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Ginger And Its Constituents Role in Prevention and Treatment of Gastrointestinal Cancer

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Abstract :

One of the most prevalent cancers worldwide is gastrointestinal (GI) cancer, which affects several digestive system organs. Some of these tumours have extremely high incidence and fatality rates. Even though a wide range of chemotherapeutic medicines have been developed in recent decades to treat gastrointestinal cancer, the majority of them are highly costly and have undesirable side effects. Consequently, the safe and reasonably priced substances that come from natural sources are required. One of the most often used natural remedies for nausea, dysentery, indigestion, flatulence, diarrhoea, loss of appetite, infections, cough, and bronchitis is ginger (Zingiber officinale). According to experimental research, 6-gingerol and 6-shogaol, two of ginger's active ingredients, have anticancer properties against GI cancer. Ginger's potential to influence several signalling molecules, including NF-κB, 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 regulating proteins, is thought to be responsible for its anticancer properties. The findings supporting the chemopreventive and chemotherapeutic potential of ginger extract and its active ingredients have been outlined in this review utilising in vitro experiments, animal models, and human subjects.

Introduction :

One of the body's vital organs is the gastrointestinal (GI) tract. The oesophagus, stomach, small and large intestines, rectum, and anus are the last organs in this system, which begins in the mouth. In a relaxed state, the human GI tract is a single tube that is around nine metres in length [1]. Any GI tract disorder can lead to a number of problems, including cancer and digestive system illnesses. The term "gastrointestinal" cancer refers to cancer that affects any organ in the digestive system, such as the pancreas, oesophagus, gallbladder, liver, stomach, small and large intestines, rectum, and anus (Figure 1) [2]. Infection, smoking, alcohol consumption, high-fat diet, age, race, gender, family history, and geographic location are among the main risk factors for GI cancer. In wealthy nations, GI cancer is extremely common. Twenty percent of newly diagnosed cancer cases in the United States are related to gastrointestinal cancer. Colorectal cancer ranks second in terms of mortality among GI malignancies and is the most frequent kind [3].

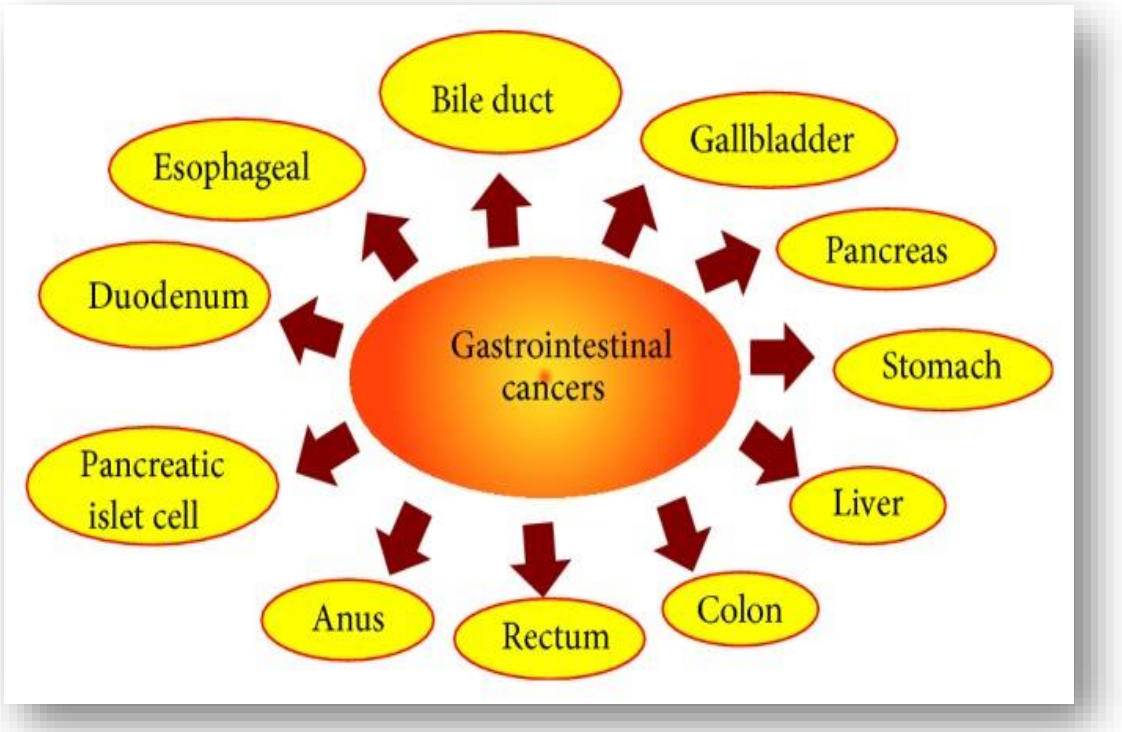

Fig No. 1 many cancer forms that fall within the category of gastrointestinal cancer.

Growing research suggested that altering one's lifestyle could stop all of these cancers. The main lifestyle modifications that have been shown to be helpful include giving up smoke, eating more fruits and vegetables, drinking alcohol in moderation, restricting calories, exercising, consuming less meat, consuming whole grains, receiving the recommended immunisations, and getting frequent checkups. Numerous studies have shown a connection between a healthy diet and cancer [4–7]. An epidemiological study conducted in the Netherlands revealed a negative correlation between the incidence of cancer and the consumption of fruits and vegetables. It has been discovered that giving patients with urothelial carcinoma nine fruits and twenty-one vegetables reduced the growth of their tumours [8]. Additionally, it has been noted that Asians are less likely than Westerners to develop cancer, and that the incidence rises significantly among Asian immigrants to the West (http://www.dietandcancerreport.org/?p=ER). Asia has a low cancer incidence rate, which may be attributed in part to the consumption of a diet high in plant products. Numerous natural compounds with anticancer qualities have been documented in the literature. Given that ginger is a spice that is consumed all over the world, this study will address the role of ginger and its active components against GI cancer.

Ginger and Its Constituents :

The Zingiberaceae family includes the ginger (Zingiber officinale), which is a widely used spice around the world, particularly in most Asian nations [9]. Ginger has about 400 distinct components, according to chemical studies. (50–70%), lipids (3–8%), terpenes, and phenolic chemicals are the main components of ginger rhizomes [10]. The phenolic chemicals in ginger include gingerol, paradols, and shogaol, whereas the terpene components are zingiberene, β-bisabolene, α-farnesene, β-sesquiphellandrene, and α-curcumene (Figure 2). These are the more common varieties of gingerols (23–25%) and shogaols (18–25%). Apart from these, other components found in it include amino acids, minerals, ash, protein, phytosterols, and vitamins (such A and Nicotinic Acid) [11–12].

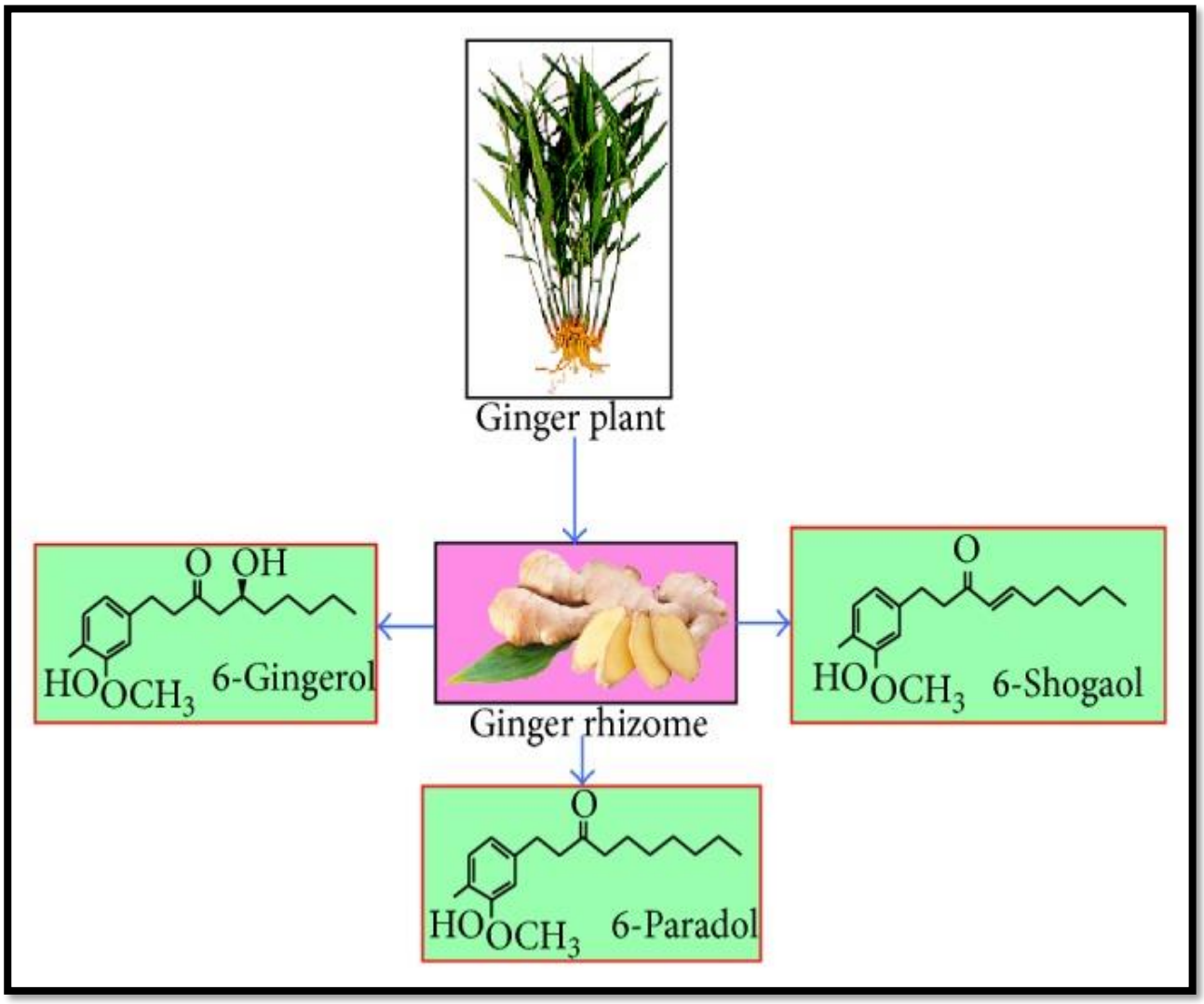

Fig No.2 The three main active ingredients in ginger are 6-gingerol, 6-shogaol, and 6-paradol.

Zingiberene and bisabolene are examples of aromatic elements, whereas gingerols and shogaols are examples of pungent constituents [58]. Additional chemicals related to gingerol or shogaol (1%–10%) found in ginger rhizome include diarylheptanoids [59, 60], 6-paradol, 1-dehydrogingerdione, 6-gingerdiol and 10-gingerdione, 4-gingerdiol, 6-gingerdiol, 8-gingerdiol, and 10-gingerdiol. A blend of volatile oils, such as shogaols and gingerols, is responsible for the distinctive flavour and smell of ginger [61].

Ginger's Use in Traditional Medicine

In ancient China and India, ginger was utilised both as a spice and a medicine. Its therapeutic qualities were also recognised in Europe as early as the ninth century and in England as early as the tenth century [62]. The rhizome of wild ginger has reportedly been used by Native Americans to control heart rate and menstruation. It is believed that ginger reduces nausea by acting directly on the gastrointestinal tract. Consequently, it is used to avoid nausea brought on by chemotherapy, car sickness, and surgical procedures [63]. Pregnancy sickness is known to respond well to ginger therapy [11]. Other GI issues like morning sickness, colic, upset stomach, gas, bloating, heartburn, flatulence, diarrhoea, loss of appetite, and dyspepsia (discomfort after eating) are also treated with ginger. Ginger is suggested by the Indian Ayurvedic medical system to improve food digestion [59].

In addition to these, ginger has been mentioned as a potential treatment for menstruation pain, arthritis, muscle aches, chest discomfort, low back pain, and stomach pain. It can be used to treat bronchitis, cough, and upper respiratory tract infections. It is advised for joint issues as an anti-inflammatory [12]. It has been demonstrated that fresh ginger juice can heal skin burns. The active ingredient in ginger is utilised as an antacid and laxative. Additionally, it is used to warm the body in an effort to improve circulation and reduce elevated blood pressure. Ginger has a warming effect and works as an antiviral to treat the flu and colds [64]. In addition, ginger is utilised as a scent in soaps and cosmetics and as a flavouring component in food and drink [65].

Ginger's and its Components' Function in Preventing and Treating Gastrointestinal Cancer

Ginger and its active ingredients may inhibit the growth and trigger apoptosis of several cancer types, such as skin, ovarian, colon, breast, cervical, oral, renal, prostate, gastric, pancreatic, liver, and brain cancer, according to data from in vitro, animal, and epidemiological research. These characteristics of ginger and its ingredients may be linked to biological activities as well as anti-inflammatory, anti-mutagenic, and antioxidant qualities [66]. In order to determine whether ginger and its active ingredients have chemopreventive and chemotherapeutic potential, this review has only focused on GI malignancies. There have also been descriptions of ginger's in vivo (Table 2), in vitro (Table 1), and clinical effects (Table 3).

Table 1

Ginger and its components' in vitro effects on several GI cancer models.

Cancer	Effects	Reference
Liver		
HepG2	Induce apoptosis by activation of caspase-3	[13]
Liver microsomes	Inhibit CYP450, 1-aminobenzotriazole, and aldo-keto reductase Prevent the formation of M14 and M15 and 18β-glycyrrhetinic acid	[14]
SMMC-7721	Inhibit the phosphorylation of eIF2α and triggered apoptosis	[15]
HeoG2	Release cathepsin D and subsequently cytochrome c Induce apoptosis and intracellular ROS generation and reduced glutathione	[16]
PC12	Inhibit xanthine oxidase and H_2O_2-induced damage	[17]
HepG2/Hep3B	Decrease the MMP-9 activity and increase the TIMP-1 expression Decrease urokinase-type plasminogen activator activity in Hep3B cells	[18]
Hep-2	Dose-dependently suppress cell proliferation	[19]
Mahlavu cells	Activate caspases 3/7 resulting in the DNA fragmentation	[20]
RL34	Activate the Nrf2/ARE-dependent detoxification pathway	[21]
Pancreas		
PaCa	Inhibit mRNA expression and protein secretion of angiogenic factors and NF-κB activity	[22]
PANC-1, BxPC	Downregulate of NF-κB signaling and cell survival regulators including COX-2, cyclin D1, survivin, cIAP-1, XIAP, Bcl-2, and MMP-9 and sensitize to gemcitabine	[23]
β-cell (INS-1E)	Induce Ca^{2+} signals in the β-cell by activating the TRPV1 channels	[24]

Cancer	Effects	Reference
PANC-1	Decrease invasion and metastasis and NF-κB translocation via downregulation of the ERK pathway	[25]
PANC-1	Upregulate p53, p21 proteins level and ROS production	[26]
HPAC, BxPC-3	Decrease cyclin A, Cdk, Rb phosphorylation, and p53 expression	[27]
Gastric Cancer		
HUVE-AGS	Inhibit cell proliferation, VEGF expression, and NF-κB activity	[28]
kBZ Jurkat	inhibit COX-2 activation and reduce *H. pylori*-induced inflammation	[29]
HGC/AGS/and KATO III	Inhibit TRAIL-induced NF-κB activation, cIAP1 expression Increase TRAIL-induced caspase-3/7 activation	[30]
JB6	Inhibit the growth of all *Helicobacter pylori* strains	[31]
Colorectal		
Caco-2	Inhibit cytochrome P450 enzymes (CYP1A2 and CYP2C8)	[32]
HCT116	Act as antiproliferative agents and enhance the chemotherapeutic effect of 5-FU	[33]
COLO 205	Induce apoptosis, cytochrome c release, caspase activation, and DNA fragmentation Upregulate the Bax, Fas, and FasL and downregulate Bcl-2 and Bcl-XL proteins	[34]
HCT116	Suppress cyclin D1 expression and induced NAG-1 expression Inhibit beta-catenin, PKC-epsilon, and GSK-3 beta pathways	[35]
HCT116	Potentiate TRAIL-induced apoptosis and upregulate of TRAIL death receptors (DR-4/-5) Inhibit extracellular signal-regulated kinase 1/2 and p38-MAPK	[36]

Cancer	Effects	Reference
Cholangiocarcinoma		
CCA (CL-6)	Upregulate MDR1 and MRP3 genes	[37]
KIM-1	Induce programmed cell death through endonuclease activation and induction of p53	[38]
KMC-1	caspase 3 activation, potentiate free-radical formation and accumulation of sphinganine	

eIF2α, eukaryotic initiation factor 2 alpha; ROS, reactive oxygen species; CYP450, cytochrome P450; ARE stands for antioxidant response element; COX-2 is cyclooxygenase-2; cIAP-1 is cellular inhibitor of apoptosis protein-1; XIAP is X-linked inhibitor of apoptosis protein; TIMP-1 is tissue inhibitor of metalloproteinase 1; Nrf2, nuclear factor (erythroid-derived 2)-like 2; NAG-1, nonsteroidal anti-inflammatory drug-activated gene-1; PKC, protein kinase C; GSK-3 beta, glycogen synthase kinase-3 beta; NF-κB, nuclear factor kappaB; ERKs, extracellular-signal-regulated kinase; Rb, retinoblastoma; VEGF, vascular endothelial growth factor; TRAIL, TNF-related apoptosis-inducing ligand; MDR1, multidrug resistance gene-1; MRP3, multidrug resistance protein 3.

Table 2

Ginger and its components' in vivo impact on several GI cancer models.

Cancer	Effects	Reference
Liver	Exhibit hepatoprotective activity against alcoholic fatty liver disease in C57BL/6 mice	[39]
Liver	Increase superoxide dismutase and glutathione reductase level in blood Increase glutathione-S-transferase, glutathione peroxidase, and superoxide dismutase enzymes in liver	[40]
	Reduce carrageenan-, dextran-, and formalin- induced chronic inflammation Reduce acetic acid induced writhing movements	[41]
Liver	Decrease the hepatic content of metallothionein and endostatin in Wister Albino rats Increase the growth factors induced by the carcinogen	

Cancer	Effects	Reference
Liver	Protect the rat liver from the carcinogenic effects of DEN and AAF Increase Bax and decrease Bcl-2 protein expression	[42]
	Downregulate serum alanine transaminase, aspartate transaminase, alkaline phosphatase, and alpha-fetoprotein	[23]
Pancreatic	Downregulate NF-κB signaling and cell survival regulators and sensitize to gemcitabine treatment in pancreatic cancer xenografted mice	
Liver	Inhibit CYP450, 1-aminobenzotriazole, and aldo-keto reductase liver microsomes of rats and prevent the formation of M14 and M15 and 18β-glycyrrhetinic acid	[14]
Liver	Downregulate NF-κB and TNF-α in Wistar rats with liver cancer	[43]
Liver	Reduce SOD activity and MDA level and increase catalase activity in liver of Wistar rats	[44]
Colon	Decrease the incidence and number of tumors in colon of Wistar rats	[45]
Gastric	Inhibit the expression of the chemokines and TNF-α in gastric cancer of rat model	[46]
Gastric	Reverse cisplatin-induced delay in gastric emptying in rats	[47]
Colon	Decrease the fecal bile acids, neutral sterols, tissue cholesterol, HMG CoA reductase, free fatty acids, triglycerides, phospholipase A, and phospholipase C in colon	[48]
Colon	Decrease the incidence and number of tumors in colon as well as the activity of beta-glucuronidase and mucinase	[49]
CCA	Exhibit anti-inflammatory, antihypertensive, and antiulcer activities in CCA xenograft nude mouse model	[37]
Colon	Block the azoxymethane-induced intestinal carcinogenesis in rats	[50]

Diethylnitrosamine (DEN), acetylaminofluorene (AAF), nuclear factor kappaB (NF-κB), cytochrome P450 (CYP450), tumour necrosis factor-alpha (TNF-α), superoxide dismutase (SOD), malondialdehyde (MDA), and cholangiocarcinoma (CCA) are some examples of substances.

Table 3

advantages of ginger and its constituents for those suffering from gastrointestinal cancer.

Effects	Reference
Decrease the gastric dysrhythmia and reduce the delayed nausea of chemotherapy	[51]
Inhibit COX and decrease PGE2 concentrations in colorectal cancer Decrease the incidence and multiplicity of adenomas	[52]
Increase the lymphocyte counts in colorectal cancer patients	[53]
Reduce proliferation (hTERT, MIB-1) and differentiation (p21waf1/cip1) in colon cancer	[54]
Decrease the hTERT, MIB-1, and Bax expression in the whole crypts of colon	[55]
Decrease COX-1 protein expression in participants at increased risk for colorectal cancer	[56]
Decrease the mean percent change in PGE-2 and 5-HETE levels in colorectal cancer	[57]
Inhibit CYP450, 1-aminobenzotriazole, and aldo-keto reductase in human liver microsomes	[14]
Prevent the formation of M14 and M15 and 18β-glycyrrhetinic acid in human liver microsomes	[14]

Gastric Cancer

According to preclinical research, ginger extract and its components have antitumor and chemopreventive effects on stomach cancer. An in vitro study revealed that 6-gingerol causes stomach cancer cells to undergo apoptosis. By enhancing caspase-3/7 activation, it promotes apoptosis mediated by TNF-related apoptosis-inducing ligand (TRAIL). 6-gingerol caused apoptosis via cytosolic inhibitor of apoptosis (cIAP)-1 downregulation and blocking TRAIL-induced nuclear factor-kappaB (NF-κB) activation. In addition to 6-gingerol, 6-shogaol also harmed microtubules, which decreased the viability of stomach cancer cells [30]. Ginger extract dramatically decreased the extent of the gastric ulcer in Sprague-Dawley rats with ulcers caused by acetic acid. Moreover, the increased levels of malondialdehyde (MDA) and xanthine oxidase and myeloperoxidase in the ulcerated mucosa were reduced by

ginger extract. As a result, ginger extract acts as an antioxidant to aid in the repair of ulcers and shield the stomach mucosa [46].

By controlling P-glycoprotein, it is also said to be useful in reducing the negative effects of traditional treatment drugs including doxorubicin, cisplatin, and γ-radiation [67]. Consequently, both in vitro and in vivo, ginger extract has chemosensitizing actions in specific neoplastic cells. Supporting this, a further study found that ginger prevents the delay in stomach emptying caused by cisplatin, suggesting that ginger functions as an antiemetic during cancer chemotherapy [47]. Therefore, it might help to lessen the adverse effects of cancer chemotherapy on the gastrointestinal system. In addition to ginger, zerumbone, a sesquiterpene obtained from the subtropical ginger plant Zingiber zerumbet Smith, has been shown to have anti-inflammatory and anticancer effects in a variety of cancer types. Zerumbone impeded VEGF expression, NF-κB activation, and cell proliferation in gastric cancer cell lines [28]. Therefore, in the treatment of gastric cancer, zerumbone functions as an antiangiogenic and antitumor medication.

Pancreatic Cancer

Additionally useful against pancreatic cancer are ginger and its components. 6-gingerol, independent of p53 status, suppresses the development of BxPC-3 and HPAC pancreatic cancer cells by cell cycle arrest at the G1 phase, as demonstrated by Park et al. [27]. Additionally, they discovered that 6-gingerol inhibited the production of cyclin A and cyclin-dependent kinase (Cdk), which was followed by a decrease in the phosphorylation of retinoblastoma (Rb) and a blocking of the S phase entry [27]. According to a different study, 6-gingerol inhibits the invasion and metastasis of pancreatic cancer cells and controls proteins linked to tight junctions. 6-gingerol's actions were facilitated by blocking the extracellular signal-regulated kinases (ERK) pathway, which in turn inhibited NF-κB/Snail. As a result, 6-gingerol inhibits PANC-1 cells' ability to invade [25]. 6-Shogaol, another ingredient in ginger, opens the TRPV1 channels in the pancreatic β-cells, causing Ca2+ signals to be triggered. 6-Shogaol enhanced intracellular Ca2+ in fura-2 loaded single rat insulinoma (INS-1E) cells in a concentration-dependent manner. It was discovered that the rise in intracellular Ca2+ resulting from 1 μM 6-shogaol was higher than the one obtained from 10 mM glucose [24].

In addition to research conducted in vitro, investigations conducted on animals revealed that 6-shogaol inhibited the growth of pancreatic cancer and enhanced the effects of gemcitabine in preventing tumour growth. The inhibition of NF-κB, cyclooxygenase- (COX-) 2, cyclin D1, survivin, cIAP-1, X-linked inhibitor of apoptosis protein (XIAP), Bcl-2, and matrix metallopeptidase- (MMP-) 9 was the mechanism by which 6-shogaol caused antiproliferation and sensitization to gemcitabine. Additionally, in a pancreatic cancer xenograft model, it suppressed tumour growth. The proliferation index (Ki-67) decreased and apoptosis increased when 6-shogaol inhibited the growth of this tumour [23]. Thus, 6-shogaol, a component of ginger, has anticancer action in both vitro and in vivo models.

Through various mechanisms, zerumbone, an ingredient in Asian ginger, also prevents the growth and spread of pancreatic cancer. According to reports, zerumbone causes PANC-1 cells to undergo apoptosis. In PANC-1 cells treated with zerumbone, the activation of apoptosis was linked to the overexpression of the proteins p53 and p21 as well as the generation of reactive oxygen species (ROS) [26]. According to this finding, zerumbone caused PANC-1 cells to undergo apoptosis by activating the p53 signalling pathway. Additionally, Sung et al. [68] demonstrated that it suppresses the expression of the chemokine receptor CXCR4, which prevents the invasion of pancreatic tumour cells. Additionally, they demonstrated that transcriptional control and suppression of NF-κB activation were the causes of the zerumbone-induced downregulation of CXCR4 [68]. Recently, Shamoto et al. [22] provided evidence in favour of this work, demonstrating that zerumbone inhibits NF-κB and NF-κB-dependent proangiogenic gene products, thereby preventing pancreatic cancer cells from undergoing angiogenesis.

Liver Cancer

Studies conducted in vitro show that components of ginger are useful in preventing liver cancer. According to a study, 6-shogaol causes Mahlavu hepatoma cells to undergo apoptotic cell death through a caspase-dependent, oxidative stress-mediated pathway. It has been demonstrated that glutathione (GSH) depletion plays a significant role in mediating the 6-shogaol-induced apoptosis of Mahlavu cells [20]. According to a recent study by Jeena et al. [40], giving mice ginger oil orally for a month enhances the antioxidant enzymes SOD, GSH, and glutathione reductase in their blood as well as glutathione-S-transferase, glutathione peroxidase, and SOD in their liver. Additionally, ginger oil significantly reduced the acute inflammation caused by carrageenan and dextran as well as the chronic inflammation induced by formalin [40], suggesting that it may have a preventive effect on the development of liver cancer.

In addition to glutathione, ROS have been implicated in the apoptosis of HepG2 hepatoma cells generated by ginger extract. When HepG2 cells are exposed to 250 μg/mL of ginger extract, their morphology is significantly altered, including cell shrinkage and chromosomal condensation [19]. According to a different study, 6-gingerol caused human HepG2 cells to undergo apoptosis via the lysosomal-mitochondrial axis, and cathepsin D was essential to this process. 6-The production of ROS and the release of cytochrome c from mitochondria were preceded by the cathepsin D produced by gingerol [16]. Additionally, it is said to shield liver tissue homogenate/mitochondria from lipid peroxidation. The ability of ginger extract to scavenge radicals can be linked to the protective mechanism [69]. In an animal model, ginger prevents the production of free radicals and lowers lipid peroxidation to prevent ethionine-induced liver cancer. Ginger thus inhibits the development of rat hepatocarcinogenesis [44].mitochondria or homogenate.

It has been demonstrated that 6-shogaol and 6-gingerol, the two main constituents of ginger, exhibit anti-invasive properties against hepatoma cells. The migratory and invasive properties of HepG2 and Hep3B cells treated with phorbol 12-myristate 13-acetate (PMA) were suppressed by both substances. Furthermore, it was found that increased expression of tissue inhibitor metalloproteinase protein-1 (TIMP-1) and decreased activity of MMP-9, urokinase-type plasminogen activator (uPA), and MMP-9 were the mediating factors for the suppression of invasion and migration [18]. Weng et al. [70] provided additional evidence in support of their finding that 6-shogaol and 6-gingerol efficiently prevent hepatocellular carcinoma invasion and metastasis through the suppression of the MAPK and PI3k/Akt pathways, downregulation of NF-κB and STAT3 activities, and inhibition of MMP-2/-9 and uPA. Ginger extract prevents liver carcinogenesis in Wistar rats by downregulating increased NF-κB and TNF-α, as demonstrated by Habib et al. [43] in animal models. As a result, ginger may have anti-inflammatory and anticancer properties that may be useful in the treatment and prevention of liver cancer.

In addition to this, the components of ginger prevent the rat hepatocarcinogenesis from developing the premalignant phenotype that is caused by diethylnitrosamine (DEN). In Wistar albino rats, it has been discovered that long-term ginger extract administration stopped the carcinogen-induced rise in growth factors and the decline in metallothionein and endostatin concentration in the liver. Additionally, it brings back the rat's serum hepatic tumour markers [41]. According to a different study, 6-shogaol activates caspase and triggers ER stress signalling in human hepatocellular carcinoma cells, which in turn controls the unfolded protein response (UPR) sensor PERK and its downstream target eIF2α. By activating caspase-3 and inactivating eIF2α, 6-shogaol reduced tumour growth in the mouse SMMC-7721 xenograft model [15]. Therefore, the PERK/eIF2α pathway is crucial for both antitumorigenesis and ER stress induced by 6-shogaol. There is evidence that components of ginger influence the cytochrome P450 enzyme. Ginger extract's active ingredients, gingerols, were not the only ones that inhibited CYP enzymes [32]. Thus, authors emphasise that eating complete foods is more important than consuming active ingredients.

Zerumbone has also been shown to stimulate phase II detoxifying enzymes in a normal liver epithelial cell line derived from cultured rats. Furthermore, it triggers the production of glutathione S-transferase in RL34 cells and demonstrates antioxidant properties by causing the nuclear localization of nuclear factor- (erythroid-derived 2) like 2 (Nrf2), a transcription factor that binds to the antioxidant response element (ARE) of phase II enzyme genes. As a result, researchers came to the conclusion that zerumbone may activate the Nrf2/ARE-dependent detoxification pathway, offering a fresh perspective on the prevention of cancer [21]. Zerumbone has additionally demonstrated an antitumorigenic activity in rat liver that has been produced by 2-acetylaminofluorene and DEN. It was discovered that zerumbone's antihepatocarcinogenic action was linked to the inhibition of many apoptotic liver cells and the suppression of PCNA through increased Bax and decreased Bcl-2 protein expression [42]. As a result, zerumbone has a lot of promise for treating liver cancer.

Colorectal Cancer

Ginger's anticancer properties against colorectal cancer are well-established. Several in vitro investigations have demonstrated that ginger and its active ingredients prevent colorectal cancer cells from growing and proliferating. 6-gingerol was shown in a study to suppress the development of HCT116 colon cancer cells. Leukotriene A4 hydrolase activity was shown to be inversely correlated with tumour development suppression, a finding that was further supported by an in silico method [71]. In addition to these, several other mechanisms have been implicated in the reduction of cell growth and death in human colorectal cancer cells produced by 6-gingerol. These include downregulation of the GSK-3β, PKCepsilon, NAG-1 beta-catenin, and cyclin D1 pathways in addition to protein degradation [35]. According to Radhakrishnan et al. [72], 6-gingerol's anticancer properties may be linked to the ERK1/2/JNK/AP-1 pathway's suppression.

Additionally, whole ginger extract inhibits colon carcinogenesis in its early stages. When animals treated with the carcinogen 1,2-dimethylhydrazine (DMH) before receiving ginger extract, the levels of tissue cholesterol, faecal bile acids, neutral sterols, HMG CoA reductase, free fatty acids, triglycerides, phospholipase A, and phospholipase C were all suppressed [48]. Because of its hypolipidemic and antioxidant properties, taking supplements of ginger lowered the risk of colon cancer significantly. In addition to preventing colorectal cancer cells from proliferating, ginger extract strengthens the antitumorous effects of the chemotherapy medication 5-fluorouracil. Additionally, research has demonstrated that Gelam honey's apoptotic efficiency is enhanced by ginger extract when combined [33]. 6-gingerol successfully inhibits tumour growth in nude mice, just as it does in vitro [71].

A multiparticulate method, consisting of ginger extract loaded with coated alginate beads, has been developed to increase the therapeutic efficacy of ginger extract against colon cancer. This bead exhibits considerably superior cancer recession than free ginger extract, according to preclinical evaluation against DMH-induced colon cancer in male Wistar rats [45]. Additionally, it has been documented that cyste-conjugated shogaols induce colon cancer cells to die by triggering the mitochondrial apoptotic pathway [73]. Additionally, it was discovered that ginger's hexahydrocurcumin proved cytotoxic to colorectal cancer cells. Hexahydrocurcumin (100 μM) treatment of SW480 colon cancer cells has been reported to cause apoptosis [74], suggesting that it may have anticancer properties.

Ginger leaf extract, in addition to ginger rhizome, was shown to decrease cell viability and cause apoptosis in human colorectal cancer HCT116, SW480, and LoVo cells. Ginger leaf extract's anticancer properties were linked to human colorectal cancer cells' elevated production of ATF3 as a result of ERK1/2 activation [75]. It has been demonstrated that the sesquiterpene zerumbone, which is derived from the edible ginger plant (Zingiber zerumbet Smith), increases the radiosensitivity of colon cancer cells. It increased the damage that radiation did to DNA and prevented DNA-PKcs and ataxia-telangiectasia mutated (ATM) from being expressed nuclearly [76].

Cholangiocarcinoma

Ginger has a promising anticancer effect against cholangiocarcinoma, according to in vitro research. In cholangiocarcinoma cells, a crude ethanolic extract of ginger causes cytotoxicity and antioxidant activity. Exposure to ginger extract was also found to cause the MDR1 and MRP3 genes to be upregulated [77]. Ginger has been reported by Thatte et al. [38] to be able to induce programmed cell death in cholangiocarcinoma (KMC-1) cell line. Ginger administered intragastrically to mice lengthens their survival period and raises the percentage of animals with tumours caused by carcinogens [77]. Ginger extract has demonstrated anticarcinogenic properties and suppressed tumour growth in a nude mice xenograft model harbouring cholangiocarcinoma tumour [37]. For this reason, ginger is regarded as one of the most promising chemotherapeutics available for the management of cholangiocarcinoma.

Clinical Studies of Ginger against GI Cancer

In addition to preclinical research, clinical investigations have demonstrated the potential of ginger in the management and avoidance of various gastrointestinal illnesses (Table 3). Research conducted on human participants revealed that ginger helps to postpone the nausea that is brought on by chemotherapy. In this clinical trial, chemotherapy-treated cancer patients were given a regular diet, a protein drink flavoured with ginger, and an extra serving of high-protein food with ginger twice a day. They discovered that protein meals with ginger decreased and postponed chemotherapy-induced nausea and decreased the need for antiemetic drugs [51].

Twenty individuals at elevated risk for colon cancer were recruited in a randomised clinical trial, and for 28 days, they were either given a placebo or 2.0 g/day of ginger. Prostaglandin (PGE)-2, leukotriene B4 (LTB4), 13-hydroxy-octadecadienoic acids, and 5-, 12-, and 15-hydroxyeicosatetraenoic acids were measured in colon samples. They discovered that while ginger did not lower eicosanoid levels in those with a higher risk of colorectal cancer, it was safe and acceptable [52]. Zick et al. [57] had previously found no discernible variation in eicosanoids levels among thirty individuals at normal risk for colorectal cancer in a phase II investigation. On the other hand, they discovered a trend towards a large decrease in 12-HETE and 15-HETE normalised to free arachidonic acid, as well as a significant decrease in PGE2 and 5-hydroxyeicosatetraenoic acid (HETE) [57]. Another study with 66 patients with colorectal cancer undergoing chemotherapy revealed that massaging the patients' cells with coconut oil and ginger enhanced their cellular immunity. They discovered that combining massage and aromatherapy increased lymphocyte counts by 11%. Additionally, it reduced cancer patients' stress, discomfort, and exhaustion [53].

Supplementing with ginger (2 g for 28 days) was also observed to decrease the proliferation of normal-appearing colorectal epithelium and promote apoptosis and differentiation of the crypts in another pilot, randomised control experiment with 20 patients at increased risk for colorectal cancer. While p21 and Bcl-2 expression was mostly unaltered, it was shown that the positive effects of ginger were linked to the downregulation of Bax, human telomerase reverse transcriptase (hTERT), and MIB-1 [55]. According to reports, studies involving 30 healthy

volunteers and 20 individuals at higher risk of colon cancer revealed that ginger exhibited anti-inflammatory properties. Ginger has been shown to greatly reduce the expression of the COX-1 protein in those with a higher risk of colorectal cancer, but not in those with a normal risk. On the other hand, neither increased-risk nor normal-risk individuals' 15-hydroxyprostaglandin dehydrogenase (PGDH) protein expression was changed by ginger [56]. These findings suggest that ginger may have chemopreventive effects on colorectal cancer.

Molecular Targets

Numerous signalling molecules have been demonstrated to be modulated by ginger and its constituents (Figure 3). Ginger has the ability to either up- or down-regulate gene expressions according on the target and cellular environment. Antioxidant enzymes such as glutathione peroxidase, SOD, and GSH are increased by ginger extract [40]. A component of Asian ginger oil also aims to enhance Nrf2/ARE nuclear localization and phase II detoxification enzymes [21]. Ginger and its constituents have been shown to target several distinct cancer models. These comprise growth factor receptors, adhesion molecules, transcription factors, enzymes, inflammatory mediators, protein kinases, drug resistance proteins, cell-cycle regulatory proteins, cell-survival proteins, chemokines, and chemokine receptors. Ginger extract inhibits transcription factor NF-κB, inflammatory cytokine TNF-α, and other proteins and enzymes, such as MDA, HMG CoA reductase, phospholipase A and C, free fatty acids, triglycerides, and xanthine oxidase and myeloperoxidase in several GI malignancies. The active components of ginger, specifically 6-gingerol and 6-shogaol, target a number of biological molecules involved in invasion, angiogenesis, cancer, and cell survival. 6-NF-κB, STAT3, Rb, MAPK, PI3K, Akt, ERK, cIAP1, cyclin A, Cdk, cathepsin D, and caspase-3/7 are all modulated by gingerol. Shogaol targets a number of similar targets, including eIF2α, cIAP-1, XIAP, Bcl-2, MMP-9, NF-κB, STAT3, MAPK, and PI3k/Akt Ca2+ signals. In addition to these, zerumbone, an Asian ginger component, modifies the expression of p53, VEGF, NF-κB, p21, and CXCR4. Therefore, these molecular targets of ginger components suggest that ginger may be useful in both treating and preventing GI cancer.

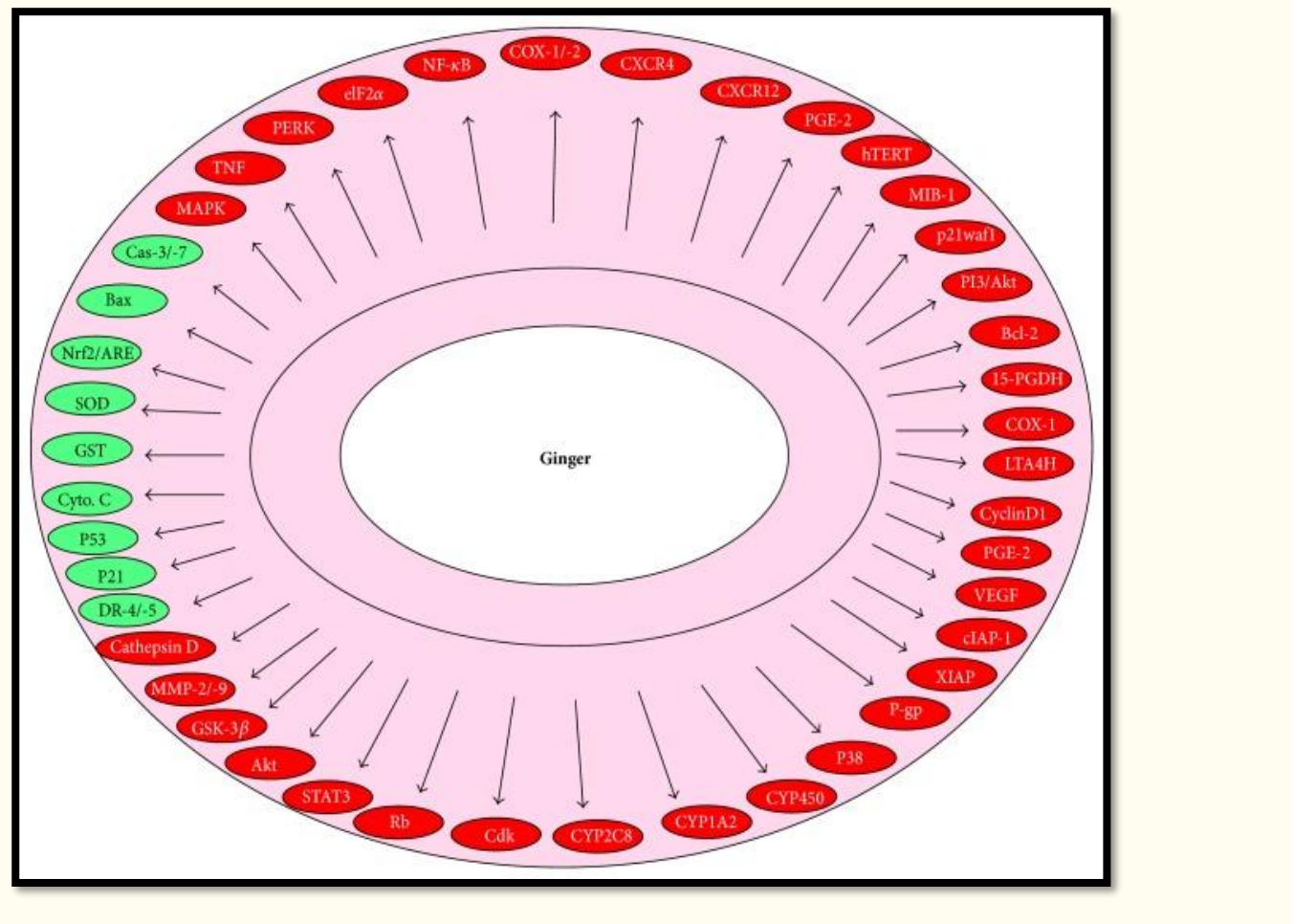

Figure 3 Ginger's active ingredients and their molecular targets in the fight against gastrointestinal cancer.

Conclusion

Even though ginger has been used for thousands of years, a large body of research in vitro, in vivo, and epidemiological studies has further demonstrated the effectiveness of ginger and its active ingredients against a wide range of human diseases, including GI cancer. Studies have shown that ginger can effectively combat a number of gastrointestinal malignancies, including cholangiocarcinoma, gastric cancer, pancreatic cancer, liver cancer, and colorectal cancer. Its anticancer effects on pancreatic islet cell cancer and other GI cancers such as duodenal, esophageal, anal, and GI carcinoid tumours are yet unknown. Thus, it is justified that such powerful drugs be effective against certain tumours. It has been demonstrated that ginger and its polyphenols target a variety of signalling molecules, which supports the use of ginger in the treatment of complex human disorders. Furthermore, except from a few human subject clinical research, the majority of the known effects of ginger components are

solely based on in vitro and in vivo studies. Since it is a safe and affordable alternative, more thorough and carefully monitored human trials are needed to confirm its effectiveness as an anticancer drug.

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