

A Review: Is Ginger (*Zingiber officinale* var. Roscoe) Potential for Future Phytomedicine?

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Abstract

Zingiber officinale Roscoe (red:ginger), one of the most widely consumed herbs in Asia, has been empirically used to treat various disorders in Indonesia. There are three known types of ginger: giant ginger or white ginger (*Zingiber officinale* var. Roscoe), small white ginger or ginger *empit* (*Zingiber officinale* var. Amarum), and red ginger (*Zingiber officinale* var. Rubrum). The main components of ginger rhizome are carbohydrates, lipids, essential oils, terpenes, and phenol compounds such as gingerol (23-25%) and shogaol (18-25%). Many studies had confirmed beneficial effects of ginger against inflammation, free radicals, diabetes mellitus, bacterial infection, cancer, nausea, etc. *Z. officinale* var. Roscoe is considered a safe herbal with not significant adverse effects. This plant is potential to be developed for future phytomedicine, however further explorations on its clinical studies in humans is expected, especially the efficacy and safety of the risk of side effects.

Introduction

Zingiber officinale is one of the most widely used plants in Asia, Australia and many other countries.^{1,2,3,5,12} Empirically, *Z. officinale* has been used in digestive disorders (indigestion, flatulence, constipation, nausea), headache, rheumatism, cold and cough.⁶

In the last few decades, *Z. officinale* is extensively studied for its medicinal properties by advanced scientific techniques and a variety of bioactive compounds had been isolated from different parts of the plant. The plant is reported for antimicrobial activity, anticancer activity, antioxidant activity, antidiabetic activity, nephroprotective activity, hepatoprotective activity, larvicidal activity, analgesic activity, anti-inflammatory activity and immunomodulatory activities.^{1,8,9,12,13}

More than seventy pharmacology studies of *Z. officinale* rhizomes have been reported. Most of the secondary metabolites of herbs are commercially important and find use in a number of pharmaceutical compounds. Flavonoids and phenolics are the most important groups of secondary metabolites and bioactive compounds in plants.⁹ Shogaol and gingerol are the most common bioactive compounds found in ginger, and have various pharmacological benefits.

The present review is focused for the taxonomy, distribution, botanical description, secondary metabolite extraction, chemical constituents, pharmacological activity, side effect and toxicity of *Z. officinale* var Roscoe.



Figure 1: Rhizome of *Zingiber officinale* var. Amarum (left), *Zingiber officinale* var. Roscoe (center), and *Zingiber officinale* var. Rubrum (right).³³

Taxonomy, Distribution, and Botanical Description

Kingdom : Plantae
Division : Magnoliophyta
Class : Liliopsida
Order : Zingiberales
Family : Zingiberaceae
Genus : Zingiber
Species : *Zingiber officinale* var. Roscoe^{8,34}

Ginger is a tropical plant, grows well in hot and humid climates. The plant is cultivated in China, Nepal, US, India, Bangladesh, Taiwan, Jamaica, Nigeria and Indonesia. India is the biggest producer of *Z. officinale*.⁸ In Indonesia, *Z. officinale* is one of the export commodities, with the development area in 2010 reaching 6,053 ha and the requirement of ginger seed is rhizome 12.106 tons/year. In accordance with the requirements of growing ginger, seed production sites

can be selected on land with climate type A, B, or C, with altitude of 300-900 dpl, average temperature 25-30°C, wet month number 7-9 months, rainfall 2,500-4,000 mm/year, with light intensity 70-100%.¹⁴

Ginger is herbaceous rhizomatous perennial, reaching up to 90 cm in height under cultivation. Rhizomes are aromatic, thick lobed, pale yellowish, bearing simple alternate distichous narrow oblong lanceolate leaves. The herb develops several lateral shoots in clumps, which begin to dry when the plant matures. Leaves are long and 2 - 3 cm broad with sheathing bases, the blade gradually tapering to a point. Inflorescence solitary, lateral radical pedunculate oblong cylindrical spikes. Flowers are rare, rather small, calyx superior, gamosepalous, three toothed; open splitting on one side, corolla of three sub equal oblong to lanceolate connate greenish segments.¹¹ Stems erect. The leaves are often clear 2 rows with stem hugging, and tongue between the borders and leaf blades. Zygomorph flowers are bandaged. Petals forms as tube, with a tip hammered, often split in a midrib. Rhizome slightly flat, bagin tip short and flat branches, at each end of the branch there is a grooved curve inside. The outer pieces are yellowish brown, grooved lengthwise.¹⁵

Extraction Method

Secondary metabolite compounds are organic compounds derived from plants that have bioactive ability, for example phenolic, flavonoid and terpenoid groups. A number of chemical and physical factors that could influence secondary metabolism in plant cell cultures have been found, including light, temperature, pH of medium, aeration, cell density, etc. Different light intensities are able to change synthesis of phenolics and flavonoids components in ginger.^{16,17}

The phenolic compounds represent one of the main groups of secondary metabolites in plants and they are present in foods and nutraceuticals. These phytochemicals have a wide range of biological actions, including the ability to act as antioxidants, ameliorate inflammation, modulate enzyme activity, and regulate gene expression. The content of total polyphenolics in ginger extract was in amount of 181.41 mg/g ginger extract, and flavonoid in amount of 14.15 mg/g ginger extract.²⁶

Flavonoids are important in plant biochemistry and play an important role in plant physiology, acting as antioxidants, enzyme inhibitors, pigments and light screens.¹⁷ HPLC analysis revealed that the synthesis of flavonoids such as quercetin, catechin, epicatechin and naringenin were enhanced under low light intensity. A decreasing of light intensity also reduced the photosynthesis rate, and consequently diminished the soluble carbohydrate and plant biomass in *Halia Bentong* and *Halia Bara*.¹⁷

Drying of ginger rhizome should be done below 70 °C for better quality dried products. For glycoside

species, a maximum temperature of 100 °C is recommended, for mucilage species 65 °C and for essential-oil species 35 to 45 °C.¹⁹

A study has been done to compare between decoct and maceration methods using water and ethanol as the solvent to extract flavonoid and phenolic contents. The ginger was oven-dried at 50°C and macerated in ethanol (10 g in 100 ml) for 3 x 24 hours and 48 hours. The other sample was decocted in distilled water for 24 and 48 hours. Both of the solvents were rotavaporated.²² The ethanol extract is more active^{20,22} than the others although its total flavonoid and phenols are lower. Water extract contains higher total flavonoid and phenols.²² Traditionally, the extraction of 6-gingerol and 6-shogaol compounds is accomplished by reflux or Soxhlet extraction. However, prolonged extraction at high temperature may degrade the 6-gingerol and 6-shogaol compounds and involves high energy cost. In acidic media and under high extraction temperature 6-gingerol can be degraded to 6-shogaol. The optimum extraction condition for all responses was at 76.9 °C for 3.4 h. Pharmaceutical quality of ginger could be improved significantly by optimizing of extraction process.²⁸

Chemical Constituent

The most important compounds responsible for ginger's therapeutic activities, are divided into non-volatile and volatile compounds. The non-volatile fraction consists of an oleoresin. Elements responsible for gingers spicy flavor have been identified as the gingerols. The composition of the volatile fraction consists mainly of sesquiterpene derivatives, responsible for the aroma. Such compounds include (-)-zingiberene, (+)-curcumene, (-)-β-sesquiphellandrene and β-bisabolene. The monoterpene derivatives are also a part of this essential oil.^{16,21}

Z. officinale rhizome contains 1–4% essential oil and oleoresin, but the chief constituent is sesquiterpene (53.57%).³⁰ Several compounds have been identified in the essential oil, it's estimated that there are 28 compounds. The most content were eudesmol (8.19%), γ-terpinene (7.88%), α-curcumene (7.28%), zingiberene (6.06%), alloaromadendrene (6.56%), α-pinene (5.76%), δ-cadinene (3.84%), elemol (3.39%), farnesal (3.45%), E-β-farnesene (3.57%), neril acetate (2.8%) and β-myrcene (2.94%).³²

The main constituents of ginger are sesquiterpenoids with zingiberene as the main component. Other components include β-sesquiphellandrene, bisabolene and farnesene, which are sesquiterpenoids, and trace monoterpene fraction, (cineol, citral and β-sesquiphellandrene).²⁰

The gingerols is the primary active constituents, 5-hydroxy-1-(4-hydroxy-3-methoxy phenyl) decan-3-one is the most abundant in this constituent. Some other active compounds are mono and sesquiterpenes; camphene, betaphellandrene, curcumene, cineole, geranyl acetate, terphineol,

terpenes, borneol, geraniol, limonene, linalool, alpha-zingiberene (30-70%), sesquiphellandrene (15-20%), betabisabolene (10-15%) and alpha-farnesene. Its Bulb is widely used because it contains gingerol, ethanol as active chemical compound. It also contains amadaldehyde, paradols, gingerdiols, gingerdiacetates, gingerdiones, 6-gingersulfonic acid, gingerenones.²¹

Gingerol very unstable in the presence of heat and high temperatures will turn into shogaol. Shogaol which is spicier than gingerol, is the main component of dry ginger.²² Gingerols are thermally labile due to the presence of a β -hydroxy keto group in the structure and undergo dehydration readily to form the corresponding shogaols.³¹ Kinetics of [6]-gingerol degradation was characterized by least square fitting of a rate equation. It was found that gingerol exhibited novel reversible kinetics, in which it undergoes dehydration-hydration transformations with shogaol, the major degradation product. Degradation rates were found to be pH dependent with greatest stability observed at pH 4. The reversible degradation of [6]-gingerol at 100 °C and pH 1 was relatively fast and reached equilibrium within 2 h. Rapid degradation of gingerol mainly occurs at high temperature and at an acidic pH, resulting in dehydration to form shogaol. Both gingerol and shogaol are most stable at pH 4 at 37 °C.¹⁸

The presence of a β -hydroxy keto functional group in the structure of gingerols is a key feature that makes them thermally labile and makes them undergo facile dehydration at high temperature and in acidic conditions. A kinetic study of the dehydration of [6]-gingerol was carried out at 120 °C over a pH range from 2.4 to 7.2. These studies showed that the dehydration of gingerol was pH and temperature dependent and followed first order kinetics. The mechanism of degradation of gingerol was considered in previous studies, including a retro-aldol reaction leading to formation of zingerone and aliphatic aldehydes, and dehydration to shogaol. Polymerization of shogaol was also demonstrated at higher temperature (120°C) in 12 h.¹⁸

In terms of lipophilic properties, [6]-shogaol is considerably more lipophilic than [6]-gingerol as a result of the loss of a hydroxyl group from gingerol on dehydration to shogaol. The difference in the lipophilicity would result in significant differences in bioavailability and pharmacokinetic parameters of these two compounds in vivo.¹⁸

Pharmacology Activity

The primary activities include antiinflammatory, antioxidant, analgesic effect, anti-proliferative and hepatoprotective activity.²¹

Antiinflammatory Activity

First group to investigate the effect of ginger on platelet aggregation by using four ginger extracts, produced using different solvents (aqueous, n-hexane,

chloroform, and ethyl acetate). They reported that ginger inhibited platelet aggregation using arachidonic acid (AA), epinephrine, adenosine diphosphate (ADP), and collagen as agonists. Others have corroborated this, reporting that certain ginger compounds inhibit in vitro platelet aggregation when using a variety of agonists (AA, collagen, platelet activating factor, and thrombin). This reduction in platelet aggregation was most potent when AA was used as the agonist, requiring lower concentrations to cause inhibition when compared to the other agonists.²⁴

While few studies investigating the effect of ginger and its compounds on the clotting cascade have been undertaken, a considerable amount of in vitro research suggests that ginger compounds interact with AA-derived eicosanoid and thromboxane synthesis. The AA cascade can produce the eicosanoids involved in inflammation (i.e. prostaglandin E2) as well as thromboxane, which is amongst the many agonists of platelet aggregation. Numerous studies indicate that ginger extract and particular ginger compounds inhibit products specific to the cyclooxygenase pathway, including a reduction in thromboxane B2 (TxB2) production prostaglandin formation (PGF2a, PGE2, and PGD2), and cyclooxygenase enzyme activity. These same compounds also interact with the lipoxygenase pathway, including reductions in 5-lipoxygenase enzyme activity.²⁴

Finally, ginger compounds might also inhibit the activity of phospholipase A2, which suggests that ginger exerts its anti-platelet aggregating as well as its potential anti-inflammatory actions through interaction with one of the initial steps in this pathway. Due to the observed in vitro effects of ginger on the AA cascade, excessive bleeding and interactions with platelet therapy during cancer chemotherapy are of clinical concern. While the results of in vitro studies are consistent, these results are not always translatable to the complex human system. Due to the potential effects of ginger on platelet aggregation, ginger is a commonly-cited example of an herbal supplement that should be avoided in patients with thrombocytopenia, platelet function defects or coagulopathy, such as populations using ginger for its antiemetic effect in cancer chemotherapy.²⁴

Antioxidant Activity

Oxidation of biological molecules induces a variety of pathological disease including atherosclerosis or cancer. These damages are caused due to the presence of free radicals. [6]-gingerol, [6]-shogaol have displayed strong antioxidant activity in vitro. It is known that the antioxidant activity of plant extracts containing polyphenol components is due to their capacity to be donors of hydrogen atoms or electrons and to capture the free radicals. The ginger extract showed antioxidant effect in inhibiting DPPH radical, IC50 was 4.25 mg/ml. DPPH analysis is one of the tests used to prove the ability of the components of the ginger extract to act

as donors of hydrogen atoms. DPPH radical does not react with flavonoids, which contain no OH-groups in B-ring as well as with aromatic acids containing only one OH-group.²⁵

Antidiabetic Activity

A double-blind, placebo-controlled, randomized clinical trial was conducted on 20–60 year old patients with type 2 diabetes who did not receive insulin. Participants in the intervention and control groups were received 3 g of powdered ginger or placebo (lactose in capsules) daily for 3 months. This report shows that the 3 months supplementation of ginger improved glycemic indices, total antioxidant capacity (TAC) and paraoxonase-1 (PON-1) activity in patients with type 2 diabetes (T2DM). In this study, 3 g/day of ginger supplementation in T2DM patients for 3 months significantly decreased glucose, insulin, insulin resistance, highsensitive C-reactive protein (hs-CRP) and malate dehydrogenase (MDA) but significantly increased PON-1 and TAC compared to the control group.²⁷

Antibacterial

Ginger extract has showed antimicrobial activity against broad spectrum of pathogenic microorganisms such as *Escherichia coli*, *Salmonella typhi*, *Bacillus subtilis* and yeast *Candida albicans*. Main components, including [6]-gingerol and [12]-gingerol, isolated from ginger rhizome displayed antibacterial activity against periodontal bacteria. Hiserodt (1998) mentioned in his research that [10]-gingerol is active inhibitor of *Mycobacterium avium* and *M. tuberculosis*.²⁵ Ethanol extract of ginger is best effective against *S. aureus* when compared with *E. faecalis*.²⁰

Cytotoxic Activity

Except for antioxidant and antimicrobial effects of phenolic compounds contained in *Zingiber officinale*, these components also have anti-carcinogenic and anti-mutagenic activities. [6]-gingerol inhibits cell adhesion, invasion, motility and activities of human breast cancer cell lines.²⁵

Antinausea/Antiemetic

The volatile oil of ginger known have antiemetic potency. The compounds as terpinolene, β -pinene and α -phellandrene known had interact with 5-HT₃ receptor channel system and antispasmodic effect at the rat ileum.³⁵

The Role of Gingerol and Shogaol in the Pharmacology Activity of Ginger

Polyphenols are an important class of antioxidant defense.²² The metabolites of ginger have recognised as potent anti-oxidants due to their ability to inhibit the oxidation of various free radicals and the

production of nitric oxide. The pharmacology activities of gingerol and shogaol are related with their possible mechanisms of action and structure–activity, as elucidated through selected in vitro and in vivo models.²³

Gingerol and shogaol which show anticancer activity against a lot of cells, metabolism of ginger found mutagenic. Metabolites against various carcinomas and cell lines of lung, colon, skin, pancreas, prostate, liver, ovarian, colon, breast, kidney.²³

[6]-gingerol is endowed with strong antioxidant activity both *in vivo* and *in vitro*, in addition to strong anti-inflammatory and antiapoptotic actions.¹⁶ [6]-Gingerol has been found to possess various pharmacological and physiological effects including analgesic, antipyretic, gastroprotective, cardiogenic, and antihepatotoxic activities. Gingerol also has a potent inhibitory effect on prostaglandin biosynthesis.¹⁸ The [6]-gingerol is the most phytochemical potent against cancer compared with the other ginger ligands like [8]-gingerol, [10]-gingerol and [6]-shogaol. The next research can be focused to develop 6-gingerol.³¹

Side effect

In generally *Z. officinale* is considered safe for use. There is a slight risk of toxicity in normal doses, but some people may have indigestion. *Z. officinale* can also cause contact dermatitis in sensitive individuals. *Z. officinale* reported to cause severe hyperkalemia in patients with cirrhosis. Use ginger with caution in people with liver disorders or liver disease who have been exposed before.³⁷

Toxicity

Acute toxicity studies with oral single dose of *Z. officinale* rhizome (2000 mg/Kg and 2500 mg/Kg) were observed for 14 day on rats, no death was found. LD₅₀ > 2000mg/Kg and LD₅₀ > 2500mg/Kg.³⁶

Sub acute toxicity study with fine powder of *Z. officinale* rhizome (up to 2000 mg/kg/day) were administered orally to male and female rats for a duration 35 days showed no toxic effect.³⁶

Dosage

Ginger doses generally are 1-4 g per day, taken in divided doses.³⁸ To prevent motion sickness: 0.5 g, 2–4 times daily in adults and children more than 6 years and for dyspepsia: 2–4 g daily, as powdered plant material or extracts.^{36, 37}

Conclusions

Z. officinale var. *rubrum* is considered a safe herbal remedy with only slight and not significant adverse effects. This plant is potential to be developed for future phytomedicine, however it needs further explorations on its clinical studies in humans is expected, especially the efficacy and safety of the risk of side effects.

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