

## BIBLIOGRAPHIC INFORMATION SYSTEM

**Journal Full Title:** [Journal of Biomedical Research & Environmental Sciences](#)

**Journal NLM Abbreviation:** J Biomed Res Environ Sci

**Journal Website Link:** <https://www.jelsciences.com>

**Journal ISSN:** 2766-2276

**Category:** Multidisciplinary

**Subject Areas:** Medicine Group, Biology Group, General, Environmental Sciences

**Topics Summation:** 128

**Issue Regularity:** [Monthly](#)

**Review Process:** [Double Blind](#)

**Time to Publication:** 21 Days

**Indexing catalog:** [Visit here](#)

**Publication fee catalog:** [Visit here](#)

**DOI:** 10.37871 ([CrossRef](#))

**Plagiarism detection software:** [iThenticate](#)

**Managing entity:** USA

**Language:** English

**Research work collecting capability:** Worldwide

**Organized by:** [SciRes Literature LLC](#)

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**IndexCopernicus  
ICV 2020:  
53.77**

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# Ginger (*Zingiber officinale*) and its Bioactive Components with Protective and Therapeutic Potential against Cancer

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## ABSTRACT

Ginger can be an important complementary medicine for prevention and treatment of different types of cancers, owing to its natural origin, safety, and low cost relative to synthetic cancer drugs. Ginger contains volatile oils, anthocyanins, tannins, phenolic compounds and sesquiterpenes anticancer effects of ginger may arise from the ability to induce changes in a number of cellular processes, including cell division, apoptosis and differentiation. In this study, anticancer activity of ginger extract against various cancer cells both *in vitro* and *in vivo* were investigated. The evidence in this review suggests that ginger and its compounds in diet may lower cancer risk and affect tumor behavior.

## INTRODUCTION

There has been a resurgence of whole food-based therapeutics categorized as natural medicines in prevention and treatment of chronic diseases like cancer. Although surgery and chemotherapy have been the most common treatment for cancer, cancer chemoprevention with dietary factors has received attention as the most effective approach. Ginger (*Zingiber officinale*) a key component in traditional herbal medicine, where its potential has been intensely exploited in health benefits. The bioactive components of ginger include volatile oils, anthocyanins, tannins, and pungent phenolic compounds known as gingerols, shogaols, and sesquiterpenes [1-3]. Ginger contains fragrant oil and the main constituents are sesquiterpenoids with (-)-zingiberene. Ginger and its pungent bioactive components, which include gingerols and shogaols, can be used in the prevention and treatment of cancer [4-7].

The health attributes associated with ginger may arise from its pharmacological properties, its anticancer effects may arise from the ability to induce changes in a number of cellular processes, including cell division, apoptosis and differentiation. The main pharmacological actions of active compounds extracted from ginger root reported by *in vitro* and *in vivo* test attributed to its active phytochemicals were: anti-inflammatory, antioxidant, antiemetic, anticancer, anticoagulant, immunomodulatory, antihyperglycemic, hypolipidemic, analgesic, and cardioprotective properties [5]. Evidence that ginger and ginger-derived compounds have inhibitory effects on various cancers is increasingly being reported in the

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DOI: 10.37871/jbres1133

Submitted: 14 August 2020

Accepted: 11 September 2020

Published: 15 September 2020

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OPEN ACCESS

Subjects: Medicine

Topic(s): Pharmacology, Therapeutics

### Keywords

- Anticancer
- Ginger
- *Zingiber officinale*
- 6-gingerol
- Shogaol

VOLUME: 1 ISSUE: 5

scientific literature. The potential mechanisms of action involve the inhibition of proliferation and the induction of apoptosis in cancer [8,9]. 6-gingerol [5-hydroxy-1-(40-hydroxy-30-methoxyphenyl)-3-decanone] is the most abundant compound in fresh ginger and is widely investigated anticancer potential [10,11]. This review reports the anticancer activity of ginger and its compounds which may be associated with the reduction of cell viability and induction of apoptosis in various cancer cells.

### Sources and methodology

The search was done in electronic databases of PubMed, Scopus, ScienceDirect, Web of Science and Google Scholar for studies using the key terms: anticancer potential, ginger, gingerol, zingerone, paradols and shogaols. The inclusion was based reported articles on anticancer activity of ginger and its compounds whose mechanism of action are discussed in detail. All the data were extracted and explained in respective subheadings.

### Breast cancer

Breast cancer is the most common type of cancer and the leading cause of cancer-related death in women [12]. Although early detection methods and multimodal approaches for breast cancer treatment have been made, there has been only modest progress in improving clinical outcomes for women with metastases.

Lee, et al. [13] studied the effect of 6-gingerol on adhesion, invasion, and motility activity was assessed by measuring the levels of MMP-2 and -9 in cultured human breast cancer cells. Anticancer effect of 6-gingerol may contribute to the inhibition of metastasis by decreasing the activities and expressions of MMP-2 and MMP-9. Ling, et al. [14] evaluated the effect of shogaols on the viability of MDA-MB-231 breast cancer cells using the CCK-8 assay. The results demonstrated that sublethal doses of 6-, 8- and 10-shogaol, by reducing MMP-9 expression and secretion, have an inhibitory effect on PMA-induced breast cancer cell invasion. Further, 6-shogaol impairs breast cancer cell invasion, at least in part, through targeting the NF- $\kappa$ B activation cascade.

Human breast cancer cell lines MCF-7 and MDA-MB-231 are considerably more sensitive to growth suppression than the normal mammary line MCF-10A when treated with ginger extracts [15]. Ginger treatment downregulated expression of prosurvival genes, such as NF- $\kappa$ B, Bcl-X, Mcl-1, and Survivin, and cell cycle-regulating proteins, including cyclin D1 and Cyclin-Dependent Kinase-4 (CDK-4). On the other hand, it increased expression of CDK inhibitor, p21. It also inhibited the expression of the two prominent molecular targets of cancer, c-Myc and the human Telomerase Reverse Transcriptase (hTERT).

Joo, et al. [16] investigated the regulatory effects and signaling pathways of 10-gingerol on cell proliferation

and invasion in MDA-MB-231 breast cancer cells. 10-gingerol treatment inhibited cell proliferation through downregulation of cell cycle regulatory proteins such as cyclin-dependent kinases and cyclins, and subsequent induction of G1 phase arrest. In addition, 10-gingerol treatment blocked cell invasion in response to mitogenic stimulation. These antitumor activities of 10-gingerol were mediated through inactivation of Akt and p38MAPK activity, and suppression of epidermal growth factor receptor expression.

Bernard, et al. [17] compared 10-gingerol with 8-gingerol and 6-gingerol in terms of their ability to inhibit the growth of human and mouse mammary carcinoma cells. The inhibitory effect of 10-gingerol on the growth of MDA-MB-231 cells was associated with a reduction in the number of rounds of cell division and evidence of S phase-cell cycle arrest, as well as induction of apoptosis due to mitochondrial outer membrane permeabilization and the release of apoptogenic molecules.

### Liver cancer

Kaewtunjai, et al. [18] found that *Zingiber officinale* extract induced telomere shortening and cellular senescence in A549 cells. The results suggest that these paradols and shogaols are likely the active compounds in zinger extract that suppress hTERT expression and telomerase activity in these cells. Likewise, Yusof, et al. [19] investigated the effect of ginger in ethionine induced rat hepatocarcinogenesis. It was found that ginger supplementation suppressed liver carcinogenesis by scavenging the free radical formation, and by reducing lipid peroxidation. Ginger polysaccharide could promote apoptosis and arrest cells in G0-G1 phase of hepatocellular carcinoma HepG2 cells. Real-time fluorescence quantification and Western blot revealed that GP could up-regulate the expression of Bax, Fas, FasL, caspase-3, p21 and p53, and down-regulate the expression of Bcl-2 [20].

Habib, et al. [21] tested the potential anti-inflammatory and anti-cancer effects of ginger extract by using an immunohistochemistry technique to detect the presence of the inflammatory marker TNF- $\alpha$  and the transcription factor NF $\kappa$ B. Ginger extract significantly reduced the elevated expression of NF $\kappa$ B and TNF- $\alpha$  in rats with liver cancer. Ginger may act as an anti-cancer and anti-inflammatory agent by inactivating NF $\kappa$ B through the suppression of the pro-inflammatory TNF- $\alpha$ . Weng, et al. [22] evaluated the anti-invasion activity of 6-shogaol and 6-gingerol, two compounds found in ginger, on hepatoma cells. The migratory and invasive abilities of Phorbol 12-Myristate 13-Acetate (PMA)-treated HepG2 and PMA-untreated Hep3B cells were both reduced in a dose-dependent manner by treatment with 6-shogaol and 6-gingerol. Upon incubation of PMA-treated HepG2 cells and PMA-untreated Hep3B cells with 6-shogaol and 6-gingerol, Matrix

Metalloproteinase (MMP)-9 activity decreased, whereas the expression of Tissue Inhibitor Metalloproteinase Protein (TIMP)-1 increased in both cell types. Further, 6-Shogaol and 6-gingerol effectively inhibit invasion and metastasis of hepatocellular carcinoma through diverse molecular mechanisms, including inhibition of the MAPK and PI3k/Akt pathways and NF- $\kappa$ B and STAT3 activities to suppress expression of MMP-2/-9 and uPA and block angiogenesis [23].

### Cervical cancer

6-gingerol was found to reduce the viability of HeLa (human cervical carcinoma) cells as shown by morphological changes in cells. HeLa cells treated with 6-gingerol showed altered nuclear and cellular morphology, cell shrinkage, and membrane blebbing, which are characteristics of apoptotic cell death. Additionally, an increase in chromatin condensation and fragmentation of HeLa cells was observed with increased dose of 6-gingerol during treatment [24]. A study involving 6-gingerol extracted from Tongling White Ginger led to several morphological changes with increased dose and longer treatment and resulted in cell cycle arrest in G<sub>0</sub>/G<sub>1</sub>-phase [25]. The mRNA and protein expression significantly decreased in cyclin A, cyclin D1 and cyclin E, while, there was slight decrease in CDK-1, p21 and p27 and cyclin B1 and E1 protein remain unchanged. Likewise, 10-gingerol inhibited the proliferation of HeLa cells at IC<sub>50</sub> (29.19  $\mu$ M) and IC<sub>80</sub> (50.87  $\mu$ M) with altered cell morphology, increased cytotoxicity, and arrested cell cycle in the G<sub>0</sub>/G<sub>1</sub> phase. Most cell cycle related genes and protein expression significantly decreased, followed by a slight decrease in a few without affecting cyclin B1 and cyclin E1 (protein). Both death receptors significantly up-regulated and activated apoptosis indicators (caspase family). Furthermore, significant changes in mitochondria-dependent pathway markers were observed and led to cell death. 10-gingerol led to PI3K/AKT inhibition and AMPK activation to induce mTOR-mediated cell apoptosis in HeLa cells [26].

Rastogi, et al. [27] explored the molecular mechanism of action of 6-gingerol in human cervical cancer cells *in vitro* and *in vivo*. 6-gingerol potently inhibited proliferation of the HPV positive cervical cancer cells. 6-gingerol was found to inhibit the chymotrypsin activity of proteasomes; induce reactivation of p53; increase levels of p21; induce DNA damage and G<sub>2</sub>/M cell cycle arrest and alter expression levels of p53-associated apoptotic markers like, cleaved caspase-3 and PARP. Ansari, et al. [28] demonstrated that ZOME inhibited the proliferation and colony formation in HeLa cells in a dose- and time-dependent manner and induced typical changes in nuclear morphology, chromatin condensation and fragmentation, membrane shrinkage and blebbing in both cells indicated apoptotic property of *Z. officinale*.

### Colon cancer

The anticancer effects of 6-gingerol on human colon cancer cell (LoVo) was studied by Lin, et al. [29]. Results showed that 6-gingerol significantly induces cell cycle arrest at the G<sub>2</sub>/M phase; has little influence on the sub-G<sub>1</sub> phase; and decreases the levels of cyclin A, cyclin B1, and CDK1. However, treatment with 6-gingerol increased levels of negative cell cycle regulators p27Kip1 and p21Cip1 and enhanced ROS levels and phosphorylation of p53. These results highlight the importance of 6-gingerol in the treatment of colon cancer.

The effects of zingerone on suppressing cell proliferation and enhancing apoptosis in colon cancer cells (HCT116) was explored by Su, et al. [30]. The results indicated that zingerone significantly enhances the production of reactive oxygen species, lipid peroxidation (Thiobarbituric Acid Reactive Substance [TBARS]), and loss of cell viability; and reduces mitochondrial membrane potential and antioxidant levels (SOD, CAT, and GSH) in ZO-treated HCT116 cells in a dose-dependent (2.5, 5, and 10  $\mu$ M) manner. Abdullah, et al. [31] reported G<sub>0</sub>/G<sub>1</sub> arrest and apoptosis induced by ginger extract in case of HCT 116 and HT 29 colon cancer cell lines. Chemopreventive efficacy of ginger extract was also described against hepatoma HepG2 and HLE cell lines [32].

Qi, et al. [33] observed that 6-shogaol (15 mg/kg) significantly inhibited colorectal tumor growth in a xenograft mouse model. 6-shogaol inhibited HCT-116 and SW-480 cell proliferation with IC<sub>50</sub> of 7.5 and 10  $\mu$ M, respectively. Growth of HCT-116 cells was arrested at the G<sub>2</sub>/M phase of the cell cycle, primarily mediated by the up-regulation of p53, the CDK inhibitor p21(waf1/cip1) and GADD45 $\alpha$ , and by the down-regulation of cdc2 and cdc25A.

### Colorectal cancer

Treatment of human HCT116 (colorectal) cancer cells with EG caused morphological and biochemical characteristics of apoptotic cell death. Induction of apoptosis was associated with mitochondrial cytochrome c release, increased Bax:Bcl2 ratio, activation of caspase-3 and -9, and PARP cleavage. Furthermore, EG (a) decreased the expression levels of antiapoptotic proteins including Bcl2, BclX, Mcl-1, survivin, and XIAP; (b) elevated expression levels of the onco-suppressive proteins, p53, p21, and p27; (c) reduced the expression of cyclin D1 and cyclin/Cdk-4; and (d) decreased expression of c-Myc [34].

Exposure of ginger leaf extract to human colorectal cancer cells (HCT116, SW480 and LoVo cells) reduced the cell viability and induced apoptosis in a dose-dependent manner. In addition, ginger leaf reduced cell viability in MCF-7, MDA-MB-231 and HepG-2 cells. Ginger leaf increased Activating Transcription Factor 3 (ATF3) expressions in both protein and mRNA level and activated ATF3 promoter activity, indicating transcriptional activation of ATF3 gene [35].

## Endometrial cancer

Treatment of the endometrial cancer cells with the steam distilled extract of ginger results in significant increase in intracellular calcium, decrease in the mitochondrial membrane potential, increase in the expression of caspase 3, phosphorylation of P53, and a significant decrease in the expression of Bcl-2 [32]. The data demonstrated that ginger extract treatment results in a rapid increase in the levels of intracellular calcium and in the activation of p53. Furthermore, inhibition of p53 attenuates the ability of ginger extract to induce apoptosis in the endometrial cancer cells.

## Melanoma skin cancer

Antiproliferative and proapoptotic activity of ginger extracts in murine melanoma B164A5 cell line was reported by earlier [36]. A possible signaling pathway involved in 6-gingerol mediated depigmentation was investigated by means of specific inhibitors [37]. The results indicated that 6-gingerol has a more potent inhibitory effect on melanin formation in B16F10 melanoma cells than kojic acid does which might lead to the activation of the Akt/protein kinase B pathway. In another study, treatment of B16F10 mouse melanoma cells with 6-shogaol reduced the melanin content in a concentration-dependent manner. It significantly decreased the intracellular tyrosinase activity, and markedly suppressed the expression levels of tyrosinase and MITF proteins in the cells. Huang, et al. [38] investigated the effects of 8-gingerol on mushroom tyrosinase activity, the expression of melanogenesis-related proteins, and melanin content in B16F10 and B16F1 melanoma cells. It was determined that 8-gingerol significantly inhibits tyrosinase activity and decreases melanin synthesis. Moreover, 8-gingerol also expresses intracellular free radical scavenging activity. The results suggest that 8-gingerol decreases melanin production, which may be attributed to its inhibitory action upon the signalling pathway that regulates tyrosinase activity or by the depletion of cellular RS and ROS. Further, the results demonstrated that 8-gingerol decreases melanogenesis in melanoma cells by inactivating PKA and MAPK signalling pathways, reducing MITF expression and inhibiting tyrosinase activity.

Cojocar, et al. [39] investigated the cytotoxicity of a fresh ginger extract on skin tumor cells and the amelanotic melanoma cells displayed profound changes in cell morphology such as cell shrinkage, rounding-up and membrane blebbing and a decrease in cell viability in a dose-dependent manner. Furthermore, 6-shogaol (10  $\mu\text{mol/L}$ ) activated ERK, which was known to negatively regulate melanin synthesis in mouse melanoma cells [40].

## Pancreatic cancer

Park, et al. [41] investigated the action of 6-gingerol on two human pancreatic cancer cell lines. The experiments

described that 6-gingerol induces apoptotic cell death in p53-mutant cancer cells. The death mechanism was characterized, revealing that 6-gingerol not only initiated cell cycle arrest but ultimately caused cell death through apoptosis. Thus, 6-gingerol, is capable of killing cancer cells expressing mutant p53, overcoming the phenotypic resistance to chemotherapy- and irradiation-induced cell death. Further, 6-gingerol regulates TJ-related proteins and suppresses invasion and metastasis through NF- $\kappa$  B/Snail inhibition via inhibition of the ERK pathway thus suppress the invasive activity of PANC-1 cells [42].

Zerumbone, a component of subtropical ginger against angiogenesis in pancreatic cancer [43]. Zerumbone blocked the pancreatic cancer associated angiogenesis through the inhibition of NF- $\kappa$ B and NF- $\kappa$ B-dependent proangiogenic gene products. Further, zerumbone induced apoptosis in pancreatic carcinoma cells through p53 signal pathway [44].

Akimoto, et al. [45] examined the anticancer activity of ginger extract against pancreatic cancer cells both *in vitro* and *in vivo* and investigated its potential mechanism. They reported that ginger extract leads to the reduction of cell viability and tumor growth of Panc-1 cells mainly through ROS-mediated autosis. Zhou, et al. [46] investigated whether 6-shogaol could suppress pancreatic cancer progress. 6-shogaol inhibited TLR4 signalling resulting in a reduced activation of NF- $\kappa$ B, which led to a delayed growth of pancreatic cancer. Moreover, pre-treatment with 6-shogaol resulted in an inhibition of constitutive and gemcitabine-induced NF- $\kappa$ B activity.

## Prostate cancer

Karna, et al. [47] showed that ginger extracts exhibits substantial growth-inhibitory effect and induced death in a panel of prostate cancer cells. Additionally, the extract reduced cell cycle progression, decreased the capacity to reproduce, and initiated a caspase-driven, mitochondrially mediated apoptosis. IN another study, treatment of androgen-dependent and -independent human prostate cancer cells in culture with 6-Shogaol inhibits survival and induces apoptosis [48]. These effects of 6-Shogaol were associated with inhibition of both STAT3 and NF- $\kappa$ B signalling and possibly other signalling pathways.

## CONCLUSION

Cancers are not an inevitable consequence of aging and changing lifestyle but are preventable diseases. Ginger can be an important complementary medicine for prevention and treatment of different types of cancers, owing to its natural origin, safety, and low cost relative to synthetic cancer drugs. The evidence in this review suggests that ginger and its compounds in diet may lower cancer risk and affect tumor behavior. Thus, ginger alone or in combination with other chemotherapeutic drugs could be an alternative drug in treating different cancers.

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**How to cite this article:** Bobde MV, Yadav S, Sibi G. Ginger (*Zingiber officinale*) and its Bioactive Components with Protective and Therapeutic Potential against Cancer. *J Biomed Res Environ Sci.* 2020 Sep 15; 1(5): 144-149. doi: 10.37871/jbres1133, Article ID: JBRES1133