

Review

Some phytochemical, pharmacological and toxicological properties of ginger (*Zingiber officinale* Roscoe): A review of recent research

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Abstract

Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) is a medicinal plant that has been widely used in Chinese, Ayurvedic and Tibb-Unani herbal medicines all over the world, since antiquity, for a wide array of unrelated ailments that include arthritis, rheumatism, sprains, muscular aches, pains, sore throats, cramps, constipation, indigestion, vomiting, hypertension, dementia, fever, infectious diseases and helminthiasis.

Currently, there is a renewed interest in ginger, and several scientific investigations aimed at isolation and identification of active constituents of ginger, scientific verification of its pharmacological actions and of its constituents, and verification of the basis of the use of ginger in some of several diseases and conditions.

This article aims at reviewing the most salient recent reports on these investigations.

The main pharmacological actions of ginger and compounds isolated therefrom include immuno-modulatory, anti-tumorigenic, anti-inflammatory, anti-apoptotic, anti-hyperglycemic, anti-lipidemic and anti-emetic actions. Ginger is a strong anti-oxidant substance and may either mitigate or prevent generation of free radicals. It is considered a safe herbal medicine with only few and insignificant adverse/side effects.

More studies are required in animals and humans on the kinetics of ginger and its constituents and on the effects of their consumption over a long period of time.

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1. Introduction

Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) is widely used around the world in foods as a spice. For centuries, it has been an important ingredient in Chinese, Ayurvedic and Tibb-Unani herbal medicines for the treatment of catarrh, rheumatism, nervous diseases, gingivitis, toothache, asthma, stroke, constipation and diabetes (Awang, 1992; Wang and Wang, 2005; Tapsell et al., 2006). Several reviews have appeared in the literature about this plant, and this may reflect the popularity of the subject and its common use as a spice and a medicinal plant (e.g. Afzal et al., 2001; Chrubasik et al., 2005). Many reviews have been devoted to specific aspects of ginger's actions. For example, the review of Grzanna et al. (2005) was on the use of ginger as an anti-inflammatory agent, while that of Shukla and Singh (2007) dealt with the cancer prevention properties of the crude drug. The actions of ginger as a post-operative anti-emetic substance were the subject of a review by Chaikyapapruk et al. (2006).

Here, the aim was to summarize the more recent and common actions and therapeutic application of ginger and its active constituents.

2. Chemistry

The constituents of ginger are numerous and vary depending on the place of origin and whether the rhizomes are fresh or dry. It is not our intention in this review to cover all the many compounds reported for ginger, but to summarize the major components that have been implicated in the pharmacological activities of the crude drug.

The odor of ginger depends mainly on its volatile oil, the yield of which varies from 1% to 3%. Over 50 components of the oil have been characterized and these are mainly monoterpenoids [β -phellandrene, (+)-camphene, cineole, geraniol, curcumene, citral, terpineol, borneol] and sesquiterpenoids [α -zingiberene (30–70%), β -sesquiphellandrene (15–20%), β -bisabolene (10–15%), (*E-E*)- α -farnesene, *ar*-curcumene, zingiberol]. Some of the oil components are converted into less odor-defining compounds on drying (Langner et al., 1998; Evans, 2002).

The pungency of fresh ginger is due primarily to the gingerols, which are a homologous series of phenols. The

most abundant is [6]-gingerol (**1**), although smaller quantities of other gingerols with different chain lengths are also present. The pungency of dry ginger mainly results from shogaols {for example, [6]-shogaol (**2**)}, which are dehydrated forms of gingerols. Shogaols are formed from the corresponding gingerol during thermal processing (Wohl-muth et al., 2005). Degradation rates of [6]-gingerol to [6]-shogaol were also found to be pH dependent, with greatest stability at pH 4, whereas at 100 °C and pH 1, the reversible degradation was relatively rapid (Bhattarai et al., 2001). Thermal degradation of gingerols to gingerone, shogaols, and related compounds was demonstrated by Jolad et al. (2004).

Jolad et al. (2004) examined organically-grown fresh ginger and identified 63 compounds, of which 31 had been previously reported as constituents of ginger and 20 were hitherto unknown compounds. The identified components included gingerols, shogaols, 3-dihydroshogaols, paradols, dihydroparadols, acetyl derivatives of gingerols, gingerdiols, mono- and di-acetyl derivatives of gingerdiols, 1-dehydrogingerdiones, diarylheptanoids, and methyl ether derivatives of some of these compounds. In addition to [6]-gingerol (**1**), [4]-, [7]-, [8]-, and [10]-gingerol (**3–6**) were identified, as well as methyl [4]-gingerol and methyl [8]-gingerol. [4]-, [6]-, [8]-, [10]- and [12]-shogaol were characterized (**2**, **7–10**), as were methyl [4]-, methyl [6]- and methyl [8]-shogaol. Paradols are 5-deoxygingerols. [6]-Paradol (**11**), along with [7]-, [8]-, [9]-, [10]-, [11]-, and [13]-paradols were detected in the fresh ginger, as was methyl [6]-paradol.

Jolad et al. (2005) also examined commercially processed dry ginger using the same techniques that they had utilized in their earlier study (2004). They identified a total of 115 compounds, of which 88 were reported. Of these, 45 had been recorded previously for fresh ginger (Jolad et al., 2004) and 31 were new compounds, which included methyl [8]-paradol, methyl [6]-isogingerol (**12**) and [6]-isoshogaol (**13**). The remaining 12 constituents had been isolated previously by other workers. [6]- (**14**), [8]-, [10]- and [12]-gingerdiones were detected, whereas they had not been previously reported in fresh white and yellow gingers. The concentrations of gingerols in the dry ginger were reduced slightly in comparison to fresh ginger, whereas the concentrations of shogaols increased (see Fig. 1).

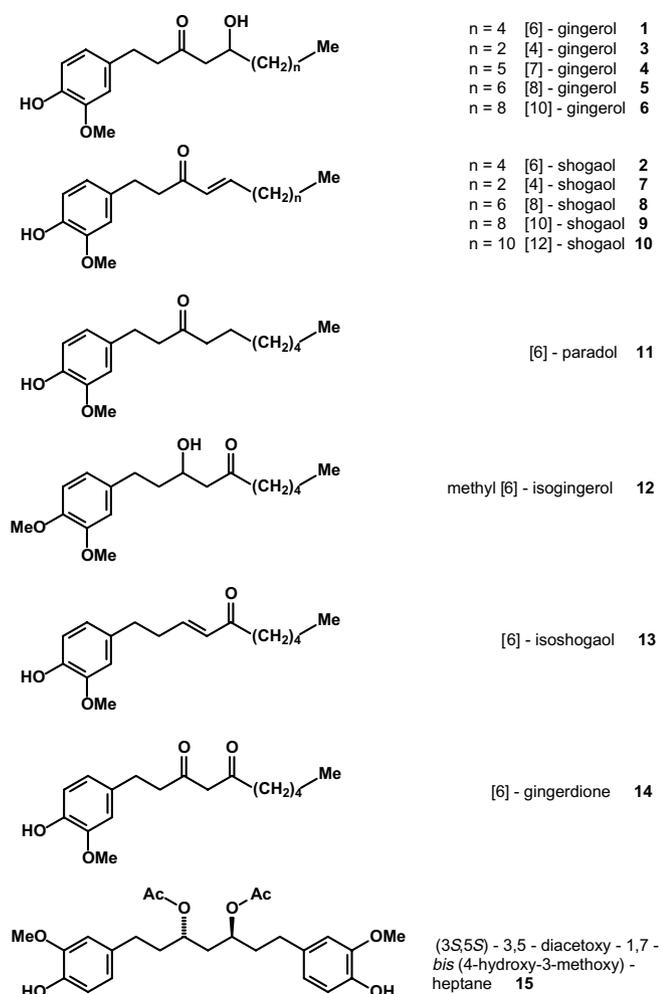


Fig. 1. Major chemical constituents of ginger.

Diarylheptanoids have been reported as components of both fresh and dry ginger (for example, Jolad et al., 2004, 2005; Ma et al., 2004, and references cited therein). Ma et al. (2004) reported the isolation of seven previously unknown diarylheptanoids from the ethanol extract of Chinese ginger, along with 25 known compounds, including 8 diarylheptanoids. An example of one of the novel compounds reported is (3*S*,5*S*)-3,5-diacetoxy-1,7-bis(4-hydroxy-3-methoxyphenyl)heptane (**15**). In a later paper, Wei et al. (2005) reported significant cytotoxic and apoptotic activities against human promyelocytic leukemia cells of several ginger constituents, including some diarylheptanoids and gingerol-related compounds. They showed that the following structural features contribute significantly to the enhancement of activity:

1. Acetoxy groups at the 3- and/or 5-positions of the side chain.
2. The appropriate longer alkyl side chain length.
3. The *ortho*-diphenoxyl functionality on the aromatic ring.
4. The α,β -unsaturated ketone moiety in the side chain.

For the analysis of the major constituents of ginger ([6]-, [8]-, [10]-gingerol and [6]-shogaol) in dietary supplements, spices, teas and beverages containing the crude drug, a high-performance liquid chromatographic procedure has recently been published by Schwertner and Rios (in press).

3. Pharmacological properties of ginger

3.1. Kinetics

Although ginger has been utilized in many studies in both man and animals, there is a relative dearth of information on its disposition in treated subjects.

After bolus intravenous administration at a dose of 3 mg/kg of [6]-gingerol (**1**), the plasma concentration–time curve was described by a two-compartment open model. [6]-Gingerol was rapidly cleared from plasma with a terminal half-life of 7.23 min and a total body clearance of 16.8 ml/min/kg. Serum protein binding of [6]-gingerol was 92.4% (Ding et al., 1991). The same group studied the kinetics in rats with experimental acute hepatic or renal failure (Naora et al., 1992) and found that there was no significant difference in either the plasma concentration–time curve or any pharmacokinetic parameters between the control and nephrectomized rats. It is suggested, therefore, that renal excretion does not contribute at all to the disappearance of [6]-gingerol from plasma in rats. In contrast, hepatic toxicity elevated the plasma concentration of [6]-gingerol at the terminal phase. Its elimination half-life increased, significantly, from 8.5 to 11.0 min, in rats with hepatic damage. The extent of [6]-gingerol bound to serum protein was more than 90% and was affected very slightly by the toxicity. These aspects indicate that [6]-gingerol is eliminated partly by the liver.

A reductive metabolism of *S*-(+)-[6]-gingerol (**1**), the major pungent principle of ginger, was investigated *in vitro* with phenobarbital-induced rat liver 10,000 \times *g* supernatant containing the NADPH-generating system (Surh and Lee, 1994). The reduction was shown to be stereo-specific. The ethyl acetate-extractable products were isolated and two metabolites were identified as diastereomers of [6]-gingerdione by gas chromatography/mass spectrometry. The same authors have previously shown that [6]-shogaol (**2**), a pungent principle of ginger, was reduced in rat liver *in vitro*. Ethyl acetate-extractable metabolites of shogaol were isolated, formed by incubation of this α,β -unsaturated ketone with a rat liver cytosolic fraction fortified with either NADPH- or NADPH-generating system; two major metabolites were identified as 1-(4-hydroxy-3-methoxyphenyl)-decan-3-one {[6]-paradol (**11**)} and 1-(4-hydroxy-3-methoxyphenyl)-deca-1-ene-3-one (dehydroparadol), a non-pungent analog of shogaol, formed the same metabolites, as did [6]-shogaol under similar incubation conditions. [6]-Paradol appears to be an intermediate in the reductive metabolism of the α,β -

beta-unsaturated ketone moiety of shogaol to the corresponding saturated alcohol (Surh and Lee, 1994). The pharmacological activities of these isolated metabolites have not been characterized.

Recently, it has been reported that [6]-gingerol, when incubated with NADPH-fortified rat hepatic microsomes, gave rise to eight metabolites, which were tentatively identified by gas chromatographic–mass spectrometric (GC–MS) analysis as two products of aromatic hydroxylation, as well as the diastereomers of two aliphatic hydroxylation products and the diastereomers of [6]-gingerdiol. Hepatic microsomes from rats and humans, fortified with UDPGA, glucuronidated [6]-gingerol predominantly at the phenolic hydroxyl group, but small amounts of a second monoglucuronide involving the aliphatic hydroxyl group were also identified by liquid chromatography–mass spectrometry/mass spectrometry (LC–MS/MS) analysis. Human intestinal microsomes formed the phenolic glucuronide only. Supersomes containing human UGT1A1 and 1A3 exclusively generated the phenolic glucuronide, albeit with very low activities, whereas UGT1A9 catalyzed the specific formation of the alcoholic glucuronide, and UGT2B7 the predominant formation of the phenolic glucuronide, with high activities. This study indicates a rather complex metabolism of [6]-gingerol, which, according to the authors, should be taken into consideration for the multiple biological activities of this compound (Pfeiffer et al., 2006).

The metabolic fate of [6]-gingerol was investigated in rats by Nakazawa and Ohsawa (2002). The bile of rats that had been orally administered [6]-gingerol was shown by high-performance liquid chromatographic (HPLC) analysis to contain a major metabolite (*S*)-[6]-gingerol-4'-*O*- β -glucuronide. Although the metabolites derived from [6]-gingerol were not detected in the urine, the ethyl acetate extract of the urine, after enzymatic hydrolysis, was shown to contain six minor metabolites {vanillic acid, ferulic acid (*S*)-(+)-4-hydroxy-6-oxo-8-(4-hydroxy-3-methoxyphenyl)octanoic acid, 4-(4-hydroxy-3-methoxyphenyl)butanoic acid, 9-hydroxy[6]-gingerol and (*S*)-(+)-[6]-gingerol}. The total cumulative amount of the major metabolite excreted in the bile and of the six minor metabolites in the urine during 60 h after the oral administration of [6]-gingerol were approximately 48% and 16% of the dose, respectively. The excretion of the six minor metabolites in the urine decreased after gut sterilization, possibly suggesting the involvement of gut flora in the metabolism. On the other hand, incubation of [6]-gingerol with rat liver showed the presence of 9-hydroxy[6]-gingerol, gingerdiol, and (*S*)-[6]-gingerol-4'-*O*- β -glucuronide. These findings suggest that both the gut flora, as well as enzymes in the liver, play an important part in the metabolism of [6]-gingerol.

3.2. Effect on lipid and glucose concentrations in blood

It has been reported that treatment with a methanolic extract of dried rhizomes of ginger produced a significant reduction in fructose-induced elevation of lipid levels,

bodyweight, hyperglycemia and hyperinsulinemia. Treatment with an ethyl acetate extract of ginger did not produce any significant change in either of the last two parameters. However, it produced a significant reduction in elevated lipid levels and body weight. The concentration of [6]-gingerol was found to be higher in the methanol extract and less in the ethyl acetate extract. The results suggest that the ginger methanolic extract produces greater effects in comparison with the ethyl acetate extract in fructose-induced hyperlipidemia associated with insulin resistance. The extent of activity appears to be dependent on the concentration of [6]-gingerol present in the extracts (Kadnur and Goyal, 2005). The same authors (Goyal and Kadnur, 2006) administered methanol and ethyl acetate extracts of ginger for 8 weeks to mice and found that the treatment reduced goldthioglucose-induced obesity in the treated mice, and further reduced the elevated glucose and insulin levels. It was suggested that ginger had significantly improved insulin sensitivity in these animals. Recently, Al-Amin et al. (2006) studied the hypoglycemic potentials of ginger in streptozotocin (STZ)-induced diabetic rats given an aqueous extract of raw ginger daily (500 mg/kg, intraperitoneally) for a period of 7 weeks. Blood serum from fasting animals was analyzed for glucose, cholesterol and triacylglycerol levels. The STZ-injected rats exhibited hyperglycemia accompanied by weight loss. At a dose of 500 mg/kg, raw ginger was significantly effective in lowering serum glucose, cholesterol and triacylglycerol levels in the ginger-treated diabetic rats compared with the control diabetic rats. The ginger treatment also resulted in a significant reduction in urine protein levels. In addition, the ginger-treated diabetic rats sustained their initial weights during the treatment period. Moreover, ginger decreased both water intake and urine output in the STZ-induced diabetic rats. These results confirmed the earlier reports that suggested that raw ginger possesses hypoglycemic, hypocholesterolemic and hypolipidemic potential. Additionally, it showed that raw ginger is effective in reversing the diabetic proteinuria and loss of body weight observed in the diabetic rats. Thus, ginger may be of value in managing the effects of diabetic complications in human subjects.

Aldehyde reductase inhibitors are now considered to have remarkable potential for the treatment of diabetes and its complications without increased risk of hypoglycemia (see e.g. Giannoukakis, 2006). It has recently been reported that the assay for aldose reductase inhibitors in ginger led to the isolation of five active compounds including 2-(4-hydroxy-3-methoxyphenyl) ethanol and 2-(4-hydroxy-3-methoxyphenyl)ethanoic acid. These two named compounds were good inhibitors of recombinant human aldose reductase, with IC_{50} values of 19.2 ± 1.9 and 18.5 ± 1.1 μ M, respectively. Furthermore, these compounds significantly suppressed not only sorbitol accumulation in human erythrocytes, but also lens galactitol accumulation in 30% of galactose-fed cataract rats, suggesting that protection against or improvement of diabetic complications could

be achieved with a dietary supplement of either ginger or its extract containing aldose reductase inhibitors (Kato et al., 2006). However, more research into this is required, not only because of the limited experimental data, but also because of the lack of information on the effects of the chronic consumption of ginger in humans (Tapsell et al., 2006).

3.3. Effect on blood clotting

The effect of an aqueous extract of ginger on platelet thromboxane-B₂ (TBX₂) and prostaglandin-E₂ (PGE₂) production was examined after giving rats a raw aqueous extract of ginger daily for a period of 4 weeks, either orally or intraperitoneally (IP). A low dose of ginger (50 mg/kg) administered either orally or IP did not produce any significant reduction in the serum TBX₂ levels. However, ginger administered orally caused significant changes in the serum PGE₂ at this dose. High doses of ginger (500 mg/kg) were significantly effective in lowering serum PGE₂ when given either orally or IP. However, TBX₂ levels were significantly lower in rats given 500 mg/kg ginger orally, but not IP. These results suggest that ginger could be used as an anti-thrombotic and anti-inflammatory agent (Thomson et al., 2002).

3.4. Effect on blood pressure

Several pieces of evidence, mainly from rat studies, have suggested that ginger exerts many direct and indirect effects on blood pressure and heart rate (reviewed by Afzal et al., 2001). More recently, Ghayur and Gilani (2005) reported that the crude extract of ginger induced a dose-dependent (0.3–3 mg/kg) fall in the arterial blood pressure of anesthetized rats. In Guinea pig paired atria, the crude extract exhibited a cardiodepressant activity on the rate and force of spontaneous contractions. In rabbit thoracic aorta preparation, the crude extract relaxed the phenylephrine-induced vascular contraction at a dose 10 times higher than that required against K-induced contraction. Ca²⁺ channel-blocking activity was confirmed when the crude extract shifted the Ca²⁺ dose–response curves to the right, similar to the effect of verapamil. It also inhibited the phenylephrine control peaks in normal Ca²⁺-plus and Ca²⁺-free solutions, indicating that it acts at both the membrane-bound and the intracellular Ca²⁺ channels. When tested in endothelium-intact rat aorta, it again relaxed the K-induced contraction at a dose 14 times less than that required for relaxing the PE-induced contraction. The vasodilator effect of the crude extract was endothelium-independent because it was not blocked by either L-NAME (a non-selective inhibitor of nitric oxide synthase used experimentally to induce hypertension) or atropine and also was reproduced in the endothelium-denuded preparations in the same dose range. These data indicate that the blood pressure-lowering effect of ginger is mediated through blockade of voltage-dependent calcium channels. In another paper, the same group (Ghayur et al., 2005) concluded that the blood pres-

sure lowering action of aqueous ginger extract was through a dual inhibitory effect mediated via stimulation of both muscarinic receptors and blockade of Ca²⁺ channels. Interestingly, they also noted that the different constituents of ginger might have opposing actions on the reactivity of blood vessels. For example, an atropine-resistant and L-NAME-sensitive vasodilator activity was also noted for the ginger phenolic constituents [6]-, [8]-, and [10]-gingerol, while [6]-shogaol showed a mild vasodilator effect.

3.5. Anti-inflammatory and analgesic activities of ginger

The anti-inflammatory properties of ginger have been known for centuries (Afzal et al., 2001; Grzanna et al., 2005). Several lines of evidence have been provided, mostly in different animal models of inflammation, and to a much lesser extent in humans or human cells, of the effectiveness of either ginger or of compounds isolated therefrom against inflammation and its mediators. In the early 1980s, it was reported for the first time that ginger has anti-inflammatory actions, as evidenced by its inhibitory effects on prostaglandins synthesis (Kiuchi et al., 1982). Subsequently, it has been demonstrated that ginger contains constituents [e.g. gingerdiones (for example **14**) and shogaols (for example **2**, **7–10**)] that have pharmacological properties mimicking dual-acting non-steroidal anti-inflammatory drugs (NSAIDs) in intact human leukocytes *in vitro* (Flynn et al., 1968). It is known that such inhibitors have fewer side effects and are more effective than conventional NSAIDs (Charlier and Michaux, 2003; Martel-Pelletier et al., 2003). Further, it has been shown that gingerols are very active in inhibiting both prostaglandins and leukotrienes in RBL-1 cells, and that gingerols with long alkyl side chains are more potent inhibitors of leukotrienes synthesis than of prostaglandins synthesis (Kiuchi et al., 1992). More recently, it has been shown that ginger (and some of its constituents) is effective against cytokines synthesized and secreted at sites of inflammation (Grzanna et al., 2005). Cytokines are small proteins secreted at sites of inflammation by lymphocytes, macrophages, fibroblasts and other cells, and act as chemical messengers between cells involved in immune and inflammatory responses. Ginger was found to modulate some biochemical pathways activated in chronic inflammation (Grzanna et al., 2005). It was found to inhibit the induction of several genes involved in the inflammatory response, and some of these genes encode cytokines, chemokines and the inducible enzyme cyclo-oxygenase-2 (COX-2). To demonstrate that ginger extract has an effect on human monocyte cell activity, Grzanna et al. (2004) conducted an experiment with cultured THP-1 monocytes and showed that the extract can inhibit beta-amyloid peptide-induced cytokine and chemokine expression (Grzanna et al., 2004). In an *in vitro* study, the same group showed that extract of *Z. officinale* suppresses inflammation due to arthritis through suppression of pro-inflammatory cytokines and chemokines produced by synoviocytes, chondrocytes, and leukocytes.

Ginger extract was found to be effective in inhibiting chemokine expression (Phan et al., 2005).

The anti-inflammatory, analgesic, and anti-pyretic actions of an ethanolic extract of ginger were studied in rats. The extract reduced carrageenan-induced paw swelling and yeast-induced fever, but was ineffective in suppressing the writhing induced by intraperitoneal acetic acid (Mascolo et al., 1989). A dose-dependent inhibition of prostaglandin release was also observed using rat peritoneal leucocytes. Thomson et al. (2002) confirmed the inhibitory action of ginger on prostaglandins when they reported that either oral or intraperitoneal administration of a raw aqueous extract of ginger (500 mg/kg) given to rats daily for 4 weeks was effective in significantly reducing serum prostaglandin-E₂ (Thomson et al., 2002). A study has recently been reported reconfirming the anti-inflammatory, analgesic, and anti-pyretic actions of an ethanolic extract of ginger in rats and mice (Ojewole, 2006).

The mechanism of action of ginger, gingerol compounds, and their derivatives has been studied by many authors. Gingerols and their derivatives, especially [8]-paradol, have been reported to be more potent anti-platelet and cyclo-oxygenase-1 (COX-1) inhibitors than aspirin, when tested *in vitro* by the Chrono Log whole blood platelet aggregometer (Nurtjahja-Tjendraputra et al., 2003). These authors proposed that the carbonyl functional group at C3 found in paradol and in the diarylheptanoid series may contribute to their potent anti-platelet activity and inhibition of COX-1. Inhibition of the arachidonic acid (AA) metabolism cascade via the COX-1/thromboxane synthase system by these phenolic compounds may underline the mechanism of their action. Koo et al. (2001) compared the ability of gingerols and related analogs to that of aspirin in inhibiting AA-induced human platelet serotonin release *in vitro*. Using the same dose range, it has been found that gingerols and related analogs were approximately two- to three-fold less potent than aspirin against the platelet release reaction initiated by AA, and two- to four-fold less potent than aspirin at inhibiting AA-induced platelet aggregation. Gingerols inhibited COX activity, assessed by measuring PGD₂, a product of AA metabolism by COX. These results suggest that inhibition of COX activity by gingerols and related analogs may be the underlying mechanism for their effect on AA-induced platelet activation. Another report by the same group in Australia suggested that gingerols act as vanilloid receptor (VR1) agonists (Dedov et al., 2002). The VR1 receptor has been shown to integrate chemical and thermal nociceptive stimuli (for a review see Ma and Quirion, 2007). Therefore, direct activation/deactivation of the VR1 receptor at the site where pain is generated during inflammation and other painful conditions provides a new strategy for the development of a new class of peripheral analgesics devoid of the well characterized side effects of currently available analgesics and anti-inflammatory drugs.

Inducible nitric oxide synthase (iNOS), a pro-inflammatory enzyme responsible for the generation of nitric oxide

(NO), has been implicated in the pathogenesis of inflammatory diseases, and as gingerols are known to have anti-inflammatory properties *in vitro* (Kiuchi et al., 1992; Kim et al., 2005), Aktan et al. (2006) examined the effect of a stable [6]-gingerol metabolite, RAC-[6]-dihydroparadol ([6]-DHP) and a closely related gingerol analog, RAC-2-hydroxy-1-(4-hydroxy-3-methoxyphenyl) dodecan-3-one [a capsaicin/gingerol (capsarol) analog referred to as ZTX42] on NO production, inducible nitric oxide synthase (iNOS) activity and protein expression levels in a murine macrophage cell line. It has been found that ZTX42 and [6]-DHP suppress NO production in murine macrophages by partially inhibiting iNOS enzymatic activity and reducing iNOS protein production, via attenuation of NF-kappa B-mediated iNOS gene expression, providing a possible mechanism of action for the anti-inflammatory activity reported for this class of compounds. More recently, Tripathi et al. (in press) tested the hypothesis that whole ginger extract has a global inhibitory effect on macrophages function *in vitro* and that this accounts for its reputed anti-inflammatory effect *in vivo*. They also hypothesized that the active constituent in ginger, [6]-gingerol, is an effective anti-inflammatory substance because of its inhibition of macrophage activation, more specifically by its inhibition of pro-inflammatory cytokines and antigen presentation by lipopolysaccharide-activated macrophages. It was concluded that [6]-gingerol selectively inhibits production of pro-inflammatory cytokines from macrophages, but does not affect the antigen presenting cells (APC) function. Therefore, [6]-gingerol acts as an anti-inflammatory compound that may be useful to treat inflammation without interfering with the antigen presenting function of macrophages.

It is established that neither ginger nor its constituents produce the gastrointestinal adverse effects that are usually produced by the conventional NSAIDs as a result of prostaglandin inhibition (Goldstein, 2004; Konturek et al., 2005). In fact, ginger has been shown to protect against ulceration in rats (Yamahara et al., 1988; Wu et al., 1990).

3.6. Effect of ginger on gastrointestinal (GIT) tract

The powdered rhizome of ginger has long been used in traditional medicine for alleviating the symptoms of GIT illnesses (for earlier reports see Afzal et al., 2001). An acetone extract of ginger and its constituents have been shown to enhance the gastric emptying of charcoal meal in mice (Yamahara et al., 1990). The effectiveness of ginger in emesis due to hyperemesis gravidarum (Fischer-Rasmussen et al., 1990), motion sickness (Stewart et al., 1991) and cancer chemotherapy (Sharma et al., 1997) has also been reported. Ginger has been recorded as being useful in preventing post-operative nausea and vomiting in humans (Phillips et al., 1993b), without a significant effect on gastric emptying (Phillips et al., 1993a). The authors have excluded a central anti-cholinergic effect of ginger as it did not reduce the nystagmus response to vestibular and

optokinetic stimuli. In rats, however, it has been shown that [6]-gingerol enhances GIT transit of charcoal meal (Yamahara et al., 1990), and the lack of this action in humans was ascribed to the inadequate doses used. Recently, it has been confirmed that ginger extract, in addition to having a direct cholinergic agonistic effect on the post-synaptic M3 receptors, also has a possible inhibitory effect on pre-synaptic muscarinic autoreceptors, similar to standard muscarinic antagonists (Ghayur et al., 2007).

In isolated Guinea pig ileum, several compounds in ginger (e.g., [6]-gingerol, [6]-shogaol, and galanolactone) have been shown to have anti-serotonin (5-hydroxytryptamine) effects (Yamahara et al., 1989; Huang et al., 1991). This may possibly suggest that the anti-emetic action of either ginger or some of its constituents may be mediated centrally via 5-HT₃ receptors, as these constituents have small molecular weights and could easily cross the blood brain barrier. In *Suncus murinus* (a house musk shrew), it has been shown that orally administered [6]-gingerol completely prevented vomiting in response to cyclophosphamide, presumably via a central effect (Yamahara et al., 1989).

Cisplatin treatment causes nausea and vomiting in man and animals. Acetone and 50% ethanolic extracts of ginger at oral doses of 25, 50, 100 and 200 mg/kg exhibited significant protection, while aqueous extract at these doses was ineffective against cisplatin emesis in dogs (Sharma et al., 1997), and rats (Sharma and Gupta, 1998).

Ernst and Pittler (2000) reviewed the evidence for the usefulness of ginger against nausea and vomiting from six clinical studies. Three on post-operative nausea and vomiting were identified and two of these suggested that ginger was superior to placebo and equally effective as metoclopramide. The pooled absolute risk reduction for the incidence of post-operative nausea, however, indicated a non-significant difference between the ginger and placebo groups for ginger (1 g) taken before operation (absolute risk reduction 0.052 (95% confidence interval –0.082 to 0.186). One study was found for each of the following conditions: seasickness, morning sickness and chemotherapy-induced nausea. These studies collectively favored ginger over placebo. The conclusion was that whether the crude drug is truly efficacious for this condition is still a matter of debate. More recently, Bryer (2005) reviewed four recent well-controlled, double-blind, randomized clinical studies that provide convincing evidence for the effectiveness of ginger in treating nausea and vomiting of pregnancy. It also provides a dosage update for the various forms of ginger.

Mahady et al. (2003) were the first to provide evidence that the active constituents of ginger (gingerols) are effective *in vitro* against *Helicobacter pylori*, the primary etiological factor associated with dyspepsia, peptic ulcer disease and development of gastric and colon cancer. This was further confirmed by Mahady et al. (2005) and Nostro et al. (2006).

O'Mahony et al. (2005) tested the bactericidal and anti-adhesive properties of ginger and several other culinary and medicinal plants against *H. pylori* and found that ginger was highly effective in killing *H. pylori*, but had lesser ability in inhibiting the adhesion of this bacterium to stomach sections. More recently, Siddaraju and Dharmesh, (2007) reported that ginger-free phenolic and hydrolyzed phenolic fractions of ginger were both potent inhibitors of gastric cell proton potassium ATPase activity and *H. pylori* growth, and suggested that the two fractions could be inexpensive multistep blockers against ulcer.

3.7. Tissue and radio-protective effects of ginger

Several extracts and fractions of *Z. officinale* have been shown to protect against chemically-induced tissue damage. For example, it has been shown by Yemitan and Ize-ghu (2006) that pretreatment of rats with an ethanol extract of the rhizome of *Z. officinale* and oil extracted from the plant were effective in ameliorating carbon tetrachloride and acetaminophen (paracetamol)-induced acute hepatotoxicity.

The radioprotective effect of the hydroalcoholic extract of ginger rhizome (ZOE) was studied in mice given the extract at an intraperitoneal dose of 10 mg/kg, once daily for five consecutive days before exposure to 6–12 Gy of gamma radiation, and were monitored daily up to 30 days post-irradiation for the development of signs of radiation sickness and mortality (Jagetia et al., 2003). The protection of ginger against radiation lethality was confirmed by the same authors in a subsequent publication (Jagetia et al., 2004). Pretreatment of mice with ZOE reduced the severity of radiation sickness and the mortality, and protected mice from gastrointestinal syndrome, as well as bone marrow syndrome. The dose reduction factor for ZOE was found to be 1.15. The optimum protective dose of 10 mg/kg ZOE was 1/50 of the LD₅₀ (500 mg/kg).

It has been shown by Sharma et al. (2005) that ginger extract mitigates the neuro-behavioral effects of gamma radiation-induced conditioned taste aversion in Sprague–Dawley rats. Administration of the extract 1 h before 2-Gy gamma irradiation was effective in blocking the saccharin avoidance response for five post-treatment observational days, both in a dose- and time-dependent manner, with 200 mg/kg b.w., i.p., being the most effective dose. More recently, the same group investigated the role of a ginger hydroalcoholic extract as a gastroprotective agent in radiation-induced taste aversion (CTA) learning and emesis in rats, and found that the extract had succeeded in protecting the rats against CTA to a degree comparable to the standard anti-emetic drugs ondasterone and dexamethasone. The mechanisms of this gastro-protection have been suggested to be multifactorial and include anti-oxidant, neuromodulatory and radioprotective mechanisms. It was concluded that ginger may be a pharmacological agent that can safely and effectively mitigate the early

damage produced in cells and tissues by ionizing radiation (Haksar et al., 2006).

3.8. Anti-oxidant actions of ginger

Several authors have shown that ginger is endowed with strong *in vitro* and *in vivo* anti-oxidant properties. The anti-oxidant action of ginger has been proposed as one of the major possible mechanisms for the protective actions of the plant against toxicity and lethality of radiation (e.g. Jagetia et al., 2003; Haksar et al., 2006) and a number of toxic agents such as carbon tetrachloride and cisplatin (e.g. Amin and Hamza, 2006; Yemitan and Izegebu, 2006), and as an anti-ulcer drug (Siddaraju and Dharmesh, 2007).

Recently, it has been shown that [6]-gingerol is endowed with strong anti-oxidant action both *in vivo* and *in vitro*, in addition to strong anti-inflammatory and anti-apoptotic actions (Kim et al., 2007). This makes it a very effective agent for prevention of ultra violet B (UVB)-induced reactive oxygen species production and COX-2 expression, and a possible therapeutic agent against UVB-induced skin disorders.

3.9. Ginger–drug interactions

Few ginger–drug interactions have been reported in the literature. Ginger does not interact with the anti-coagulant drug warfarin in rats or man (Weidner and Sigwart, 2000; Vaes and Chyka, 2000). This has recently been confirmed in a study by Jiang et al. (2005) in an open label, three-way crossover, randomized study in 12 healthy volunteers. Ginger was given orally at a dose of 400 mg (three times per day for 1 week) before warfarin, and was continued for a further 1 week after it. Ginger was found to exert no significant effect on either the clotting status or the kinetics and dynamics of warfarin.

The synergistic effect of ginger and nifedipine on anti-platelet aggregation in normal human volunteers and hypertensive patients has been studied in Taiwan (Young et al., 2006). It has been found that the percentage of platelet aggregation induced by collagen, adenosine diphosphate (ADP) and epinephrine in hypertensive patients was larger than that in normal volunteers. Either aspirin or ginger could potentiate the anti-platelet aggregation effect of nifedipine in normal volunteer and hypertensive patients. These results suggested that ginger and nifedipine have a synergistic effect on anti-platelet aggregation. It has been recommended that combination of 1 g ginger with 10 mg nifedipine per day could be valuable to combat cardiovascular and cerebrovascular complication due to platelet aggregation.

3.10. Anti-microbial actions of ginger

Ginger extract (10 mg/kg) intraperitoneally had a dose-dependent anti-microbial activity against *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Escherichia coli* and

Candida albicans (Jagetia et al., 2003). Yin and Cheng (1998) showed that ginger had no significant action against some fungi (*Aspergillus niger* and *Aspergillus flavus*) *in vitro*. However, Ficker et al. (2003b) found that, out of 29 plant extracts, ginger extract had the broadest range of anti-fungal activity measured either by the fungi inhibited or as the average diameter of the zones of inhibition. The ginger extract was the only one that was active against *Rhizopus* sp., an organism that was not inhibited by any of the other plant extracts tested or by the anti-fungal agent ketoconazole or berberine. Using bioassay-guided isolation and identification of anti-fungal compounds from ginger, the same authors (Ficker et al., 2003a) reported that [6], [8]-, and [10]-gingerols and [6]-gingerdiol are the main anti-fungal principles. The compounds were active against 13 human pathogens at concentrations of <1 mg/ml. The gingerol content of the African land race was at least three times higher than that of typical commercial cultivars of ginger. Therefore, these authors suggested that ginger extracts standardized on the basis of the identified compounds could be considered as anti-fungal agents for practical therapy.

Iqbal et al. (2006) investigated the anthelmintic activity of crude powder (CP) and crude aqueous extract (CAE) of dried ginger (1–3 g/kg) in sheep naturally infected with mixed species of gastrointestinal nematodes. Both CP and CAE exhibited a dose- and a time-dependent anthelmintic effect with respective maximum reduction of 25.6% and 66.6% in eggs per gram (EPG) of feces on day 10 post-treatment. Levamisole (7.5 mg/kg), a standard anthelmintic agent, exhibited 99.2% reduction in EPG. Although the authors of this study concluded that ginger possesses *in vivo* anthelmintic activity in sheep, thus “justifying the age-old traditional use of this plant in helminth infestation”, it is clear that the reduction in the EPG induced by ginger is too small compared with the safe and effective anthelmintics currently available.

3.11. Miscellaneous effects

Iwasaki et al. (2006) investigated the components of ginger that are involved in increasing body temperature. All the gingerols and shogaols increased intracellular calcium concentration in rat transient receptor potential vanilloid subtype 1 (TRPV1)-expressing HEK293 cells via TRPV1. In this regard, the shogaols were more potent than the gingerols. Adverse responses were induced by [6]- and [10]-gingerol, and [6]-shogaol (5 mmol/l) in rats when these compounds were applied to the eye. However, no response was observed with [10]-shogaol (5 and 10 mmol/l). [10]-Shogaol induced nociceptive responses via TRPV1 in rats following its subcutaneous injection into the hind paw; the pungent compound capsaicin (CAP) and [6]-shogaol were observed to have similar effects. Moreover, adrenal catecholamine secretion, which has similar influences on energy consumption, was promoted in rats in response to [6]- and [10]-gingerols and [6]- and [10]-shogaols

(1.6 $\mu\text{mol/kg}$, i.v.). [10]-Shogaol-induced adrenaline secretion was inhibited by administration of capsazepine, a TRPV1 antagonist. It was concluded that gingerols and shogaols activated TRPV1 and increased adrenaline secretion. Interestingly, [10]-shogaol is the only non-pungent compound among the gingerols and shogaols, suggesting its usefulness as a functional ingredient in food.

Parabens are a group of chemicals widely used as preservatives in the cosmetic and pharmaceutical industries. These compounds, and their salts, are used primarily for their bacteriocidal and fungicidal properties. They can be found in shampoos, commercial moisturizers, shaving gels, cleansing gels, personal lubricants, topical/parenteral pharmaceuticals and toothpaste. They are also used as food additives. Asnani and Verma (2006) reported that an aqueous ginger extract has an ameliorative effect on cytotoxicity induced by paraben (*p*-hydroxybenzoic acid) on healthy human erythrocytes *in vitro*. Addition of paraben to RBC suspension caused significant increase in the rate of hemolysis. However, concurrent addition of paraben (150 $\mu\text{g/ml}$) and ginger extract caused significant concentration-dependent retardation in paraben-induced hemolysis. More recently, Verma and Asnani (2007) evaluated the effect of paraben (*p*-hydroxybenzoic acid) on acidic, basic, and neutral proteins content, as well as carbohydrate and cholesterol contents in liver and kidney of mice. They have found that oral administration of aqueous extract of *Z. officinale* (3 mg/animal/day) along with paraben for thirty days caused significant amelioration in all the protein types, carbohydrate and cholesterol of liver and kidney.

In a recent paper, Tripathi et al. (in press) cited unpublished results that suggest that ginger prolongs survival of mice heart allografts *in vivo*, and inhibits several macrophage functions *in vitro*.

The phenolic alkanone 6-gingerol and the related compound 6-shogaol reduced gastric cancer cells via different mechanisms (Ishiguro et al., in press). The former affected the viability of cancer cells only slightly, while the latter compound has a significant inhibitory effect by damaging microtubules and inducing mitotic arrest.

4. Toxicological properties of ginger

Ginger is generally considered a safe herbal medicine (Weidner and Sigwart, 2000). A patented ginger extract EV.EXT 33 was administered by oral gavage in concentrations of 100, 333, and 1000 mg/kg, to three groups of 22 pregnant female rats from days 6 to 15 of gestation. For comparison, a fourth group received the vehicle, sesame oil. Body weight and food and water intake were recorded during the treatment period. The rats were killed on day 21 of gestation and examined for standard parameters of reproduction performance. The fetuses were examined for signs of teratogenic and toxic effects. The ginger preparation was well tolerated. No deaths or treatment-related adverse effects were observed. Weight gain and food consumption were similar in all groups during gestation.

Reproductive performance was not affected by the ginger treatment. Examination of fetuses for external, visceral, and skeletal changes showed neither embryotoxic nor teratogenic effects of the ginger preparation. Based on these results, it was concluded that the ginger preparation EV.EXT 33, when administered to pregnant rats during the period of organogenesis, caused neither maternal nor developmental toxicity at daily doses of up to 1000 mg/kg body weight (Weidner and Sigwart, 2001).

Conversely, some adverse effects of ginger have been reported in pregnant rats (Wilkinson, 2000). Ginger tea (15 g/l, 20 g/l or 50 g/l) was given in the drinking bottles of pregnant Sprague–Dawley rats on day 6 of gestation onwards until day 15 of gestation, and they were sacrificed at day 20. No maternal toxicity was observed, but embryonic loss in the treatment groups was double that of the controls. No gross morphologic malformations were seen in the treated fetuses. Fetuses exposed to ginger tea were found to be significantly heavier than controls, an effect that was greater in female fetuses and was not correlated with increased placental size. Treated fetuses also had more advanced skeletal development as determined by measurement of sternal and metacarpal ossification centers. The results of this study suggest that *in utero* exposure to ginger tea results in increased early embryo loss with increased growth in surviving fetuses (Wilkinson, 2000). Although ginger has been proposed as a safe and effective alternative to conventional anti-emetic drugs (Boone and Shields, 2005), it may be prudent to avoid using either ginger or compounds extracted therefrom during pregnancy in women, pending more studies (Marcus and Snodgrass, 2005).

Some minor adverse effects have been associated with the use of ginger in humans. In one clinical trial that involved 12 healthy volunteers who received ginger orally at a dose of 400 mg of ginger (3 times per day for two weeks), one subject in the study reported mild diarrhea during the first 2 days of ginger pretreatment. Ginger may cause heartburn, and in doses higher than 6 g may act as a gastric irritant. Inhalation of dust from ginger may produce IGE-mediated allergy (Chrubasik et al., 2005).

5. Conclusions

The present review sought to document and comment on the publications that have appeared on ginger and its constituents in the last 10 years or so. The papers reviewed provide another example of how it may be possible to explain the action(s) of folk medicines in terms of conventional biochemistry and pharmacology. Ginger and many of its chemical constituents have strong anti-oxidant actions. As several metabolic diseases and age-related degenerative disorders are closely associated with oxidative processes in the body, the use of either ginger or one or more of its constituents as a source of anti-oxidants to combat oxidation warrants further attention. Ginger and many of its chemical constituents have been shown, in

numerous clinical studies, to be useful in combating post-operative vomiting and vomiting of pregnancy. It may be worthwhile investigating the effect of ginger on vomiting during cancer chemotherapy, as the crude drug and its constituents have themselves anti-cancer actions. More studies are also required on the kinetics of ginger and its constituents and on the effects of their consumption over a long period of time. Ginger is considered to be a safe herbal medicine with only few and insignificant adverse/side effects.

Further trials in humans are required to determine the efficacy of ginger (or one or more of its constituents) and to establish what, if any, adverse effects are observed. However, double blind clinical trials are difficult to perform because the taste and smell of ginger are very pronounced.

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