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Review Article

Role Of Ginger And Its Constituents In Prevention And Treatment Of Colon Cancer

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ABSTRACT

Gastrointestinal (GI) cancer is a cancer that affects different organs of the digestive system and is the most common cancer in the world. Some of these cancers have high morbidity and mortality. Although many drugs have been introduced to the market over the years to combat colon cancer, most of them are expensive and have side effects. Therefore, it should be a connection made of natural materials that are considered safe and cost-effective. Ginger (Zingiber officinale) is one of the most common natural ingredients used as spices and medicines to treat nausea, stomach pain, high blood pressure, bloating, and diarrhea, loss of appetite, infections, cough and bronchitis. Clinical studies have shown that ginger and its components 6-gingerol and 6- shagoal have anti-inflammatory properties against intestinal infections. The anti-cancer effect of ginger is due to its ability to regulate various signaling components such as NF-KB, STAT3, MAPK, PI3K, ERK1/2, Akt, TNF- α, COX-2, cyclin D1, cdk, MMP-9., Survivin , cIAP-1, XIAP, BCl-2, caspases and other cell growth regulatory protiens. This review describes the evidence regarding the chemopreventive and chemotherapeutic potential of ginger extract and its active components in vitro, in animal models and in patients.

INTRODUCTION

The gastrointestinal (GI) system is an important part of the body. The canal begins at the mouth, includes the esophagus, stomach, small intestine, large intestine, and anus, and ends at the anus.The human intestine is a tube about nine meters long at rest. Colon cancer; It is defined as cancer of the digestive system, including the esophagus, gallbladder, liver, pancreas, stomach, small intestine, large intestine, rectum and anus. , age, race, gender, family history and geographic location. (39) The incidence of stomach cancer is quite high in developing countries. Colon cancer accounts for 20% of all new cancer cases in the

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United States. Among the different types of colon cancer, colon cancer is the most common cancer and the second leading cause of death. (5) Key lifestyle changes that have been shown to be effective include avoiding smoking, increasing fruit and vegetables, drinking alcohol in moderation, limiting calories, exercising, eating as little meat as possible, eating whole grains, getting the right vaccinations, and getting regular checkups. (4) Various studies show the link between health and cancer. The study found that eating 21 types of vegetables and 9 types of fruits could reduce tumor growth in urothelial cancer patients. Many natural products with anti- cancer properties have been reported in the literature. Science ginger is consumed as a spice all over the world, this article discusses the anti-cancer effects of ginger and the active substances it contains. (12)

Ginger and its constituent

Ginger (Zingiber officinale), a member of the Zingiberaceae family, is a popular spice used worldwide, especially in many Asian countries. Chemical analysis of ginger shows that it contains more than 400 different compounds. The main components of the ginger rhizome are carbohydrates (50 to 70%), lipids (3 to 8%), terpenes and phenolic compounds. (18) Ginger's terpene profile includes zingiberene, beta-bisabolene, alpha-farnesene, beta-sesquiphelandrene and alpha-curcumene, while phenolic compound include gingerols, paradoles, and shogaol. Gingerols (23-25%) and shogaols (18-25%) are abundant than other gingerols. (2) It also contains amino acids, crude fiber, ash, protein, plant sterols vitamins (such as nicotinic acid and vitamin A) and minerals. Aromatic components include zingiberene and bisabolene, while pungent components are called gingerols and shogaols. Ginger rhizome is also reported to contain other compounds containing gingerol or shogaol (1-10%), including 6-paradol, 1-dehydrogingerdione, 6-gingerdione and 10-gingerdione, 4-gingerdiol, 6-gingerdiol, 8-gingerdiol, 10- gingerdiol and diarylheptane. The characteristic smell and taste of ginger are due to the combination of essential oils such as shagoal and gingerol. (29)

Uses of ginger as a traditional medicine

Ginger has been used as a spice and medicine in India and china since ancient times. It was also known for its medicinal properties in Europe in the 9th century and in England in the 10th century. Native Americans also use wild ginger rhizome to regulate menstrual bleeding and heart rate. Ginger is thought to act directly on the digestive system to reduce nausea. Therefore, medication use is used to prevent nausea through medical treatment and surgery. Ginger is considered as a good remedy for nausea during pregnancy. (26) Ginger is also used to treat many gastrointestinal problems, including morning sickness, colic, abdominal pain, gas, stomach ache, high blood pressure, flatulence, diarrhea, loss of appetite and indigestion (discomfort after eating). (8) According to the Indian Ayurvedic system of medicine, ginger is recommended to improve digestion. It can be used to treat upper respiratory tract infections, cough and bronchitis. As an anti-inflammatory agent, it is recommended in the treatment of joint problems. (19) Fresh juice has been shown to heal skin burns. The active ingredient in ginger is used as a laxative and antacid. It is also used to warm the body, promote blood circulation and lower blood

pressure. Since ginger has a warming feature, it can be used as an antibiotic in the treatment of colds and flu. Ginger is also used as a flavoring agent in foods and beverages and as a spice in soap and cosmetic products. (31)

Role of ginger and its constituents in prevention and treatment of gastrointestinal cancer

Cancer	Effect	Reference
Liver		
HepG2	Induces apoptosis by activating Caspase-3	
Liver Microsomes	Inhibits CYP450, 1-aminobenzotriazole and aldehyde-keto reductase Inhibits the formation of 18β-glycyrrhetinic acid by M14 and M15	(6)
SMMC-7721	Inhibits eIF2a phosphorylation and induces apoptosis	(11)
HeoG2	Releases cathepsin D and after cytochrome Induces apoptosis and intracellular ROS formation and reduces glutathione	(14)
PC12	Inhibits xanthine oxidase and damage caused by H2O2	(17)
HepG2/Hep3B	Reduces MMP-9 activity and increases TIMP -1 expression Decreased urokinase type plasminogen activator activity in Hep3B cells	(40)
Hep-2	dose-dependent cell proliferation	(38)
Mahlavu cells	activate caspase 3/7, causing DNA fragmentation	(15)
RL34	Activates Nrf2/ARE-dependent detoxification pathway	(25)

Gastric cancer

Figure 2 Gastric Cancer

Preclinical studies have shown that ginger extract and its components are chemopreventive and antitumor against colon cancer. In vitro studies have shown that 6-gingerol can induce apoptosis in colon cancer cells. It promotes TNF-related apoptosis-inducing ligand (TRAIL-)-induced apoptosis by activating caspase-3/7. (16) 6-Gingerol induces apoptosis through downregulation of inhibitor of apoptosis (cIAP)-1 and inhibition of TRAIL-induced nuclear factor-κB (NF-κB) activation. In addition to 6-gingerol, 6-shogaol also reduces the likelihood of colon cancer by activating microtubules. (36) When Sprague-Dawley rats with acetic acid-induced ulcers were given ginger extract, it significantly reduced the ulceration. Ginger extract also reduced xanthine oxidase and myeloperoxidase activities as well as malondialdehyde (MDA) levels in ulcerated mucosa. Therefore, ginger extract promotes ulcer healing and prevents damage to the gastric mucosa by acting as an antioxidant. It has also been reported to be effective in ameliorating the side effects of conventional chemotherapy, including gamma radiation, doxorubicin, and cisplatin, by altering P-glycoprotein. (30) Supporting this, another study showed that ginger could reverse cisplatin-induced stomach cancer; this suggested that ginger may act as an anti-cancer drug. Therefore, cancer treatment may help improve gut health. Besides ginger, zingiberone, a sesquiterpene derived from the subtropical ginger Zingiber zerumbet Smith, has also been reported to have anti-tumor and anti-inflammatory properties. In colon cancer cells, zerumbone

inhibited cell proliferation, VEGF expression, and NF-κB activation. Therefore, Zerumbone acts as an anti-angiogenic and anti-cancer agent in cancer treatment. (21) Ginger and its products are also effective in fighting pancreatic cancer. Parker et al. Studies have shown that 6-gingerol inhibits the growth of pancreatic cancer HPAC and BxPC-3 cells through cell cycle arrest in G1 phase, regardless of p53 status. Additionally, they found that 6-gingerol reduced the expression of cyclin A and cyclin-dependent kinase (Cdk), subsequently reducing retinoblastoma (Rb) phosphorylation and blocking S phase entry. Another study found that 6-gingerol regulates tight junction-associated proteins and inhibits the invasion and metastasis of pancreatic cancer cells. (18) This activity of 6-gingerol is mediated by inhibition of NF-κB/Snail through inhibition of the extracellular signal-regulated kinase (ERK) pathway. Thus, 6-gingerol inhibits the activity of PANC-1 cells. 6-shogaol, another component of ginger, increases Ca2+ signaling in pancreatic beta cells by activating TRPV1 channels. In single mouse insulinoma (INS-1E) cells loaded with Fura-2, 6-shogaol increased the amount of intracellular Ca 2+ in a concentration-dependent manner. The increase in intracellular Ca 2+ obtained with 1-μM 6-shogaol was found to be greater than that obtained with 10-mM glucose. (42) In vitro studies as well as animal studies have shown that 6-shogaol inhibits the growth of pancreatic cancer and improves the effect of gemcitabine in inhibiting tumor growth. The anti-proliferative and gemcitabine-responsive effects of 6-shogaol are mediated through inhibition of NF-κB, cyclooxygenase- (COX-) 2, cyclin D1, survivin, cIAP-1, and X-linked inhibitor of apoptosis protein (XIAP). (40)

Bcl-mediated 2 and matrix metallopeptidase-(MMP-) 9. Inhibition of tumor growth by 6-shogaol was associated with a decrease in growth index (Ki-67) and an increase in apoptosis. Therefore, 6-shogaol, a component of ginger, exhibits antitumor activity both in vitro and in vivo. (8)

Curcumin, a component of Asian ginger, may also inhibit the growth and development of pancreatic cancer through different mechanisms. Zerumbone was reported to induce apoptosis in PANC-1 cells. Induction of apoptosis is associated with upregulation of p53 and p21 proteins and production of reactive oxygen species (ROS) in zerumbone-treated PANC-1 cells. This result indicates that zerumbone induces PANC-1 cell apoptosis via the p53 signaling pathway. Add Song and others. Studies have shown that it inhibits the invasion of pancreatic tumor cells by downregulating the expression of the chemokine receptor CXCR4. They also found that zerumbone-induced downregulation of CXCR4 was due to transcriptional regulation and inhibition of NF-κB activation. Results show that zerumbone blocks angiogenesis in pancreatic cancer cells by inhibiting NF-κB and NF-κB-dependent pro-angiogenic gene products. (19)

Liver cancer

Figure 3 Liver Cancer

In vitro studies show that ginger content is effective against cancer. One study reported that 6-shogaol induces apoptosis in Mahlavu hepatoma cells through oxidative stress-mediated caspase-dependent mechanism. Glutathione (GSH) depletion has been shown to be an important factor in regulating 6-shogaol-induced apoptosis in Mahlavu cells. (31) Recently, Gina et al. Studies have shown that taking ginger oil orally for one month can increase the antioxidant SOD, GSH,

and glutathione reductase in the blood of rats, as well as glutathione-S-transferase and glutathione peroxidation in the liver of enzymes and SOD enzyme. Ginger oil can also reduce pain caused by chronic pain caused by carrageenan, dextran, and formalin, indicating its role in preventing hepatitis. Induced apoptosis of HepG2 liver cancer cells. (22) Ginger extract at a dose of 250 µg/mL changed the cell morphology of HepG2 cells, including cell shrinkage and chromosome condensation. Another study found that 6-gingerol induces apoptosis in human HepG2 cells through the lysosome-mitochondria axis, in which cathepsin D plays an important role in the apoptosis process. (41) 6-Gingerol-induced cathepsin D release precedes ROS production and cytochrome c release in mitochondria. It has also been reported to prevent lipid peroxidation in liver homogenates/mitochondria. This protection may be related to the free radical scavenging properties of ginger extract. In animal models, ginger inhibits ethionine-induced liver carcinogenesis by scavenging free radical formation and reducing lipid peroxidation. Therefore, ginger may prevent liver cancer in mice. (32)

Colorectal cancer

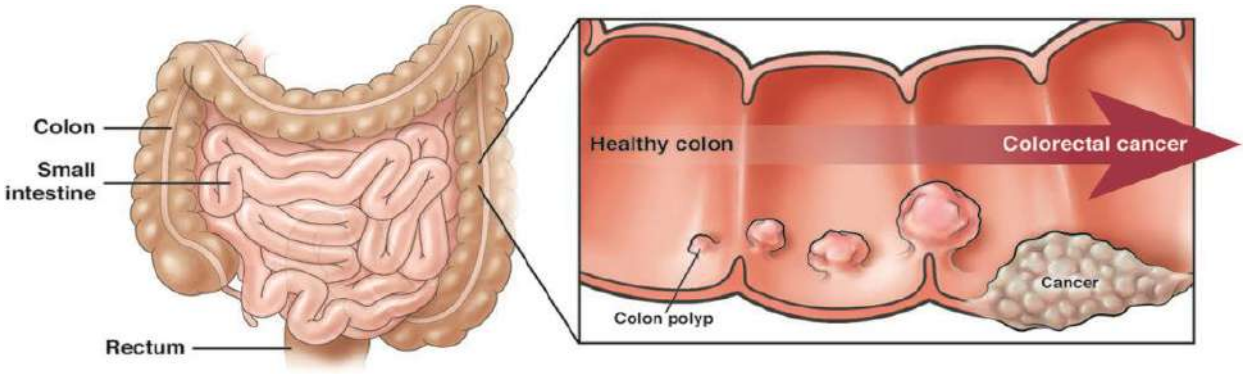

Figure 4 Colorectal Cancer

Ginger's antibacterial properties against cancer are well documented. Various in vitro studies have shown that ginger and its active ingredients inhibit the growth and development of colon cancer cells. In one study, 6-gingerol inhibited the growth of colon HCT116 cells. (1) Inhibition of tumor growth has been shown to be associated with inhibition of leukotriene A4 hydrolase activity, and this was also confirmed by computer. In addition, many other mechanisms have been reported to be involved in 6-gingerol-induced growth inhibition and apoptosis in human colon cancer cells. (39) These include protein degradation and downregulation of cyclin D1, NAG-1 β-catenin, PKCepsilon, and GSK-3β pathways. Radhakrishnan et al. It has been reported that the anti-inflammatory effect of 6-gingerol may be related to the inhibition of the ERK1/2/JNK/AP-1 pathway. In mice pretreated with the carcinogen 1, 2-dimethylhydrazine (DMH), ginger extract inhibited fecal bile acids, moderate sterols, tissue cholesterol, HMG CoA reductase, free fatty acids, triglycerides, Phospholipase A, and phospholipase C levels. Therefore, ginger supplement may reduce the risk of cancer due to its hypolipidemic and antioxidant effects. Ginger extract not only inhibits the carcinogenesis of colon cancer but also enhances the anti-cancer effect of 5-fluorouracil. Studies have also shown that ginger extract can induce the apoptotic effects of honey. In vitro, 6-gingerol effectively inhibits tumor growth in nude mice. (29) A combination (ginger extract loaded with coated alginate particles) was developed to enhance the anti-cancer effect of ginger extract. Preliminary tests on DMH-induced colon cancer in

male Wistar rats showed that the beads were more effective than plain ginger in preventing cancer. It has been reported that cysteine-conjugated shogaol can cause gastric cancer death by activating the mitochondrial apoptotic pathway. (43) Hexahydrocurcumin extracted from ginger has also been found to be cytotoxic against colon cancer cells. Treatment of SW480 breast cancer cells with hexahydrocurcumin (100 μM) has been shown to induce apoptosis, demonstrating its potential as an anti-inflammatory agent. In addition to ginger rhizome, exposure to ginger leaf extract was also found to reduce cell viability and induce apoptosis in human cancer HCT116, SW480, and LoVo cells. This anticancer activity of ginger leaf extract is attributed to increased expression of ATF3 through activation of ERK1/2 in human brain cancer. Another compound, zerumbone, a sesquiterpene derived from edible ginger (Zingiber zerumbet Smith), has been shown to improve the radiosensitivity of colon cancer. It ameliorates radiation induced DNA damage and inhibits nuclear expression of DNA repair proteins ataxia telangiectasia mutated (ATM) and DNA-PKcs. (7)

Cholangiocarcinoma

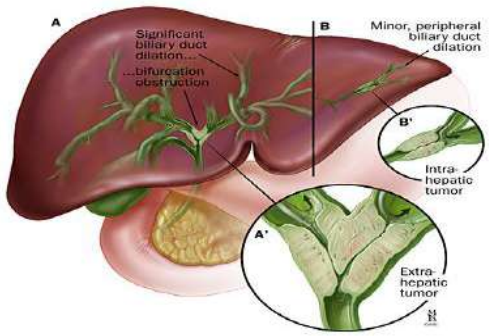

Figure 5 Cholangiocarcinoma

In vitro studies have shown that ginger has anti-inflammatory properties against cholangiocarcinoma. Crude ethanol extract of ginger induces cytotoxicity and antioxidant activity in cholangiocarcinoma cells. Upregulation of MDR1 and MRP3 genes was also observed upon exposure to ginger extract. Using the human cholangiocarcinoma (KMC-1) cell line, Thatte et al. It has been reported that ginger can slow down the process of cell death. Catheterization treatment with ginger in animals can increase the survival time of animals and the survival rate of animals with carcinogenic tumors. In a nude mouse xenograft model bearing cholangiocarcinoma tumors, ginger extract also inhibited tumor growth and exhibited anti-inflammatory properties. Therefore, ginger can be considered as one of the effective chemotherapies in the treatment of cholangiocarcinoma. (25)

Effect of Ginger on Colon Cancer

Cancer	Effects
Colon	Decrease the incidence and number of tumors in colon of Wistar rats
Gastric	Inhibit the expression of the chemokines and TNF-α in gastric cancer of rat model
Gastric	Reverse cisplatin-induced delay in gastric emptying in rats
Colon	Decrease the fecal bile acids, neutral sterols, tissue cholesterol, HMG CoA reductase, free fatty acids, triglycerides, phospholipase A, and phospholipase C in colon
Colon	Decrease the incidence and number of tumors in colon as well as the activity of beta-glucuronidase and mucinase
Colon	Block the azoxymethane-induced intestinal carcinogenesis in rats
Colon	Decrease the incidence and number of tumors in colon of Wistar rats
Gastric	Inhibit the expression of the chemokines and TNF-α in gastric cancer of rat model

Clinical Studies of Ginger against GI Cancer

In addition to preclinical studies, clinical studies have shown that ginger has the ability to prevent and treat different diseases of the colon. Human studies show that ginger can delay nausea that occurs when taking painkillers. In this clinical

study, cancer patients receiving treatment were given normal nutrition, drinking fruit juice, and ginger protein supplements twice a day. They found that protein-rich foods, including ginger, reduced and slowed chemotherapy-induced nausea and reduced drug resistance. (21) In a randomized clinical trial, 20 people at high risk for colon cancer took 2.0 g of ginger or a placebo daily for 28 days. Colon biopsies were taken to determine levels of prostaglandin (PGE)-2, leukotriene B4 (LTB4), 13-hydroxyoctadecadienoic acid, and 5-, 12-, and 15-hydroxyeicosatetraenoic acid. They found that ginger did not reduce eicosanoid levels in people at high risk of colon cancer but was tolerable and safe. Early in the Phase II study, Zick et al. This study showed no significant differences in eicosanoid levels among 30 normal risk factors for colon cancer. However, they found a decrease in PGE2 and 5-hydroxyeicosatetraenoic acid (HETE) and a significant decrease in 12-HETE and 15-HETE, normalized by free arachidonic acid. Another study conducted on 66 colon cancer patients receiving chemotherapy showed that massage with ginger and coconut oil improved the immune system in these patients. They found that using this aroma with massage increased the lymphocyte count by 11%. It also reduces fatigue, symptoms, pain and stress in cancer patients. (26)

In another randomized controlled trial on 20 patients at high risk for colon cancer, ginger supplementation (2 g for 28 days) was shown to reduce the growth of colon cancer and induce crypt Apoptosis and differentiation. This beneficial effect of ginger was found to be associated with the reduction of Bax, human telomerase reverse transcriptase (hTERT) and MIB-1, while the expression of p21 and Bcl-2 remained unchanged. Ginger was reported to have anti-inflammatory properties in a study of 30 participants and 20 participants at risk of colon cancer. It has been shown that ginger reduces COX-1 protein expression in participants at risk of colon cancer, but does not have this effect in participants without risk. However, ginger did not alter 15-hydroxyprostaglandin dehydrogenase (PGDH) protein expression in high-risk or normal-risk participants. (40)

Molecular Targets

Ginger and its components have been shown to modulate many signaling molecules. Ginger can increase or decrease gene expression depending on the target and the context of the cell. Ginger extract increases antioxidant enzymes such as GSH, SOD and glutathione peroxidase. Asian ginger oil components have been shown to activate phase II detoxification enzymes as well as nuclear localization of Nrf2/ARE. Multiple targets of ginger and its products have been documented in different cancer models. These include transcription factors, enzymes, inflammatory mediators, protein kinases, immune proteins, adhesion molecules, growth factor receptors, cell cycle regulatory proteins, cell survival proteins, chemokines, and chemokine receptors. In different cancers, ginger extract inhibits transcription factor NF-κB, inflammatory cytokine TNF-α, and other enzymes and proteins such as xanthine oxidase and myeloperoxidase, MDA, HMG CoA reductase, free fatty acids, triglycerides, phospholipase A and C. The active components of ginger, especially 6-gingerol and 6-gingerol, target various drugs that cause cancer, cell survival, cell proliferation, invasion and angiogenic cellular molecules. 6-Gingerol regulates NF-κB, STAT3, Rb, MAPK, PI3K, Akt, ERK, cIAP1, cyclin A, Cdk, cathepsin D and caspase-3/7. Similarly, shogaol inhibits NF-κB, STAT3, MAPK, PI3k/Akt Ca2+ signaling, COX-2, cyclin D1, survivin, cIAP-1, XIAP, Bcl-2, MMP-9, caspase Enzyme activation, ER stress and eIF2α'. It targets. In addition, the Asian ginger ingredient zerumbone also modulates the expression of NF-κB, p53 VEGF, p21 and CXCR4. Therefore,

ginger's molecular targets suggest that it may prevent and treat cancer. (33)

CONCLUSION

The medicinal properties of ginger have been known for thousands of years, and various in vitro, in vivo and epidemiological studies have provided significant evidence that ginger and its active compounds have effective anti-inflammatory properties in human diseases, including cancer. Ginger has been shown to be effective against many types of cancer, including stomach, pancreatic, liver, colon and colon cancer. However, its antitumor effect on other gastrointestinal cancers such as duodenal cancer, colon cancer, rectal cancer, gastric carcinoid and pancreatic islet cell carcinoma has not yet been determined. Therefore, the effectiveness of this drug against these tumors is guaranteed. Ginger and its polyphenols have been shown to target various signaling molecules, forming the basis for its use in combating many human diseases. Additionally, except for a few studies in human subjects, most of the known activities of ginger components have been found only in in vitro and in vivo studies. Therefore, further and well-controlled studies in humans are needed to safely and effectively demonstrate its effectiveness as an anti-inflammatory agent.

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