Recent Updates on the Bioactive Compounds of Ginger (*Zingiber officinale*) on Cancer: A Study with Special Emphasis of Gingerol and Its Anticancer Potential

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Effect of Ginger and Its Compounds in Cancer Subjects

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Abstract

Medicinal plants have been used as therapeutic agents since the origin of mankind. Many medicinal plants like *Tinospora cordifolia, Andrographis paniculata, Curcuma longa, Withania somnifera, Zingiber officinale,* etc. are used to treat cancer. Ginger is reported to show anticancer effect in many cancer types like liver cancer, gastric cancer, oral cancer, prostate cancer, breast cancer, and ovarian cancers in animal models and cell lines. To date, over 400 bioactive compounds have been identified in ginger, they are gingerols, shogaols, and paradols. These

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compounds possess antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. Gingerol especially shows anticancer effects in different cancer subjects. Gingerol may act on the TNF-α, IL-6, NF-κB, cyclooxygenase-2 (COX-2), and caspase-3, and other tumor-metabolic pathway factors in the prevention of cancer. We hope that this chapter will attract more attention on ginger's therapeutic potential and impact on cancer subjects.

Keywords

Ginger · Bioactive compounds · Gingerol · Cancer

Introduction

The biological term cancer refers to a set of diseases in which the cells of an organ or tissue split uncontrollably and acquire the ability to attack other tissues. Cancer is a global health problem, and it is the top cause of deaths in the world. Cancer occurs through the mutations by stepwise process which results in malignancies. Metastasis is the process whereby cancer cells rupture from a malignant tumor and travel to and invade other tissues in the body (Butt and Sultan 2009).

The most common types of cancer are liver cancer, esophageal cancer, breast cancer, oral cancer, lung cancer, prostate cancer, ovarian cancer, and stomach cancer. According to GLOBOCAN 2020 database in 2020, there were 19.1 million new cases of cancer and 10 million deaths from cancer worldwide, and the new cases will be upto 20 million globally by 2025 (Ferlay et al. 2019). The principle malignant conditions of the cancer are breast cancer (2.26 million cases), lung cancer (2.20 million cases), stomach cancer (1.08 million cases), liver cancer (0.90 million cases), esophagus cancer (0.60 million cases), pancreatic cancer (0.49 million cases), and colorectum cancer (0.73 million cases) in 2020 (Table 1).

Table 1 New cancer cases and deaths as per global cancer statistics 2020

S. no	Cancer type	No of cases (2020)	No of deaths
1.	Breast cancer	2,261,419	684,996
2.	Lung cancer	2,206,771	1,796,144
3.	Prostate cancer	1,414,259	375,304
4.	Skin cancer	1,198,073	63,731
5.	Colon cancer	1,148,515	576,858
6.	Liver cancer	905,677	830,180
7.	Cervical cancer	604,127	341,831
8.	Esophageal cancer	604,100	544,076
9.	Thyroid cancer	586,202	43,646
10.	Pancreatic cancer	495,773	466,003
11.	Leukemia	474,519	311,594
12.	Kidney	431,288	179,368
13.	Oral cancer	377,713	177,757

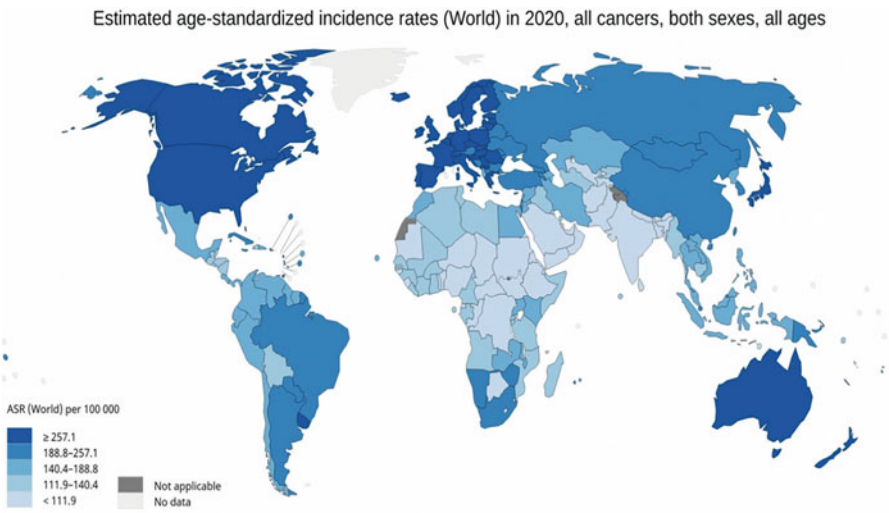

Fig. 1 Cancer patients in the world as per the Global Cancer report 2020 by WHO. Source:https://www.uicc.org/news/globocan-2020-new-global-cancer-data#

India has 1.32 lakh new cancer cases in 2020, also the lowest rates of cancer in the world. Breast cancer, oral cancer, cervical cancer, and lung cancer are the top four cancers in India. Cancer deaths in India doubled from 1990 to 2016. It has been reported that genetic mutations, viruses, smoking, heavy metal ingestion, and dietary patterns are actively involved in cancer pathogenesis (Noonan et al. 2007). Despite huge progress and efforts have been made in the field of medicine for the prevention and treatment of cancer for years, cancer still remains the leading cause of deaths around the world (Fig. 1).

Carcinogenesis

Carcinogenesis is the process by which a normal cell is transformed into a tumor cell and its progression to a clinically observable tumor with high probability of metastasis. Cancer is considered a process with three steps: 1. initiation, 2.promotion, and 3. progression (Weston and Harris 2003). This process can vary depending on the etiology of cancer. Normally, cancers are caused by chemical agents, viruses, and others by mutations of DNA, epigenetic changes of DNA (Baylin and Jones 2016).

Mechanism of Cancer

Cancer: Reactive Oxygen Species (ROS)

Cancer is one of the stress-related disorders. During cancer condition, many free radicals or reactive oxygen species (ROS) are produced. The existence of oxidative

stress resulting from increased free radicals has been postulated in cancer. Animal models and human studies and *in vitro* experiments suggest a role for oxidative stress, via an increased formation of free radicals in the pathophysiology of many complications, such as neurological, cardiovascular, renal, cancer, rheumatoid arthritis, cancer, and diabetes (Brownlee 2001). According to Sies (Sies et al. 2017), oxidative stress is defined as a shift in balance in cellular oxidation-reduction reactions in favor of oxidation, which leads to damage to the cell and formation of molecular products that are indicators of oxidative stress.

Reactive oxygen species are radicals or ions or molecules that have a one unpaired electron in their outermost shell of electrons. Due to this nature, ROS are highly reactive. Examples of ROS are superoxide (O_2-), hydrogen peroxide (H_2O_2), hydroxyl radicals (OH), and nitric oxide (•NO). ROS and oxidative stress have been implicated in many diseases like cancer, diabetes, and hepatitis. ROS plays an important role in various cascading of the signals for the cancer cells to survival, proliferation, resistance to apoptosis, neovascularization, invasion, and extravacation. (Cullen et al. 2003). In order to survive from oxidative stress condition, cancer cells adapt and acquire many mechanisms to counteract the potential toxic effects of ROS stress in order to promote proximal protumorigenic signals. ROS also alters the DNA-binding sites of redox-sensitive transcription factors such as hypoxia-inducible factor-1 alpha (HIF-1α), NFκB, activator protein-1 (AP-1), and p53 (Trachootham et al. 2008). The antioxidant enzymes like SOD, CAT, GPx, GR, and GSH may act on these ROS, and hence these antioxidant enzymes activities are depleted in various cancer subjects.

Warburg (Liberti and Locasale 2016) described about cancer as metabolic alterations that represent a hallmark of cancer cells. Metabolic alterations and redox alterations which are important steps of cancer cell transformation make the mitochondria an attractive therapeutic target. Increased knowledge in the field of redox biology, its reactions, signaling networks, and interplay in disease and physiology has enabled not only a better realization of potential benefits but also grave dangers of ROS with respect to cancer phenotypes and drug resistance.

Cancer Biomarkers

A thorough understanding of the roles of cancer biomarkers is essential for diagnostic purposes. A biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." Because early diagnosis of cancer will treat cancer patients early, we can save the patient's life. Cancer biomarkers are produced by tumors or by the body in response to the presence of cancer. Cancer biomarkers can be used to determine the presence of malignancy and for the study of disease transmission. The important cancer biomarkers are Urokinase plasminogen activator (uPA), Carbonic anhydrase XII (CAXII), Cyclooxygenase (COX), Cytochrome P450 (CYP450), Telomerase, and Matrix metalloproteinases (MMPs).

The medical treatments for cancer are surgery, radiotherapy, and chemotherapy. These types of treatment are usually accompanied by a large number of side effects

on patient health, like nausea, loss of appetite, weight loss, anemia, spinal cord injury, kidney damage, and mucositis. Hence, there is need for alternative therapy for cancer. So herbal medicine is practiced to treat cancer.

Medicinal Plants for the Treatment of Cancer

Medicinal plants are used to treat many diseases like diabetes, cancer, epilepsy, alzheimer's, cough, fever, and other diseases. Drugs from medicinal plants focus on the most important active principles in terms of the quantity and the pharmacological actions. The information available on these medicinal plants has allowed the quantification of the active principle and the production of bioactive compounds. The bioactive compounds of medicinal plants have different chemical, pharmacological properties and actions. This has enabled us to evaluate the anticancer drugs from medicinal plants.

Many medicinal plants have been reported to possess anticancer properties. Due to the development of resistance against cancer effects, various plant-derived drugs have gained much attention in the recent years. Hence, it is of importance to focus on medicinal plants with anticancer properties that are easily available, culturally acceptable, and economically free. Herbal medicine has been used for thousands of years to cure cancer. Chemotherapeutic and chemopreventive effects of many herbal plants are attributed to phytochemicals, quinines, which are reported to induce antitumor effects *in vovo* and *in vitro* of cancer cells.

Recently, many well-known plant-derived compounds have been studied in animal models and cell lines. Among the above described plants and their formulations, *Terminalia chebula, Panax ginseng, Arachis hypogaea, Rauwolfia vomitoria, Azadirachta indica, Zingiber officinale, Commiphora mukul,* and *Rosa rugosa* are reported to be beneficial for cancer with less side effects as compared to conventional drugs. Hence, these medicinal plants could be a relatively safer and better therapeutic alternative for cancer treatment (Fig. 2).

Ginger

Ginger is the rhizome of *Zingiber officinale.* Roscoe belongs to the family Zingiberaceae. Ginger has been used as a spice, food, supplement, and flavoring agent. Ginger is used to cure diseases and symptoms, such as headache, nausea, cold, rheumatism, diarrhea, and arthritis. It is also used as a carminative, digestant, and antiflatulent (Ali et al. 2008). Ginger and its compounds are used as medicine in India, China, Burma, Germany, Japan, Indonesia, and the United States.

Ginger is reported to possess various medicinal properties like antibacterial, antiviral, antifungal, antiparasitic, anti-insecticidal, antianalgesic, antimutagen, anticarcinogenic, antispasmolytic, and anti-inflammatory and antioxidant activities (Shanmugam et al. 2021). Ginger have radioprotective, hepatoprotective, gastroprotective, nephroprotective, and neuroprotective properties, and its mechanism

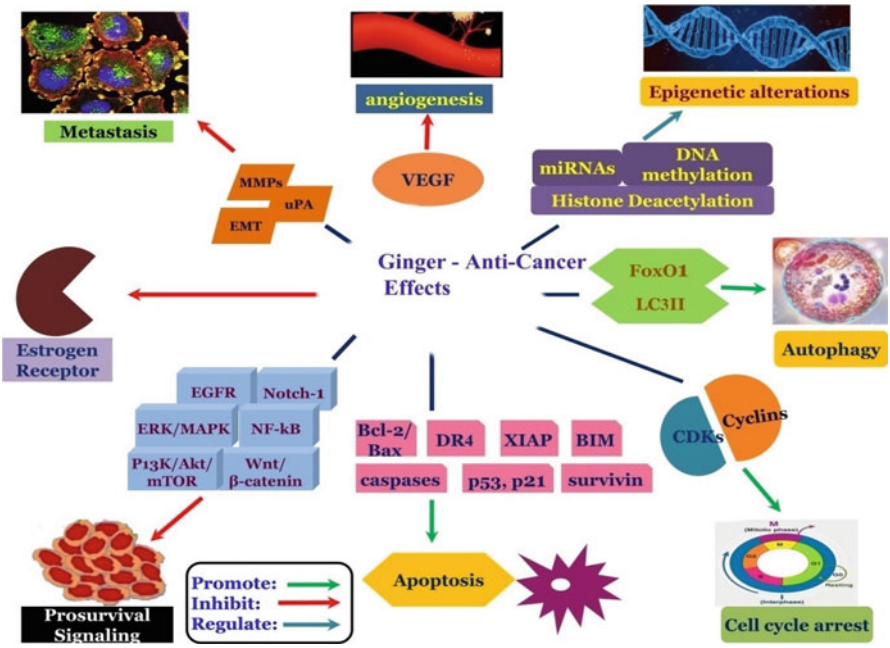

Fig. 2 Ginger and anticancer mechanism

of action at the cellular level has been studied by many scientists (Ali et al. 2008; Shanmugam et al. 2009, 2021) (Fig. 3).

Compounds of Ginger

The main constituents in ginger are terpenes, phenolic compounds, carbohydrates (50–70%), and lipids (3–8%). The terpenes (monoterpenes, sesquiterpenes, and sesquiterpene alcohols) are of 20–25%. The terpene compounds of ginger are zingiberene, α-farnesene, β-sesquiphellandrene, β-bisabolene, and α-curcumene. It has been identified that ginger has monoterpenes (such as α-pinene, camphene, myrcene, α-phellandrene, geranial, citronellal, neral, linalool, borneol, and alpha-terpineol). Phytosterols, amino acids, minerals, proteins, vitamins (vitamin A and nicotinic acid), and raw fiber, ash, are present in ginger (Shukla and Singh 2007).

The phenolic compounds of ginger are gingerol, shogaol, and paradols. In ginger, gingerols are in higher concentration. Ginger-specific smell and odor are due to the presence of gingerol and shogaols. The other compounds of ginger are 6-paradol, 1-dehydrogingerdione, 8-gingerdiol, 10-gingerdiol, 4-gingerdiol, 6-gingerdiol, 6-gingerdione, and 10-gingerdione. Ginger also contains diterpenes, galanolactone, diterpenoid, and ginger glycolipids (Yeh et al. 2014). Ginger has ascorbic acid, alkaloids, beta-carotene, and polyphenols. Ginger also has key volatile oils such as

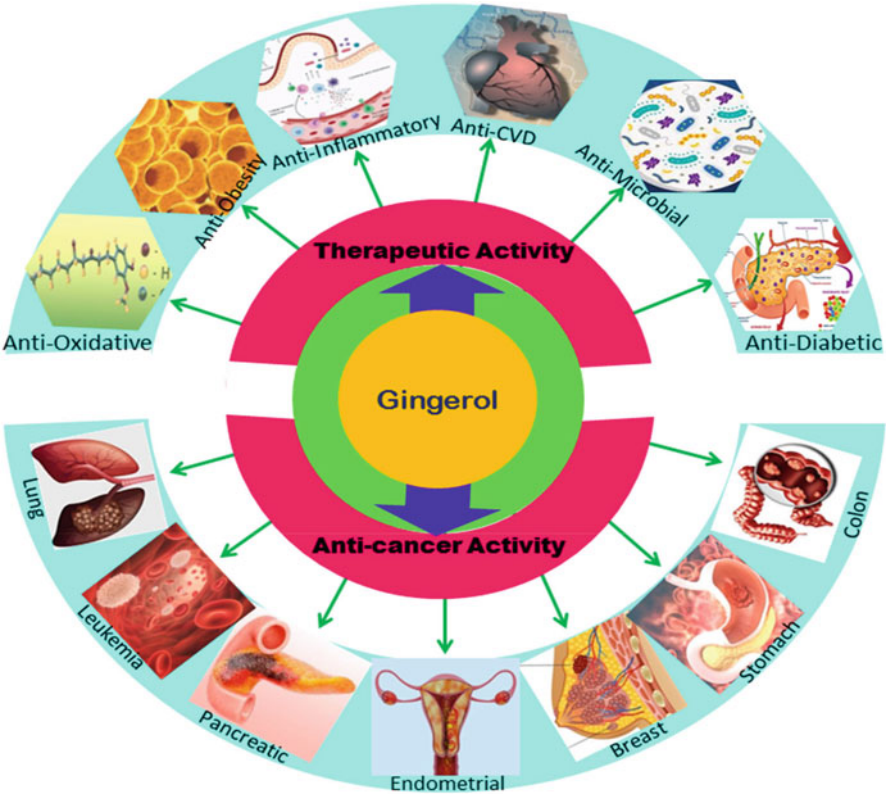

Fig. 3 Pharmacological and anticancer properties of Gingerol

oleoresins, bisabolene, cineol, phellandrene, citral, borneol, and citronellol, vitamin B6, vitamin c, and linoleic acid. As per the available information, there are more than 400 bioactive compounds in ginger (Shukla and Singh 2007) (Fig. 4).

Anticancer Effects of Ginger

Ginger has anticancer properties. In the methanolic, ethanolic, aqueous, n-hexane, and ethyl acetate, benzene extracts of ginger, many bioactive compounds are present which show antiproliferative, cytotoxic, and antiangiogenic activities. These pharmacological effects are due to bioactive compounds of ginger, which show antioxidant, anti-inflammatory, antioxidant, antihyperglycemic, antitumorigenic, and antilipidemic activities. These compounds may modulate the genetic expression and cause induction of apoptosis in cancer cells.

The anticancer effect of ginger may be due to the reduction of initiation, promotion, and progression. Hence, ginger can be used as anticancer agent (Zhang et al. 2017). Ginger has been reported to show its positive effects against many cancers,

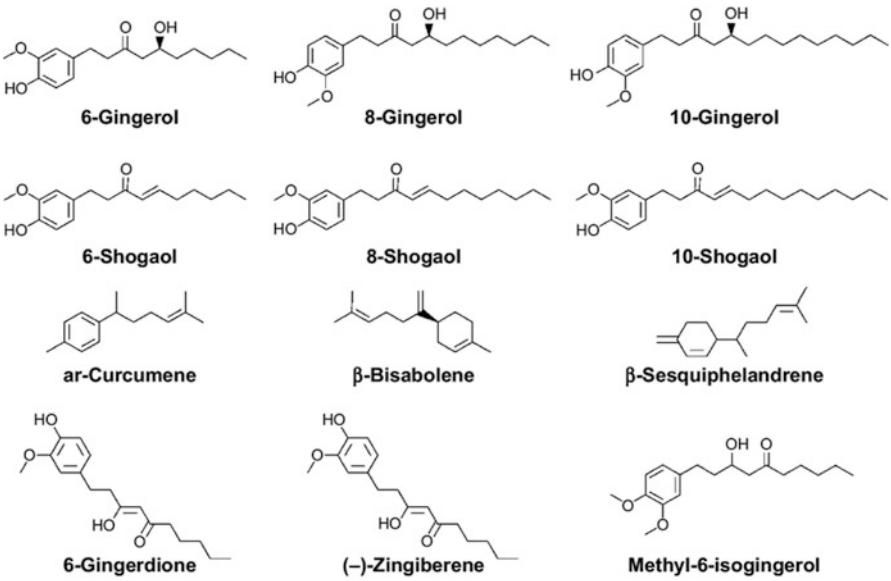

Fig. 4 Compounds of Ginger

like liver cancer, gastric cancer, pancreatic cancer, breast cancer, prostate cancer, and other types of cancers. Ginger also has anticancer effects in different cancer cell lines in vitro, like lung, ovarian, liver, colon, cervical, and prostate cancer, through the stimulation of apoptosis and the reticence of cell proliferation (Zhang et al. 2017) (Table 2).

Ginger has an antitumor activity by modulating of genetic pathways. It helps for the activation of suppressing gene of the tumor. Furthermore, ginger can inhibit the vascular endothelial growth factors and modulate apoptosis; thus, ginger supplementation can reduce cancer. Ginger extract prevents the initial stage of colon cancer. Supplementation of ginger to the mice with carcinogen 1,2-dimethylhydrazine (DMH) inhibited the levels of tissue cholesterol, HMG CoA reductase, free fatty acids, and triglycerides (Manju et al. 2006). Hence, ginger treatment reduces the risk of cancer by antioxidative compounds.

For instance, it has been identified that the terpenoids, compound of ginger, induce apoptosis in uterus cancer cells via the activation of tumor protein p53. Water and organic solvent extracts of ginger reported to show anticancer activities in THP-1 AMoL cells in vitro. These reports show that ginger has anticancer activity (Prasad and Tyagi 2015).

Ginger constituents ([6]-gingerol, [10]-gingerol, [6]-shogaol, and zerumbone) show anticancer effects. They are effective against many cancers (Habib et al. 2008). Habib et al. (2008) reported that ginger extract inhibits liver carcinogenesis in wistar rat through the downregulation of elevated NF-κB and TNF-α. Hence, ginger may act as an anticancer agent, which may be helpful in treatment of cancer subjects. Ginger ingredients inhibit the development of diethylnitrosamine-(DEN-)

Table 2 Effect of ginger and its compounds on different cancer subjects

S. no.	Ginger extract/ compounds of ginger	Study type	Subjects	Dose	Potential mechanisms	Reference
1	Ginger ethanolic extract	*In vivo*	Wistar rats	50 mg/kg	NADH dehydrogenase activity elevated	Ali et al. (2008)
2	Ginger extract	*In vitro*	HepG2 human hepato-cellular carcinoma cells	1.11 mg/mL	Increasing the level of ROS levels increased and elevated p53 levels, thus promoting apoptosis	Li et al. (2013)
3	6-gingerol	*In vitro*	He La human adenocarcinoma cervical cells	60, 100, and 140μM	Cyclin A, cyclinD1, and cyclin E1 levels decreased, and caspase levels increased	Zhang et al. (2017)
4	10-gingerol	In vitro	Human and mouse breast carcinoma cells	50, 100, and 200μM	Cell growth and cell division are reduced	Bernard et al. (2017)
5	6-gingerol,10-gingerol,6-shogaol, and 10-shogaol	*In vitro*	PC-3 human prostate cancer cells	1,10, and 100μM	Inhibiting prostate cancer decreased, and the expression of MRP1 and GSTπ are lowered	Liu et al. (2017)
6	6-shogaol	*In vitro*	LNCaP, DU145, and PC-3 human prostate cancer cells	10, 20, and 40μM	Cyclin D1, surviving, c-Myc, and Bcl2 expression are decreased Inhibition of STAT3 and NF-κB signals	Saha et al. (2014)

induced premalignant phenotype in rat hepato-carcinogenesis. It has been reported that supplementation of ginger prevented decrease of the content of metallothionein and endostatin in the liver and elevated the growth factors induced by the carcinogen in wistar albino rats. Ginger also reverses the altered serum-hepatic tumor markers (Mansour et al. 2010).

Wang et al. (2008) reported that beta-elemenean compound of ginger induces caspase-3, −7, −9 activities, decreases Bcl-2 expression, which releases cytochrome c, and elevated the levels of cleaved caspase-9 and poly (ADP-ribose) polymerase in cells. Application of ginger extract to mouse skin afforded significant inhibition of TPA-caused epidermal edema (56%) and hyperplasia (44%) (Katiyar et al. 1996). Kim et al. (2005) also reported that ginger induces programmed cell death in cell lines. Ethanol extract of ginger has antitumor-promoting effects in mouse skin tumorigenesis model, and it was concluded that animals pretreated with ginger showed depleted tumor compared with unginger-treated rats.

Zingerone with a dose of 100 mg mL suppressed LPS-induced NF-kB activities in cells. Dietary zingerone reduces proinflammatory cytokines. This study reports zingerone anti-inflammatory activity due to suppressing the activation of NF-kB, production of IL-1b, and the infiltration of inflammatory cells (Ganaie et al. 2019). Ganaie et al. (2019) also reported the anticancer effect of zingerone due to activation of cytochrome P4502E1 and suppression of NF-kB-p65, iNOSCOX-2, and PCNA in cancer subjects.

Zerumbone, seen in ginger, shows antiproliferative and anti-inflammatory effects and mediates its activity through the modulation of NF-kB activation (Takada et al. 2005). Zerumbone also inhibits the activation of NF-kB, and this inhibition may provide basis for the prevention and treatment of cancer. The antihepato-carcinogenic effect of zerumbone was due to suppression of PCNA and elevation of Bax and depletion of Bcl-2 protein expression (Gross et al. 1998). Hence, zerumbone may act as anticancer agent in liver cancers (Fuzer et al. 2017). Fuzere et al. (2017) reported that zerumbone induces the phase II detoxification enzymes depletion in rat liver epithelial cell line RL34. Hence, Zerumbone may act as a potential activator for the Nrf2-dependent detoxification pathway and provides a new insight into cancer management (Tsuboi et al. 2014) (Fig. 5).

Ginger-Bioactive Compound: Gingerol and Its Anticancer Effects

Gingerols are part of the phenolic compounds and volatile organic compounds of ginger. 4-, 6, 8-, 10-, and 12-gingerol are types of gingerol. 6-gingerol is the main compound which is responsible for the strong aroma of ginger. The biological properties of gingerols are antimicrobial, anticancer, antioxidant, anti-inflammatory, and antiallergic (Akinyemi et al. 2015).

6-gingerol has been identified to show anticancerous effects. Gingerol helps in the suppression of the hyperproliferation, inflammatory processes, and transformation that engaged in various steps of angiogenesis and metastasis. For instance, through the activation of CD8+ T cells, it inhibited B16F10 melanoma cells of pulmonary

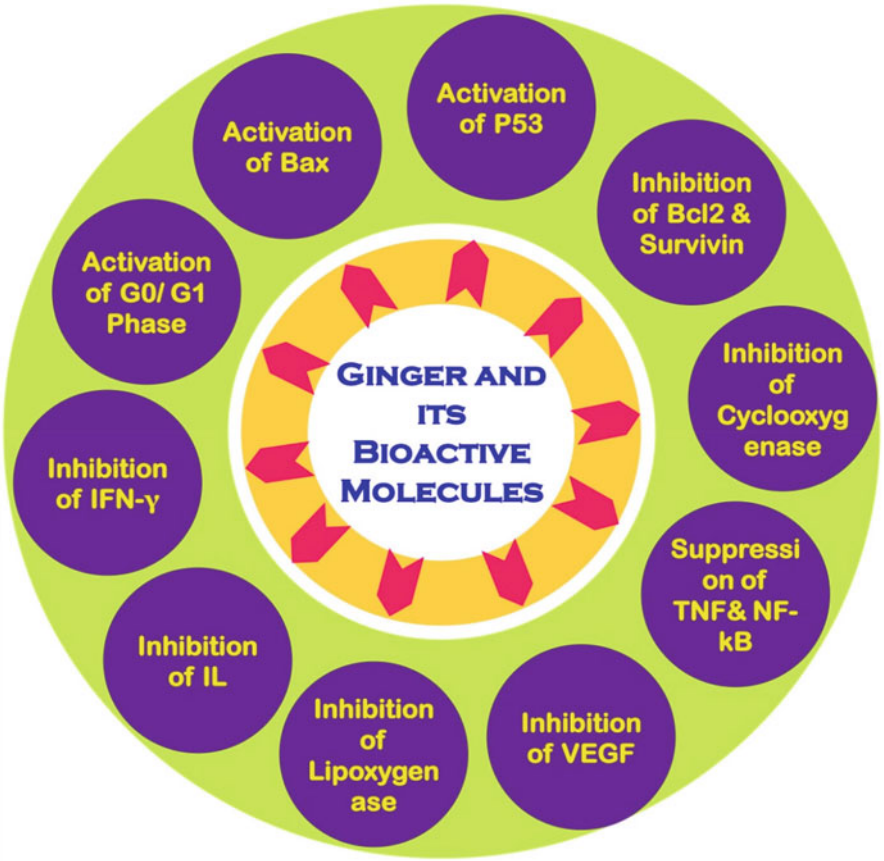

Fig. 5 Suppression of tumors markers by ginger and its compounds

metastasis in mice. Antitumoral activity showed by 6-gingerol through induction of reactive oxygen species (ROS) which, trigger p53 activation, apoptosis, and arrest the cell cycle (Lee et al. 2008). The study found that 6-G induced arrest of the cell cycle in both cell lines by reducing the expression of cyclin A and CDKA. In addition, Radhakrishnan et al. (2014) reported that 6-G induced cell death by apoptosis in the cell line with the mutated p53 gene. [6]-gingerol stimulated death receptor-mediated apoptosis in glioblastoma cells or p53-mediated apoptosis in skin tumor cells (Nakamura et al. 2004).

6-gingerol demonstrates an important potential to treat pancreatic cancer and has been shown to have a potential inhibitor of metastasis in *in vitro* and *in vivo* studies by different mechanisms, including a reduction in the expression of MMP and inhibiting angiogenesis (Kim et al. 2005). 6-gingerol targets many cellular molecules which promote cancer, for cell survival, cell proliferation, invasion, and angiogenesis. 6-Gingerol supplementation alters STAT3, NF-κB, Rb, MAPK, Akt, ERK,

PI3K, and caspase-3/7, cIAP1. Thus, gingerol treatment may modulate molecular targets of cancer components, so gingerol may have the therapeutic potential for preventing and treating many cancers.

In vitro and *in vivo* analysis of [10]-gingerol has been reported against the metastatic triple negative breast cancer (TNBC) [97]. In addition, it was experimented that 10-gingerol inhibits cervical cancer (Zhang et al. 2017). A study carried out by Martin et al. (2017) showed the anticancer activity of 10-G *in vivo* and *in vitro* in triple negative breast cancer models through proapoptotic activity and the inhibition of metastasis. The activity of 10-G in vitro was dose dependent, finding that at the highest concentration (100μM) colony formation was completely inhibited and extensive cell death occurred. 10-gingerol caused a considerable upsurge in the initiation of caspase-3 and inhibited orthotopic tumor growth of spontaneous breast cancer metastasis. Zhang et al. (2017) reported that 10-gingerol inhibits metastasis to multiple organs like lung, bone, and brain.

Therapeutical Potential of Gingerol and Its Effect on Metabolic Pathways in Cancer

Anticancer mechanisms of gingerol include free radical scavenging effect, antioxidant effect, modulation of various enzymes of inflammation, modulation of cell cycle proteins, induction of apoptosis, and arrest the cell cycle at G2/M phase in carcinoma which will provide basis for inhibition of tumor progression in experimental animals. TNF-α, IL-6, NF-κB, cyclooxygenase-2 COX-2, and caspase-3 are the most important cancer metabolic factors.

Free Radical Scavenging and Antioxidant Activity of Gingerol

Gingerol possesses antioxidant activity due to their free radical scavenging activity. It has been investigated that gingerol may modulate the antioxidant enzymes and suppress the lipid peroxidation products in cancer subjects. Hence, gingerol may prevent the pathogenesis of cancer-related disorders by its free radical scavenging activity. Alsahli et al. (2021) reported anticancer activity of gingerol in colon cancer, breast cancer, by elevating antioxidant enzymes and depleting lipid peroxidation in cancer condition.

Effect of Gingerol on Apoptotic Genes

Apoptosis is one of the prerequisites to maintain the normal and healthy internal milieu. Alteration in the normal process of apoptosis may raise cell survival and support the tumor growth and progression (Kim et al. 2005). Gingerol plays a vital role in the elevation of different proapoptotic genes and at the same time depletion of the antiapoptotic genes and by this way balances the apoptosis process. An interesting study showed that gingerol induces apoptosis in scleroderma lung fibroblasts without affecting normal lung fibroblasts. Furthermore, gingerol has shown an

antitumor activity and was involved in the apoptosis induction and the modulation of key apoptotic proteins such as Bax and bcl-2 (Yu et al. 2011).

A study has reported that growth arrest and apoptosis of B cell lymphoma occur through the downregulation of c-myc, bcl-XL, and p53 with the treatment of gingerol. Another report in human breast cancer cell line showed that CD437 induces G0-G1 arrest and apoptosis via regulation of p21WAFI/CIPI, Bcl-2, and Bax in a p53-independent manner after treatment with gingerol. Another study on p53-null cells, as well as TR9-7 cells, reported that gingerol induces apoptosis in tumor cells via a p53-dependent pathway, and Bax acts as downstream effectors of p53.Gingerol induces apoptosis in a range of tumor cell lines through activation of caspase-3, cytochrome c release, and depletion of bcl-2 (de Lima et al. 2018).

Gingerol has shown an apoptotic effect by inhibiting various genes such as proteintyrosine kinase, protein kinase C, c-myc mRNA expression, and bcl-2 mRNA expression and also mitochondrial pathway. Earlier studies have shown that gingerol possesses an apoptotic activity in different types of cancer cells such as human colon cancer cells, stomach, and skin tumors, breast cancer cells, and prostate cancer cells (Nakamura et al. 2004). Gingerol may lower the incidence of various cancers and also induce apoptosis in MBT-2 cells and G2/M arrest of T24 cells (Park et al. 2014). Experimental studies showed that the downregulation of the expression of antiapoptotic protein occurs with gingerol treatment (Nakamura et al. 2004).

Effect of Gingerol on Tumor-Suppressor Genes

Tumor-suppressor genes play a vital and significant role in the inhibition of cancer formation and its progression. An alteration or mutations may occur in a gene, then tumor suppressor gene loses its ability to perform normal function and it transforms into tumor gene. p53 is one of the important suppressor genes, and it is the guardian of all genes and regulates the various cellular and molecular pathways and prevents the formation of cancer.

Numerous *in vivo* and *in vitro* reports showed that gingerol has a significant role in cancer prevention or inhibition. Another study showed that gingerol downregulates the expression of p53, as well as the survival genes egr-1,c-mycandbcl-XL in B cells. Another report also indicated that gingerol inhibits cell cycle progression of immortalized human umbilical vein-endothelial cells via upregulating the CDK inhibitors p21WAF1/CIP1, p27KIP1, and p53 (Park et al. 2014).

Another tumor-suppressor gene, phosphatase and tensin homolog deleted on chromosome ten (PTEN), has a role in the progression of the cell cycle and apoptosis. The alteration or mutation of PTEN gene has been noticed in several types of cancers. A study of the gingerol has shown that PTEN increases the gingerol-induced apoptosis, whereas inactive PTEN decreases/inhibits the gingerol-induced apoptosis.

In mice, [6]-gingerol suppressed the promotion of skin cancer. Park et al. (Park et al. 2014) reported that [6]-gingerol inhibited TPA skin tumor promotion in

addition to the inhibition of epidermal ornithine decarboxylase activity in ICR mice. In a study, Surh et al. [1999] reported antitumor-promoting properties of both [6]-gingerol and [6]-paradol. [6]-gingerol treatment attenuated the skin papilloma genesis and inhibited the tumor-promoter genes, TNF-alpha production, and activation of epidermal ornithine decarboxylase in ICR mice (Nakamura et al. 2004).

Effect of Gingerol on Cycloxygenase Enzyme

COX is an inducible enzyme in the conversion of arachidonic acid to prostaglandins (PGs). There are two types of cyclooxygenase COX-1 that play a vital role in physiological functions and COX-2, an enzyme responsible for inflammation and pain. COX-2 is upregulated or overexpressed in various types of cancers (Pournaderi et al. 2017). It was previously stated that gingerol inhibits the critical stage of tumor initiation and promotion stages and COX inhibition. Gingerol also inhibits the COX2 expression on colon cancer cell lines (Nonn et al. 2007). Previous reports states that gingerol plays an important role in the downregulation of the expression of COX-2 and finally suppresses the cancer progression (Kim et al. 2005). Gingerol plays a significant role in the cancer prevention via controlling the activities of various genes in the initiation, promotion, and progression stage of tumor development and progression.

NF-κB and Gingerol in Cancer Prevention

NF-κB family of transcription factors shows an important role in immune, inflammatory response and also stimulates the development and progression of cancer. In this regard, an important study demonstrated that gingerols have anticancer, antioxidant, and anti-inflammatory effects via the downregulation of the transcription factors NF-κB, AP-1, and Egr-1 (Han et al. 2002) and repression of the genes for cell adhesion molecules (chemokines, TNF, Cox-2, and MMP-9). Another study showed that gingerol has been involved in the suppression of NF-κB activation and NF-κB gene products (Plummer et al. 1999). An important study in pancreatic cancer cells reported that gingerol shows a vital role in the suppression of NF-κB activation by inhibiting IκB kinase, ultimately induces IκBα phosphorylation, and inhibits the NF-κB downstream gene expression. [6]-gingerol inhibited both the vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (b-FGF)-induced proliferation of human endothelial cells and caused cell cycle arrest in the G1 phase (Vijaya Padma et al. 2007). Recently, anticancer and anti-inflammatory potential of 6-gingerol was reported by inactivating NF-kB through the suppression of the proinflammatory TNF-alpha (Kim et al. 2005; Habib et al. 2008). Numerous studies have shown that gingerol is a potent inhibitor of NF-κB activation.

Kim et al. (2005) reported that 6-gingerol regulates tight junction-related proteins and suppresses invasion and metastasis of pancreatic cancer cells. 6-gingerol mediated through NF-κB inhibition via inhibition of the extracellular signal-regulated kinases (ERK) pathway. Thus, 6-gingerol suppresses the invasive activity of PANC-1 cells.

Impact of Gingerol on Angiogenesis

Angiogenesis is a complex process involving widespread interaction between the cells, soluble factors, and ECM components. During cancer development, tumor growth is triggered by many signals in chain reaction manner. In cancer formation, there are stages and angiogenic factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiogenin, transforming growth factor (TGF-α, TGF-β), and epidermal growth factors, which play vital role in tumor angiogenesis through cancerous tumor cells by releasing molecules and sending signals to surrounding normal host tissue. VEGF is a crucial survival factor for endothelial cells in the process of physiological, tumor angiogenesis, and it induces the expression of antiapoptotic proteins in the endothelial cells (Shukla and Singh 2007). Many reports showed that many medicinal plants suppress the VEGF and other factors of cancer. We also reported that gingerol is best inhibitor of VEGF in different types of cancer (Weng et al. 2010).

In vitro studies on hepatic cancer cell lines conducted so far have demonstrated that ginger suppressed the growth of human hepatic cancer cell lines by inhibiting the phosphorylation of tyrosine-kinase receptor IGF-1R, inducing apoptosis by activating Caspase 9 and downregulating Bcl-2 and cyclooxygenase-2 (COX-2), modulating the levels of VEGF and its receptor (VEGFR-2), NF-κB, p53, and extracellular signal-regulated kinase 1/2 (ERK1/2), reducing the expression of lipogenic enzymes, certain types of RTKs, and their downstream pathways, and activating adenosine monophosphate-activated protein kinase (AMPK) and ROS-mediated lysosomal membrane permeabilization. Based on various liver carcinogenesis animal models with the intake of ginger, the inhibition of hepatoma growth, restriction of hepatic cancer cell line progression, and activation of apoptosis were observed; the probable mechanisms behind might be associated with suppression of hepatocyte progenitor cell/stem cell population, activation of AMPK protein in the liver, and modulation of self-renewal pathways and their related genes. *In vitro* and *in vivo* studies reported that gingerol suppresses the proliferation of human vascular endothelial cells and also abrogates the FGF-2-induced angiogenic response. Moreover, gingerol has the ability to inhibit both VEGF and its receptor in various cancer types; it might be useful as an antiangiogenic agent. Hence, gingerol acts as anticancer agent against many cancers through suppressing proliferation, angiogenesis, NF-κB, and NF-κB-regulated gene products.

Conclusion and Future Perspectives

Cancer is one of the deadliest diseases and a major health problem in the world. The present modes of treatments like chemotherapy and radiotherapy are very expensive and also exhibit many side effects in cancer patients. Ginger and its bioactive compounds are used to treat cancer. Gingerol a bioactive compound of ginger has been shown to target multiple signaling molecules in cancer metabolism and provides a basis for its therapeutic applications for cancer subjects. Moreover, most of

the known activities of gingerol are based only on *in vitro* and *in vivo* studies, and some clinical studies in human subjects. Therefore, more extensive and well-controlled animal and human studies are required to demonstrate efficacy of gingerol and other compounds of ginger against cancer.

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