



Review Article

Ethnopharmacological review of ginger for anticancer activity

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ABSTRACT

Zingiber officinale is a plant found locally in India that has been widely used as a flavouring agent in savoury dishes such as curries and sweets such as cakes and cookies, alcoholic beverages as well as in alcoholic beverages. like in tea. Ginger is a well-known herb, commonly used in traditional medicine all over the world. Ginger has been used for thousands of years to treat colds, nausea, arthritis, migraines, and high blood pressure. The many pharmacological activities of ginger are antiemetic, antidiabetic, analgesic, anti-inflammatory, anticancer, antioxidant, anticoagulant, antibacterial, anti-inflammatory, estrogenic and cardiovascular activities. Chemical irritants and an unsaturated phenolic ketone liquid C17H24O3 are responsible for the spicy taste of ginger. The main components of ginger are aromatic essential oils, antioxidants and pungent resins. These aromatic or pungent compounds have been identified as C6H5C(O)CH3, known as a chemical irritant, liquid unsaturated phenolic ketones C17H24O3 and Vanillylacetone.

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1. Introduction

Ginger (Canton ginger) belongs to the family Zingiberaceae.¹ It is herbaceous perennial plant.² It is commonly used as a spice and medicinal plant.² The part of the plant used is the rhizome. The plant produces an orchid-like flower with purple-flecked yellow-green petals. Ginger (*Zingiber officinale* (L.) Roscoe) has been used as a spice for over 2000 years.³ Ginger contains up to 3% of the essential oils responsible for the aroma of the spice.⁴ In India and countries with hot and humid climates, ginger is consumed in large quantities and is good for digestive problems.⁵ Ginger belongs to the plant family that includes cardamom and turmeric. Its spicy taste is mainly due to the presence of ketones, especially ginger root, which seems to be the main component of ginger studied in most of

the health-related scientific studies.⁶ The rhizome, which is the horizontal stem from which the roots grow, is the main part of the ginger that is consumed. Ginger's current name comes from the Middle English *gingivere*, but the spice dates back more than 3,000 years to the Sanskrit word *srngaveram*, meaning "horny root", based on its shape.⁷ In Greek it is called *ziggiberis*, and in Latin *zinziberi*. Interestingly, ginger does not grow in the wild and its true origin is uncertain. The Indians and Chinese are said to have produced ginger as a root tonic for over 5000 years to cure many ailments, and the herb is now grown throughout the humid tropics. India is the largest ginger producer. Ginger was used as a salting agent long before official history was recorded. It was an extremely important trade item and was exported from India to the Roman Empire over 2000 years ago, where it was particularly prized for its healing properties. Ginger continued to be a much

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sought-after commodity in Europe even after the fall of the Roman Empire, with Arab traders controlling the trade in ginger and other spices for centuries.⁸ In the 13th and 14th centuries, the value of a pound of ginger was equivalent to the price of a sheep. Raw and preserved ginger was brought to Europe in the Middle Ages, where it was included in the official accumulations of various countries. During the Middle Ages, it was imported in canned form for use in sweets. Queen Elizabeth I of England is credited with inventing the gingerbread man, which has become a popular Christmas treat.⁹

1.1. Classification

Taxonomic	Dry ginger plant
Domain	Eukaryota
Kingdom	Plantae
Phylum	Spermatophyta
Subphylum	Angiosperms
Class	Monocotyledon
Order	Zingiberales
Family	Zingiberaceae
Genus	Ginger
Species	Zingiber officinale

1.2. Active Constituents

At least 115 components of fresh and dried ginger varieties have been identified through multiple analytical procedures. Ginger has many active components, such as phenolics and terpenoids.¹⁰ The phenolic compounds in ginger are mainly ginger root, ⁶-shogaol and paradols. In fresh ginger, ginger root has the main polyphenols such as 6-gingerol, 8-gingerol and 10-gingerol. Ginger root is the major constituent of fresh ginger and was found to be slightly reduced in dried ginger, while concentrations of ⁶-shogaol, which is the main dehydration product of gingerol, were more abundant¹¹ in drier ginger than fresh ginger. At least 31 compounds related to gingerol have been identified from crude methanolic extracts of fresh ginger rhizomes (Jiang, Solyom et al. 2005). Ginger is rich in active ingredients, such as phenolics and saponins. Ginger has been subdivided into at least 14 bioactive compounds, including z⁴-gingerol, ⁶-gingerol, ⁸-gingerol, ¹⁰-gingerol, ⁶-paradol, ¹²-shogaol, ⁶-shogaol, 1-dehydro-¹⁰-gingerdione, ¹⁰-gingerdione, 3-heptanone, 5-hydroxy-1,7-bis (4-hydroxy-3-methoxyphenyl), C₂₁H₂₄O₆, linear log heptanoids, 1, 7-bis- (4' hydroxyl-3' methoxyphenyl)-5-methoxyheptan-3-one and methoxy-¹⁰-gingerol.¹³ The proportions of each individual ingredient in a sample of ginger depend on the country of origin, commercial processor and fresh, dried or processed ginger.¹⁴ Among the pungent bioactive

components of Jamaican ginger, including, ⁶-, ⁸-, and ¹⁰ roots and ⁶-shogaol, ⁶-gingerol appears to be the pungent compound. has the most abundant biological activity in most of the petroleum resins.¹² Although phylogenetic analysis revealed that all ginger samples from different geographical origins were genetically indistinguishable, metabolic profiling revealed quantitative differences. on the content of ⁶-, ⁸- and ¹⁰- ginger root.¹⁵ An evaluation of the concentrations of ⁶-, ⁸-, and ¹⁰ root and ⁶-shogaol in 10 different ginger root dietary supplements randomly purchased from pharmacies. Various drug and grocery stores, natural foods have given amazing results. Perhaps unsurprisingly, the amounts of these active ingredients vary widely, from none or very small amounts to several milligrams per gram. In addition, the recommended dietary intake ranges from about 250 mg to 4.8 g/day. The basis for the wide dosage range is unclear. These studies show that ginger contains many bioactive compounds and standardization of the content is very lacking.¹⁶

2. Ethnopharmacological review of anticancer activity

Vallinoids in Ginger possess anticancer activities. Vallinoids are certain pungent active constituents like ⁶-gingerol and ⁶-paradol, and some other constituents like ⁶-shogaol, vanillylacetone etc. It was demonstrated that ⁶-gingerol, ⁶-shogaol and vanillylacetone possess anti-angiogenesis dependent human diseases properties that helps to fight the cancer. There has been substantial research on the anticancer activities of active constituents of ginger and its various components and were reviewed the properties of ginger and its chemoprophylaxis effects of numerous dietary and medicinal plants. Studies were conducted on anticancer activities of various parts and forms of ginger especially ⁶-gingerol, ⁶-shogaol, especially ⁶-shogaol; and zerumbone, a sesquiglucoside compound derived from ginger and a number of minor components and metabolites.¹⁷⁻²¹ The effectiveness of ginger in preventing or suppressing cancer growth has been examined in a variety of cancer types such as lymphoma, hepatoma, colorectal cancer, breast cancer, skin cancer, liver cancer, and bladder cancer. The mechanisms showed the anticancer activities of ginger and its components include antioxidant activity and induction of apoptosis, decrease proliferation, cause cell-cycle arrest, and suppress activator protein 1 (AP-1) and NF- κ B/COX-2 indicating pathways.²²

The antitumor activities of ⁶-gingerol and zerumbone are related to their antioxidant activities. Several components of ginger were reported to have potent anticancer promoter activity based on their ability to inhibit TPA-induced Epstein-Barr virus early antigen (EBV-EA) in B lymphocytes in humans.^{6,23} -Gingerol was reported to block the potent invasive capacity of reactive oxygen species of AH109A liver cancer cells ascites by reducing peroxide levels.²⁴ In normal mouse RL34 hepatic epithelial

Table 1: It shows anticancer activity of ginger with mechanism of action

Compound Name	Cancer	Mechanism	Cell Lines/System
Ginger extract	Liver cancer	Reduced the elevated expression of TNF- α and NF-kB and tumor growth	In-vitro
Ginger-whole and ⁶ -gingerol	Non-small-cell lung cancer cells	Release of cytochrome c	In-vitro
β -Elemene	Non-small-cell lung cancer cells	Release of cytochrome c	In-vitro
6-gingerol	Breast cancer	Inhibits cell adhesion invasion motility	In-vitro
	Skin cancer	Enhance apoptosis	Mouse
	Colon cancer	Inhibition of leukotriene activity	Mice
	Lung and colon cancer	Suppresses modulatory mechanism of growth and induces apoptosis, Reduces expression of NF-kB	Mouse
Zerumbone	Colon cancer	Activation of extraction signal-regulated kinase $\frac{1}{2}$ p38 mitogen-activated protein kinase	In-vitro
	Osteoclastogenesis	Blocks NF-kappa B expression.	Mouse nonocyte
6-Shogaol	Lungs cancer	Inhibition of AKT	In-vitro
6-Shogaol	Breast cancer	Anti-metastasis	In-vitro
Enone-diaryl heptanoid, 6-shogaol, ¹⁰ -gingerol	Liver/against nine human tumor cell (lines)	Inhibition of lipid peroxidation Antioxidant activity, cytotoxic	In-vitro
Terpenoids	Endometrial Cancer Cell	Induces apoptosis by activation of p53	In-vitro
6-Shogaol	Cancer cell	Anticancer	In-vitro

cells, zerumbone was found to induce glutathione S-transferase and localize the transcription factor Nrf2, which binds to the antioxidant response factor gene (ARE) of the phase II enzyme.²⁵

Zerumbone promotes the expression of several Nrf2/ARE-dependent phase II enzyme genes, including Y-glutamyl-cysteine synthetase, glutathione peroxidase, and hemeoxygenase-1.²⁶ Others have reported that zerumbone reduces TPA-induced hydrogen peroxide formation and water retention in proportion to increased levels of various antioxidant enzymes.²⁶ These types of alterations were associated with decreased incidence of 7,12-dimethylbenz[a]anthracene (DMBA)-inducing/promoting TPA tumors, number of tumors per mouse, and tumor volume.²⁷

Zerumbone has also been reported to downregulate CXCR4 chemokine receptor 4 (CXCR4), which is abundantly expressed in various tumors including breast, ovarian, prostate, gastrointestinal tract, head and neck, bladder optic nerve, brain and melanoma.²⁸ Because CXCR4 mediates the migration of tumor cells to specific organs expressing its ligand, CXCL12, zerumbone has been suggested as a potent and potent cancer metastasis inhibitor effective in blocking CXCR4 in a variety of cancers, including pancreatic, lung, kidney, and skin cancers.²⁸ In addition, zerumbone effectively attenuated human mammary gland tumor cell cytotoxicity and multiple myeloma-induced osteoclastogenesis and dose-dependently reduced bone resorption in MDA-bearing Athiorhodaceae nude mice -

MB-231, suggests that it may be effective in preventing bone cancer-related bone loss or osteoporosis.^{6,29} Gingerol has also been reported to suppress adhesion, invasion, mobility, matrix metalloproteinase (MMP)-2 and MMP-9 messenger ribonucleic acid (mRNA) expression and protein activities. in the human breast cancer cell line MDA-MB-231.^{30,31}

Ginger and its components have been reported to inhibit tumor promotion in rat skin.³² In particular, ⁶-gingerol was found to be highly effective as an anti-skin cancer agent in vivo in a rat skin model encouraging two-step initiation. In this model, tumors were initiated with a single application of DMBA, followed by repeated topical TPA applications beginning several days later.³³ Topical application of ⁶-gingerol on the shaved backs of female ICR rats reduces the rate of DMBA-initiated/TPA-promoted skin papilloma formation and also inhibits epidermal ornithine decarboxylase activity and inflammation caused by TPA.³⁴ The results of a similar study indicated that in the DMBA/TPA skin tumor model, the application of ⁶-paradol or ⁶-dehydroparadol before TPA application significantly reduced the number of tumors per mouse. and the number of mice with tumors.³⁵

Previous studies showed that gingerol was an effective inhibitor of azoxymethane-induced intestinal carcinogenesis in rats.³⁶ Ginger supplementation (50 mg/kg body weight) has been reported to reduce the number of tumors as well as the incidence of 1,2-dimethylhydrazine (DMH)-induced colon cancer.³⁷ The effect is attributed to decreased oxidative damage associated with increased

activity of catalase, superoxide dismutase, glutathione peroxidase and glutathione transferase as well as increased GSH.³⁷ This group then reported that administering ginger to mice treated with DMH significantly reduced the incidence and number of tumors as well as the activity of microbial enzymes (GUSB) and mucopolysaccharidase.³⁷ Finally, Wistar rats fed ginger extract (1% dietary blend) showed a significantly lower number of ureteral lesions (hyperplasia and neoplasia) compared with the untreated groups.³⁸

Studies show that compounds in ginger prevent the proliferation of human cancer cells through the induction of apoptosis.^{39,40} A salt extract prepared from ginger extract suppressed HEP-2 cell proliferation by inducing cytotoxic effects and DNA fragmentation.⁴¹ Ginger extract and especially⁶ -gingerol were reported to effectively reduce YYT colonC.^{10,42} -Gingerol has been reported to induce a significant and prolonged increase in intracellular calcium and cytotoxicity in human colorectal cancer SW480 cells.^{6,43} -Gingerol has been reported to inhibit both proliferation and infiltration of AH109A ascites cells and appears to work by inducing S phase arrest, prolonging cell replication time. of liver tumors and increased apoptosis.⁴⁴ This compound also induces cell cycle arrest and suppresses the growth of human pancreatic cancer cell lines, human pancreatic carcinoma (HPAC) cells, which express wild-type p53 and BxPC-3 cells expressing a mutant p53 protein.⁴⁵ Interestingly,⁶ gingerol appeared to be most effective in inducing apoptosis in p53 mutant cells and inducing arrest, but not apoptosis in epithelial cells. present p53.⁶ -Gingerol was further reported to suppress proliferation and induce apoptosis or G1 cell cycle arrest in several colorectal cell lines, including HCT116, SW480, HT29 cells, LoVo and Caco2.⁴⁶ These effects are associated with decreased levels of cyclin D1 (a proto-oncoprotein overexpressed in cancer) and increased expression of the nonsteroidal anti-inflammatory drug (NSAID) activating gene (NAG-1), a protein autophagy and antibiotics.⁴⁶

Through the comparison of promotion-sensitive (P+) and promotion-resistant (P-) derivatives of the JB6 mouse epidermal cell lines, AP-1 was reported to play an important role in promoting promote tumorigenesis.⁴⁷ In addition, blocking promoter-induced AP-1 activation inhibited neoplastic transformation⁴⁸ Epidermal growth factor (EGF) is known to induce AP-1 activity and cell transformation at relatively high levels.⁴⁷ Previously, we investigated the effects of two structurally related compounds from the ginger family,⁶ -gingerol and⁶ -paradol, on EGF-induced cellular transformation and activation. AP.1 chemistry . Our results provided the first evidence that both compounds block EGF-induced cellular transformation, but through different mechanisms.⁶ -Gingerol appears to act by directly inhibiting AP-1 DNA-binding activity and metabolism, while⁶ -

paradol appears to act by inducing apoptosis^{49,50} Others reported that⁶ -gingerol induced DNA fragmentation and suppressed Bcl-2 expression in HL-60 myeloid leukemia cells (Wang et al. 2003), and also induced growth inhibition and caspase-mediated apoptosis in human squamous cell carcinoma A431 cells.^{6,51,52} -paradol and other structurally related derivatives, such as¹⁰ -paradol,³ -dehydroparadol,⁶ -dehydroparadol and¹⁰ -dehydroparadol, inhibited proliferation cells of KB oral squamous cell carcinoma in record time. and is dose dependent.^{6,53} -dehydroparadol was more potent than the other compounds tested and induced apoptosis by a caspase-3-dependent mechanism.^{6,52} -Shogaol [1-(4-hydroxy-3-methoxyphenyl)-4-lie-3-one], a ketone from ginger, exhibits the strongest cytotoxicity against humans A549, SK-OV -3, SK-MEL-2, and HCT15 tumor cells, compared with⁴ -⁶ -,⁸,- and¹⁰ -gingerroot.⁵⁴ This compound also inhibited the proliferation of several transgenic mouse ovarian cancer cell lines, including C1 and C2.⁵⁴ In addition,⁶ -shogaol has been reported to inhibit growth and induce apoptosis in COLO 205 cells.⁵⁵ Treatment with⁶ -shogaol, but not⁶ -gingerol, induces DNA fragmentation in COLO 205 colon cancer cells. Death is mediated by activation of caspase-9, -3 and -8, leading to mitochondrial cytochrome c release, modulation of pro-apoptotic Bax and negative effects of anti-apoptotic Bcl2, and induction of growth arrest and DNA damage (GADD)-factor transcribed 153 (GADD153) mRNA and protein.⁵⁵

NF- κ B is a rapidly induced stress-responsive transcription factor that enhances the transcription of many genes, including cytokines, growth factors, and acute-responsive proteins.⁵⁶ Its activation is also implicated in the mitogen-activated protein (MAP) kinase signaling pathways.⁵⁷ The mechanism of NF- κ B activation is well known. In its inactive form, NF- κ B found in the cytosol binds to an inhibitory protein known as kappa inhibitor B (I κ B). When stimulated, I κ B is phosphorylated by an I κ B kinase, releasing it from NF- κ B and subsequently degraded. After detaching from I κ B, NF- κ B is transferred to the nuclear region, where it activates gene transcription by binding to its specific DNA sequence present in certain genes. Importantly, NF-B activation has been implicated in the initiation or acceleration of tumorigenesis,⁵⁸ and in JB6 cells, NF- κ B inhibition also suppresses tumorigenesis. cell changes induced by tumor promoters (60, Li et al. 1997).⁶ -Gingerol may exert its effects by blocking the NF- κ B/COX-2 pathway. This idea is supported by data indicating that the reduction of UVB-induced expression and COX-2 metabolism by⁶ -gingerol is associated with inhibition of I κ B α (Ser32) phosphorylation leading to to reduce NF- κ B translocation from the cytosol to the nucleus in HaCaT cells.⁵⁹ A ginger extract given to mice with experimentally induced liver cancer reduced NF- κ B and TNF- α .^{6,60} -Gingerol has been reported to block

TNF-linked apoptosis.

Zerumbone has been reported to block NF- κ B activation induced by a variety of stimuli, including tumor necrosis factor (TNF), cigarette smoke condensation, and hydrogen peroxide.⁶¹ It also blocks phosphorylation and degradation of I κ B α kinase, leading to downregulation of constitutively active NF- κ B and some of its upregulated gene targets, such as COX-2, cyclin D1, Bcl2. and anti-apoptotic genes, thereby enhancing chemotherapy-induced cell death.⁶² Zerumbone has also been reported to block the activity of the NF- κ B ligand receptor activator (RANKL) in mouse monocytes (progenitor cells of osteoclasts) by inhibiting the activity, phosphorylation and degradation of kinase I κ B α (Sung et al. 2009). Oral administration of zerumbone (100, 250, or 500 ppm) to ICR mice reduces the inflammation and diversity of colon adenocarcinoma induced by intraperitoneal injection of azoxymethane (AOM, 10 mg/kg body weight; Kim et al. 2009). In addition, zerumbone (250 or 500 ppm) effectively suppressed 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung adenoma formation in female A/J mice.⁵² This ginger derivative appears to exert its effects through inhibiting proliferation, inducing apoptosis, and inhibiting the expression of NF-B and heme oxygenase in colon cancer tissues. and lungs⁶³ In a previous study,⁶ -gingerol was reported to be able to inhibit both vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) inducing proliferation. human endothelial cells and induce cell cycle arrest in the G1 phase.^{6,64} -Gingerol also suppresses capillary-like tubule formation by endothelial cells in response to vascular endothelial growth factor (VEGF), and strongly inhibits endothelial cell germination. in the rat aorta and the formation of new blood vessels in the rat cornea in response to VEGF.⁶⁵

Researchers have suggested that the effectiveness of ginger may be related to its ability to inhibit prostaglandin and leukotriene biosynthesis.⁶⁶ Some researchers have shown that gingerol actively inhibits arachidonate 5-lipoxygenase, an enzyme in leukotriene biosynthesis.⁶⁷ The protein leukotriene A4 hydrolase (LTA4H) was considered a suitable target for cancer therapy and our prediction in silico using reverse splicing suggested that LTA4H could be a potential target for⁶ - gingerol.⁶⁸ The prediction is supported by the study that⁶ -gingerol suppresses the growth of cancer cells independent of the anchorage by binding to LTA4H and inhibiting the activity of LTA4H in HCT116 colorectal cancer cells. It was also found that⁶ -gingerol effectively suppressed tumor growth in vivo in nude mice, an effect mediated by inhibition of LTA4H activity. Taken together, these results point to an important role for LTA4H in cancer and also support the antitumor efficacy of⁶ -gingerol targeting LTA4H in preventing colorectal cancer.⁶⁸ More importantly, these are the first results to identify a direct target of⁶ -gingerol to explain its antitumor activity.⁶⁹

It was found that when cultured ovarian cancer cells were treated with⁶ -shogaol, they exhibited marked inhibition associated with NF- κ B inhibition as well as inhibition angiogenic factors, VEGF and IL-8. Therefore, this compound plays an active role in preventing cancer angiogenesis.⁷⁰ Furthermore, it was concluded that people consuming dietary ginger (0.5% or 1.0%) showed no activity on malformation of aberrant crypt foci formation (ACF). or decreased proliferation index or crypt cells of the apoptotic colon induced by DMH. in DMH-treated rats. Furthermore, as demonstrated,^{70,71} ginger extract could not inhibit the growth of N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN)/N-methyl- N-nitrosourea (MNU)-induced bladder cancer in male Swiss rats and in mice treated with BBN/MNU/2% ginger, the incidence of grade 2 translocation cell carcinoma was increased.⁷²

3. Conclusion

Ginger and its active components inhibit growth and proliferation of many cancer cells. Also 6-gingerol and other active constituents in ginger inhibited the growth of many cell-lines and showed cyto-toxic properties. Thus, the anticancer properties of ginger described in this review may give a new direction for anticancer drug discovery.

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5. Conflict of Interest

None.

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