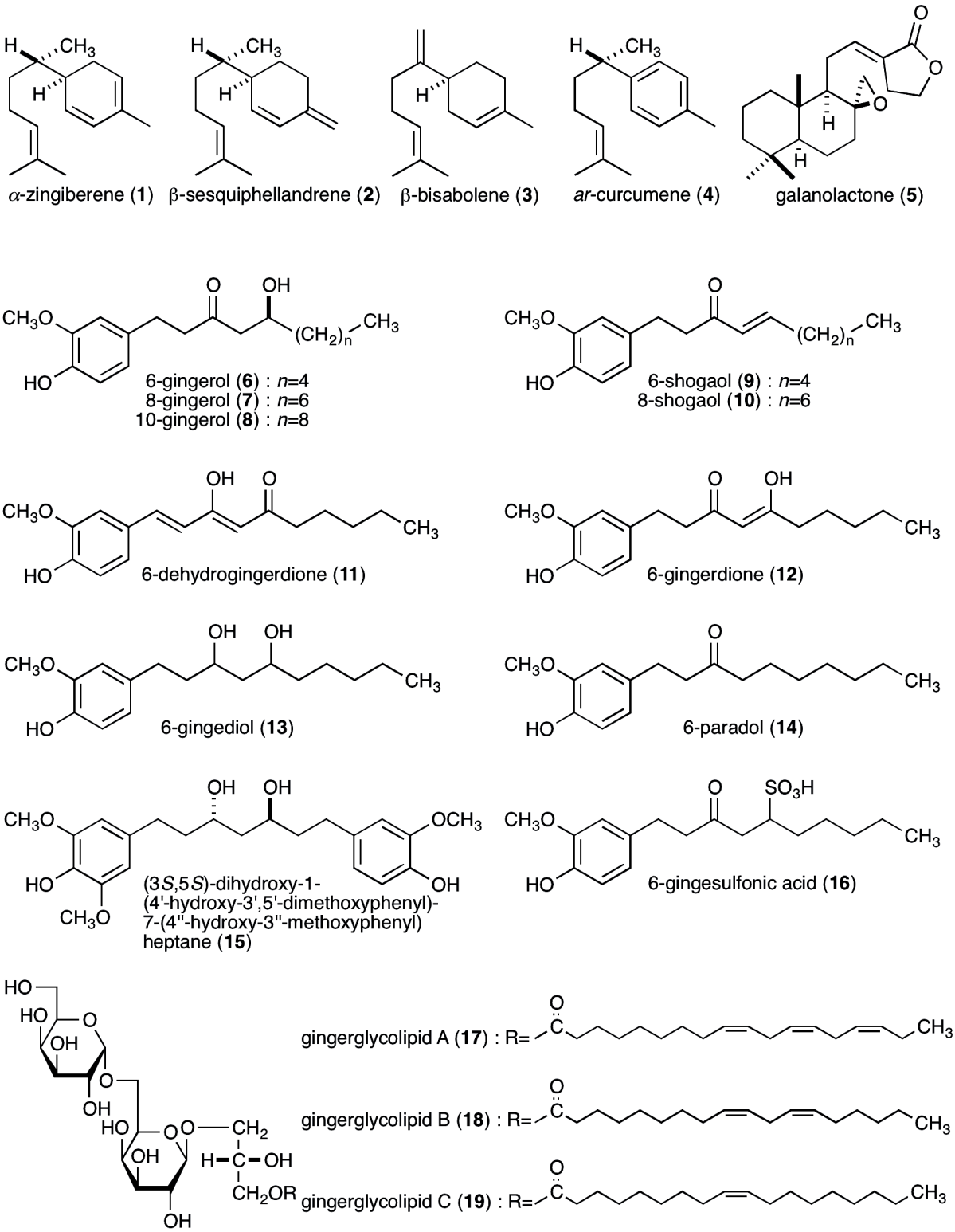

Fig. 1. Chemical structures of constituents (1–19) from ginger.

(GLC). Compound **1** is highly contained in most of the ginger studied, and their contents in Japanese fresh ginger also decrease during the processing procedure.[8] We have also reported the chemical fluctuation of constituents during the drying process using HPLC and GLC analyses for pungent principles (**6**–**11**), galanolactone (**5**), and bisabolane-type sesqiterpenes (**1**–**4**). As a result, the far-infrared (IR) drying method was found to be efficient, and the yield is without marked decreases in the contents of bioactive constituents.[9]

Ginger (shokyo) is usually peeled and dried, and is sometimes fumigated by sulfur for breaching and as a repellent. Hori *et al.* have reported that sufonic derivatives, such as 6-gingesulfonic acid (**16**), are found in sulfur-fumigation of ginger (shokyo), suggesting that the derivatives are formed by the sulfer-fumigation.[10]

As mentioned above, it is generally accepted that differences in contents of gingerols, shogaols, and the essential oil ingredients and pharmacological effects of individual preparations are related to differences between the clinical effects of fresh ginger, ginger (shokyo), and processed ginger (kankyo).

3. Pharmacological/biofunctional effects

Ginger (shokyo) is contained in Kampo formulae for stimulation of perspiration and antiemetic effects, while processed ginger (kankyo) is contained in Kampo formulae for eliminating interior cold, improving chills, and for relieving pain as well as coughing and wheezing. Ginger and processed ginger have pharmacological effects including antiemetic, gastric mucosal protective, and anti-inflammatory and anti-allergic effects. Differences in the medicinal effects of 'ginger' and 'processed ginger' are related to differences in the contents of gingerols, shogaols, and essential oil constituents which affect their pharmacological effects and potency.

3.1 Antiserotonergic effects

The anti-nauseous/antiemetic effects of ginger have been applied in folk medicines worldwide, including Japan. Experimetal studies of this effect have been reported. For example, pressed ginger juice inhibited copper sulfate-induced vomiting in dogs, and pungent ingredients gingerols and shogaols were identified as the active ingredients responsible for this effect.[1,2] Yamahara *et al.* have reported that 6-gingerol (**6**) inhibits vomitting induced by cytotoxic drugs in an experimental animal, suncus, and its efficacy is similar to that of the reference drug, metoclopramide.[11] Sharma *et al.* have also demonstrated that the extract inhibits cisplatin-induced emesis in dogs.[12] Huang *et al.* have further documented that galanolactone (**5**) antagonizes the effects of a serotonin 3 (5-HT_3) agonist, suggesting the antiemetic effect is intrinsic of ginger.[13] In addition, the acetone extract and pungent constituents (**6**–**8** at 5 mg/kg and **9** at 2.5 mg/kg p.o.) have been reported to enhance gastrointestinal motility using a charcoal meal transport method in mice, and their effects are slightly weaker than those of metoclopramide and donperidone.[14] Recently anti-5-HT_3 effects of the pungent constituents (**6**–**9**), which result in amelioration of nausea, vomiting and gastric hypomotility, have also been documented.[15–18]

With regard to clinical trials, Ernst and Pittler have authored a systematic review of six studies comprising double-blind placebo-controlled randomized clinical trials for nausea and vomiting. They conclude that the studies collectively favor ginger over placebo intake, although one study shows no significant differences in the effects.[19] Furthermore, despite the fact that many patients use ginger for prevention or treatment of nausea and vomiting induced by cancer chemotherapy, the results are controversial. According to a large population-sample investigation of the efficacy of ginger in reducing chemotherapy-induced nausea, they have demonstrated that 3 different daily doses of ginger (0.5 g, 1.0 g, 1.5 g) are effective in reducing acute chemotherapy-induced nausea (compared to placebo) in 644 adults receiving chemotherapy for primarily breast, lung, and alimentary cancers (90% female, mean age: 53 yo). In contrast to other studies, they began the administration of ginger 3 days prior to chemotherapy: i.e. as a pretreatment. They conclude that cancer patients can alleviate chemotherapy-induced nausea by using ginger supplementation (0.5 to 1.0 g/day), and no adverse reactions are observed when ginger is used along with the standard 5-HT_3 receptor antagonist anti-emetics and dexamethazone.[20]

Ginger is known to remove chills caused by common cold and to warm the body. We have previously demonstrated that the acetone extract of ginger (100 mg/kg) and **9** at 10 mg/kg inhibit 5-HT-induced hypothermia in mice. Furthermore, the extract, 8-gingerol (**7**), 10-gingerol (**8**), and **9** inhibit 5-HT-induced

diarrhea in mice. Among these, **9** shows the most potent effect.[5] Sesquiterpenes (**1–4**) and pungent constituents (**6**, **9**, **16)** prevent hydrochloric acid/ethanol-induced gastric mucosal damage in rats after oral administration (Fig. 2).[3–5]

Recently, a Kampo preparation, Daikenchuto (大建中湯) has clinically been evaluated for postoperative ileus,[21,22] as it experimentally promotes gastrointestinal motility and increases intestinal blood flow in rats: viz., serotonin receptors (5-HT_3 and 5-HT_4)-mediated acetylcholine release is involved in gastrointestinal motility,[23] and improvement in blood flow has been found to result from transient receptor potential vanilloid 1 (TRPV1)-stimulated release of calcitonin gene-related peptide (CGRP) from sensory nerve endings, TRP ankyrin 1 (TRPA1)-stimulated release of adrenomedullin from intestinal mucosal epithelial cells, and mobilization of these receptor-related genes.[21–23] Furthermore, 6-shogaol (**9**) in processed ginger (kankyo), a crude drug derived from daikenchuto, stimulates not only TRPV1 but also TRPA1, and a monoterpene (linalool) and pungent constituent (hydroxy-α-sanshool) in zanthoxylum fruit (山椒, sansho); another constituent crude drug, which stimulates TRPA1.[24,25]

3.2 Analgesic/anti-inflammatory effects

The extracts, 6-gingerol (**6**) and 6-shogaol (**9**) have antipyretic, analgesic, and anti-inflammatory effects which are all attributable to inhibition of prostaglandin and leukotriene biosynthesis.[1,26] As for anti-allergic effects, **6** and **9** potently inhibit 5-lipoxygenase activity,[1,26] and **6** and **9** further inhibit passive cutaneous anaphylaxis in rats and compound 48/80- or calcium ionophore A23187-stimulated histamine re-

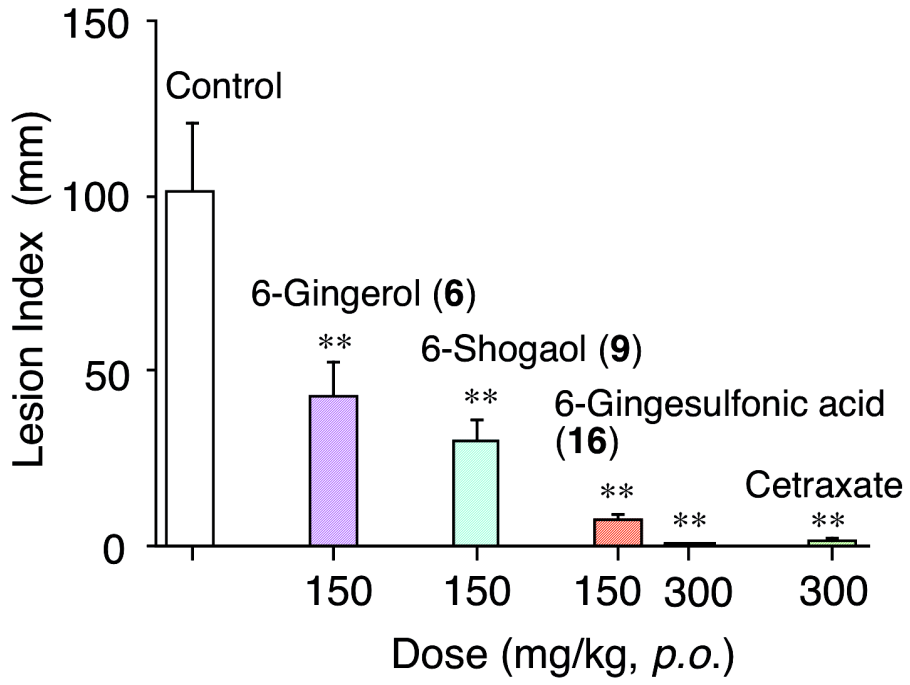

*Fig. 2. Effects of pungent constituents (**6**, **9**, **16**) on HCl/ethanol-induced gastric lesions in rats.*[a]

After 24-h fasting, the test sample was given orally to male Wistar rats. One hour thereafter, 1 mL of HCl/ethanol (150 mM HCl in 60% ethanol) was administered orally to each rat. Rats were then sacrificed under ether anesthesia after the administration of the necrotizing agent, and the stomachs were excised. Followed by treatment of the stomach with 2% formalin solution, the lesion index was calculated as the sum of the lengths (cm) of lesions in the mucous membrane. Cetraxate hydrochloride was used as a reference drug.

Each bar represents the mean ± S.E.M. (n=5 - 6). Values significantly different from controls:
**$p<0.01$.

[a] Data taken from reference 4.

Table 1. Inhibitory effects of 6-gingerol (6) and 6-shogaol (9) on 48-h passive cutaneous anaphylaxis in rats.[a]

Groups	Dose (mg/kg, *p.o.*)	n	Inhibition[b] (%)
Control	–	8	0.0±9.6
6-Gingerol (**6**)	25	10	9.2±3.7
	50	8	43.8±8.2**
6-Shogaol (**9**)	25	8	17.4±4.6*
	50	8	20.5±13.7
	100	8	45.2±11.0**
Tranilast	100	10	38.4±11.0*
	300	10	64.7±11.8**

Rats were sensitized passively with anti-DNP IgE for 48 h. Each test compound was given orally 2 hours prior to the challenge with DNP-BSA solution containing 1% Evans blue. Tranilast was used as a reference compound.
[a] Data taken from reference 27.
[b] Each value represents the mean ± S.E.M. Values significantly different from controls:
*p<0.05
**p<0.01

lease from the peritoneal mast cells of rats (Table 1).[27] However, these pungent constituents are not applicable for asthma because of contractions of bronchial smooth muscles *via* activation of TRPV1. Pan *et al.* have demonstrated that 6-shogaol (**9**) down-regulates inflammatory inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) gene expression in macrophage-like cells (RAW 264.7) by inhibiting the activation of nuclear factor-κB (NF-κB).[28]

3.3 Activation of TRPV1

TRPV1 is a non-selective cation channel and multimodal sensor protein. TRPV1 is activated by noxious stimuli such as heat, acid, and pungent constituents such as capsaicin, a principal constituent of red pepper.[29,30] TRPV1 is expressed in primary sensory neurons, where its activation results in the perception of pain. Therefore, inhibition or desensitization of TRPV1 is thought to be a therapeutic strategy for neuropathic pain.[31,32] The thermogenetic action of red pepper and ginger in particular has recently attracted much attention in health-related practices.[33] Thermogenetic action of ginger is strongly suggested to have been attributed to the activation of TRPV1.[34] The activation of TRPV1 promotes an increase in the adrenaline concentration in the blood by stimulating the vagus nerve through signal transmission. This adrenaline promotes the expression of uncoupling protein (UCP) in brown adipocytes and results in thermogenesis. Also *via* another pathway, it was proposed that adrenaline released in the blood acts on β-adrenergic receptors of adipose tissues.[29,30,34]

Ginger also activates TRPV1, and the pungent constituents such as 6-gingerol (**6**) and 6-shogaol (**9**) are identified as the biologically active compounds. These components have a vanilloid moiety as the common structure, and the structure-activity relationship with TRPV1 receptors has been well studied.[34–36]

In previous studies, including our reports, inotropic effects of gingerols and shogaols on the isolated atria of guinea pigs have been observed, suggesting that the release of CGRP by activation of TRPV1 may have involved in the mechanism of action (Fig. 3, 4).[27,37] Gastroprotective effects and contractions of the smooth muscle of tracea by ginger and its pungent constituents might have also been attributed to the activation of TRPV1.[27,36,37]

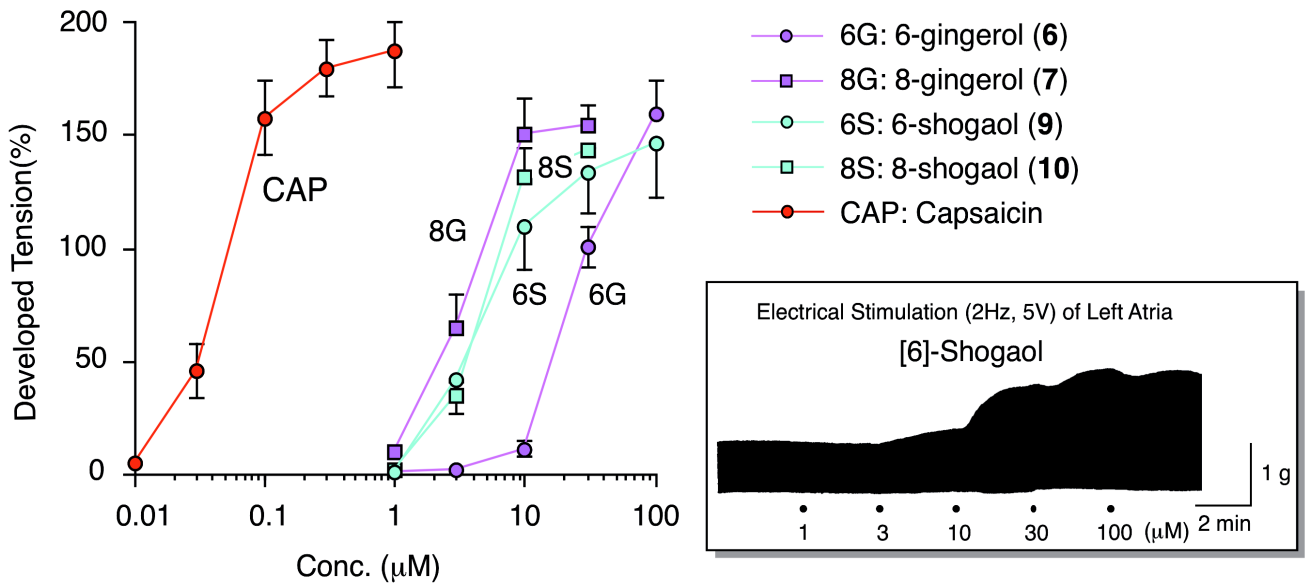

*Fig. 3. Inotropic effects of gingerols (**6**, **7**) and shogaols (**9**, **10**) on isolated left atria of guinea pig.*[a]

The left atria were stimulated electrically using platinum electrodes at a frequency of 2 Hz by rectangular pulses of 5-ms duration and 5-V intensity. Capsaicin was used as a reference compound.
Each point represents the mean ± S.E.M. (n=3–9).
[a] Data taken from reference 27.

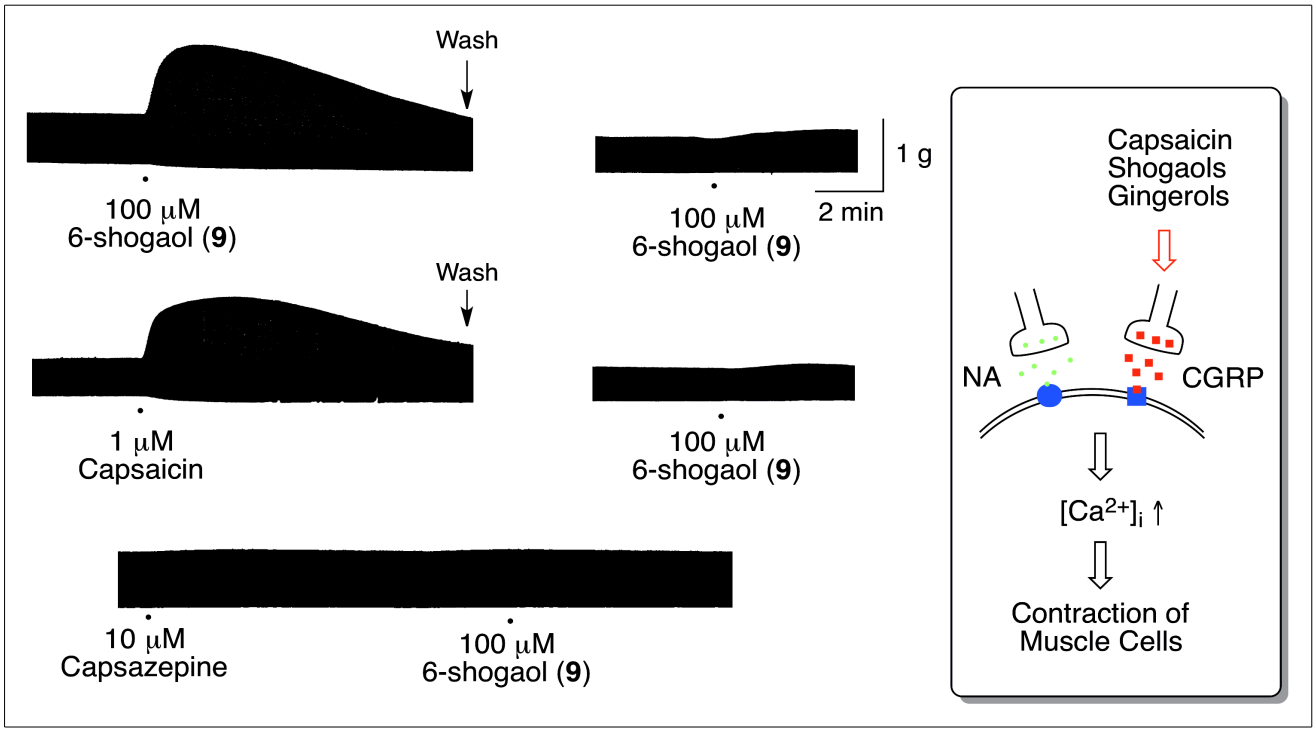

*Fig. 4. Inotropic effects of 6-shogaol (**9**) via TRPV1 activation.*[a]

The isolated left atria of guinea pig were stimulated by electrical stimulation. After treatment with a high concentration of 9 or capsaicin, the reduction of effect was probably depended on the depletion of CGRP. Pretreatment with a TRPV1 antagonist, capsazepine, apparently inhibited the inotropic effect of 9.
CGRP: calcitonin gene-related peptide, NA: noradrenaline
[a] Data taken from reference 27.

Table 2. Pungent effects of constituents of ginger.[a]

Samples	Pungent effect (μmol/L)				
	0.1	1.0	10	100	1000
6-Shogaol (**9**)	−	+	+	++	++
8-Shogaol (**10**)	−	−	±	+	++
6-Paradol (**14**)	−	−	±	+	+
6-Gingerdione (**12**)	−	−	±	+	+
6-Gingerol (**6**)	−	−	−	+	+
6-Gingediol (**13**)	−	−	−	±	+
15	−	−	−	−	+
6-Gingesulfonic acid (**16**)	−	−	−	−	+

Quality test: (++) conspicuous; (+) evident; (±) slight; (−) absent.
[a] Data taken from reference 4.

Furthermore, when we evaluated the pungency of the principal constituents of ginger, 6-gingesulfonic acid (**11**) showed weaker pungency than 6-gingerol (**6**) and 6-shogaol (**9**) (Table 2). This compound **(11)** was obtained as a stable white powder and it showed higher water solubility than the oily compounds **6** and **9**. This property of **11** may be important for its use as a stomachic, although safety study of it has not been clarified as yet.

3.4 Antitumor effects

Chemopreventive potentials of 6-gingerol (**6**) and 6-shogaol (**9**) have been reported.[38–41] For example, Ishiguro *et al.* have reported that **6** facilitates TRAIL-induced apoptosis by increasing TRAIL-induced caspase-3/7 activation; however, unlike **6**, **9** alone reduces the viability of gastric cancer cells. Compound **9** has been shown to damage microtubules and induce mitotic arrest. They conclude that, in gastric cancer cells, **6** enhances TRAIL-induced viability reduction by inhibiting TRAIL-induced NF-κB activation while **9** alone attenuates the viability by causing damage to microtubules.[38]

3.5 Antiobesity effects

Obesity has become increasingly prevalent on a global scale, and is now a worldwide health problem. Food-derived peroxisome proliferator-activated receptor δ (PPAR δ) stimulators represent potential treatment options for obesity. Ginger has previously been shown to regulate the PPARγ signaling pathway in adipocytes.[42] Misawa *et al.* have reported the antiobesity effects of ginger *in vivo* and the mechanism of action *in vitro*.[43] According to their studies, energy expenditure is increased, and diet-induced obesity attenuates in C57BL/6J mice treated with dietary ginger extract. The extract also increases the number of type-I muscle fibers, improves running endurance capacity, and upregulates PPARδ-targeted gene expression in skeletal muscles and the liver. Constituents 6-gingerol (**6**) and 6-shogaol (**9**) act as specific PPARδ ligands, and stimulate PPARδ-dependent gene expression in cultured human skeletal muscle myotubes. They conclude that sustained activation of the PPARδ pathway with the ginger extract attenuates diet-induced obesity and improves exercise endurance capacity by increasing skeletal muscle fat catabolism, and where **6** and **9** are thought to be responsible for the regulatory effects of dietary ginger on PPARδ signaling.[43]

3.6 Absorption and metabolism

Recently, several reports about plasma levels of pungent constituents after administration of ginger have been documented.[44–46] Mukkavilli *et al.* have reported that the pungent constituents (**6–9**) is rapidly absorbed, and their β-glucronide conjugations are mainly detected after oral administration of the ginger extract, suggesting low systemic exposure.[45] They have also demonstrated that **6–9** are potent inhibitors of cytochrome P450 (CYP) isozymes, although the ginger extract exhibits a higher half-maximal inhibition value, thus indicating less herb-drug interactions.[46] Furthermore, Gundala *et al.* have observed that **6–8** exhibit enterohepatic circulation, suggesting possible enhancement of their effects.[47]

4. Conclusion

Ginger has been cultivated and used therapeutically for thousands years throughout the world. Traditional medicine systems all over the world have applied this herb to a wide range of illnesses and disorders, including nausea and bowel conditions. In this review, we introduced the chemical structures of pungent constituents which serve as important bioactive constituents of ginger. The various pharmacological effects such as anti-serotonergic, activation of TRPV1, anti-tumor, and anti-obesity effects of ginger extract and constituents suggest the many beneficial effects that ginger use provides for human health, although this herb should not be applied to patients with asthma and clonic abdominal inflammations, and pregnant women because of limited safety studies.

5. Acknowledgments

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