

PHARMACOLOGICAL ACTIVITIES OF *ZINGIBER OFFICINALE* (GINGER) AND ITS ACTIVE INGREDIENTS: A REVIEW

Rasna Gupta, Pradeep Kumar Singh, Rajani Singh and *Ram Lakhan Singh

Department of Biochemistry, Dr. Ram Manohar Lohia Avadh University, Faizabad, Uttar Pradesh, India

*Address for correspondence: Dr. Ram Lakhan Singh, Professor and Head, Department of Biochemistry,
Dr. Ram Manohar Lohia Avadh University, Faizabad, Uttar Pradesh, India
Email: drllsingh@rediffmail.com

ABSTRACT

Ginger, the rhizome of the Zingiber officinale, has shown therapeutic role in health management since ancient times and considered as potential chemo-preventive agent in various human diseases. It is widely used in traditional and Ayurvedic medicines for the treatment and management of various health ailments including rheumatism, asthma, stroke, constipation, diabetes etc. There are scientific evidences that ginger may alleviate the symptoms of nausea and vomiting following pregnancy, surgery, cancer therapy or motion sickness and suggestive evidence that ginger reduces inflammation and pain. Ginger produces a hot, fragrant kitchen spice and often pickled in vinegar or sherry as a snack or cooked as flavoring ingredient in many Indian dishes and herbal remedies. Numerous chemical components of ginger have been reported with their significant biological activities. Phytochemical analysis of ginger showed the presence of active ingredients such as gingerol, shogaol, zingerone, paradol, zingerberene and other terpenoids and flavonoids, which are responsible for its various ethnomedical significance and biological activities. Molecular mechanism of active ingredients for antioxidant, anti-tumour anti-inflammatory, analgesic, hepatoprotective and anticancerous activities has been involved in induction of apoptosis and modulation of genes. The main aim to write this review is to give insight on active ingredients of ginger and their valuable nutritional and pharmacological properties which will help students and researchers to get the overall information about published nutritive and pharmacological properties of its ingredients.

Keywords: Active Ingredients; Ginger; Gingerol; Shogaol; Zingerone; Paradol; Zingerberene

INTRODUCTION

Ginger is the rhizome of *Zingiber officinale*, a perennial plant, used either alone or in combination as a spice or remedy (Figure 1). This plant is endemic to India and cultivated in South and South-East Asia, Africa, Latin America and Australia. It has been widely used in Ayurvedic and traditional medicines since ancient times. It is an effective tonic for the memory and digestive system. It is used for treatment of various ailments

including arthritis, rheumatism, sprains, muscular aches, pains, sore throats, cramps, constipation, indigestion, vomiting, hypertension, dementia, fever, infectious diseases and helminthiasis^[1, 2] (Figure 2). The most well known application of ginger is to promote blood circulation for the removal of blood stasis, a mechanism that is related to anti-platelet aggregation activity^[3].



Figure 1: Types of ginger (a) fresh (b) dry

Ginger has recently been studied scientifically for its effect on nausea and vomiting associated with motion sickness, surgery, pregnancy and cancer chemotherapy. There may be several mechanisms of action in play related to the antiemetic properties of ginger. It has been reported that antiemetic qualities may be derived from ginger's anti-serotonin effects on the gastrointestinal and central nervous system^[4]. Anti-serotonin activity prevents serotonin from binding to 5-hydroxytryptamine (5-HT₃) serotonin

receptors at the ends of the vagus nerve's afferent branches, which send signals directly to vomiting center in the medulla oblongata. Preventing activation of ginger to anti-serotonin, disrupts one of the pathways leading to vomiting. In a study of guinea pig ileum, it was found that certain ingredients of ginger inhibit the anti-serotonin receptor function^[5]. In addition, these active ingredients have been shown to affect gastric motility and potentially have an antispasmodic effect on the gastrointestinal system^[6].

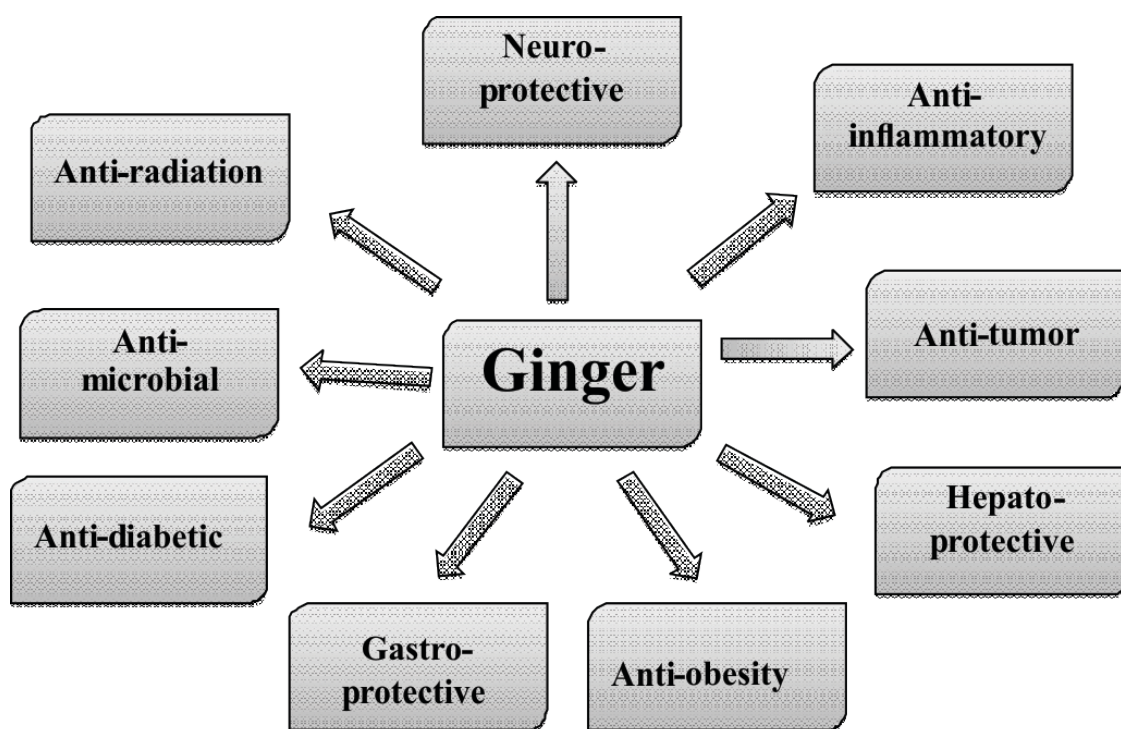


Figure 2: Pharmacological properties of ginger

Numerous chemical investigations of the pungent and bioactive principles of ginger have been carried out^[7, 8]. The bioactive compounds reported from rhizomes are gingerols, shogaols, zingerone, paradol, gingerenone, galanal, gingerdiols, gingerdiones (Figure 3). The main pungent compounds in fresh ginger are gingerols, whereas the pungency of dry ginger is mainly due to shogaols. Most abundant gingerol found in ginger is [6]-gingerol^[9]. Other gingerols with different chain lengths are also present in comparatively small quantities^[1]. Jolad et al.^[10] reported that they have identified 51 compounds through GC-MS analysis and the major identified

compounds were gingerols, zingernone, shogaols, paradols, dihydroparadols, dihydroshogaols, acetyl derivatives of gingerols, zingiberene and methyl ether derivatives of some of these compounds. These compounds were also identified by using HPLC-MS analysis^[11, 12]. Figure 3 shows chemical structures of the major active compounds and their analogs present in ginger. Masuda et al.^[13] suggested that the substituents on the alkyl chain of gingerol and related compounds might contribute to antioxidant properties. Over 50 components in ginger have been characterized and these are mainly monoterpenoids and sesquiterpenoids.

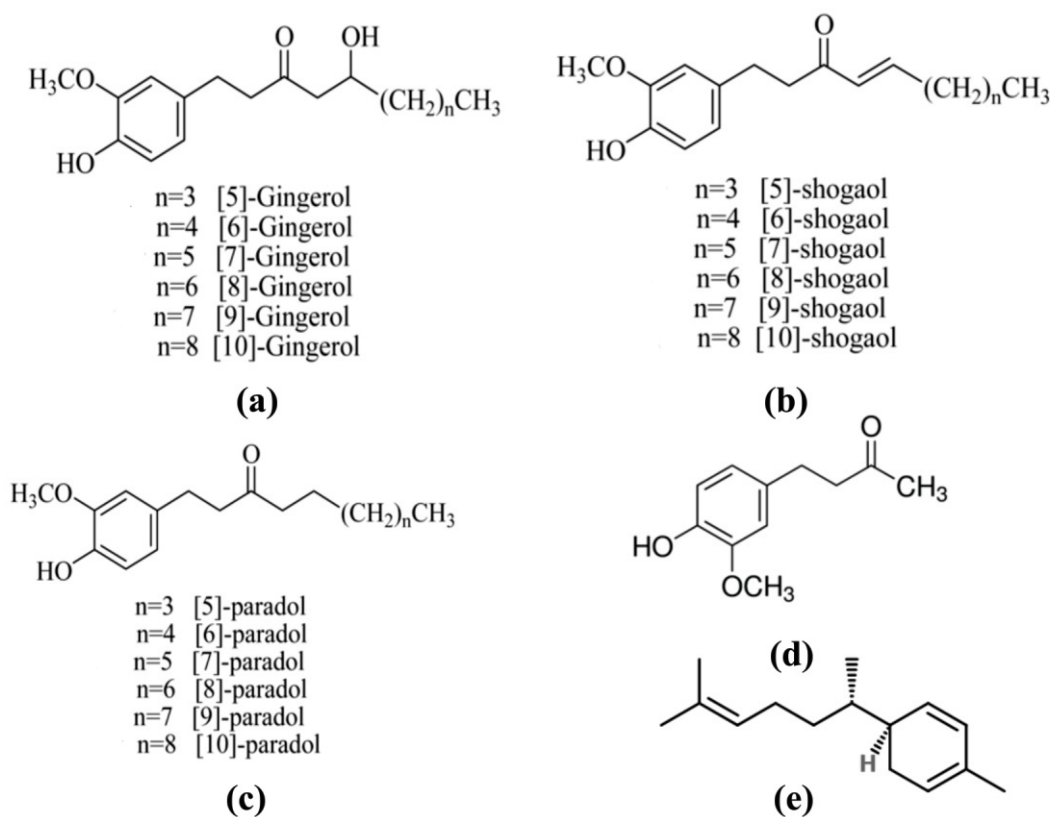


Figure 3: Major active ingredients of ginger and their analogs; (a) Gingerols (b) Shogaols (c) Paradols (d) Zingerone (e) Zingiberene

The extract of fresh ginger has a better flavor and is more pungent due to presence of these active ingredients^[14]. In many studies researchers have found that shogaol exhibits most potent antioxidant properties among the three gingerols^[15]. Gingerol is extracted from lipophilic rhizome of

ginger which can be converted to shogaol and zingerone sequentially by thermal degradation when fresh ginger is heated^[17, 18, 19, 20]. Figure 4 shows chemical reactions involve in the conversion of gingerols into shogaols and zingerone.

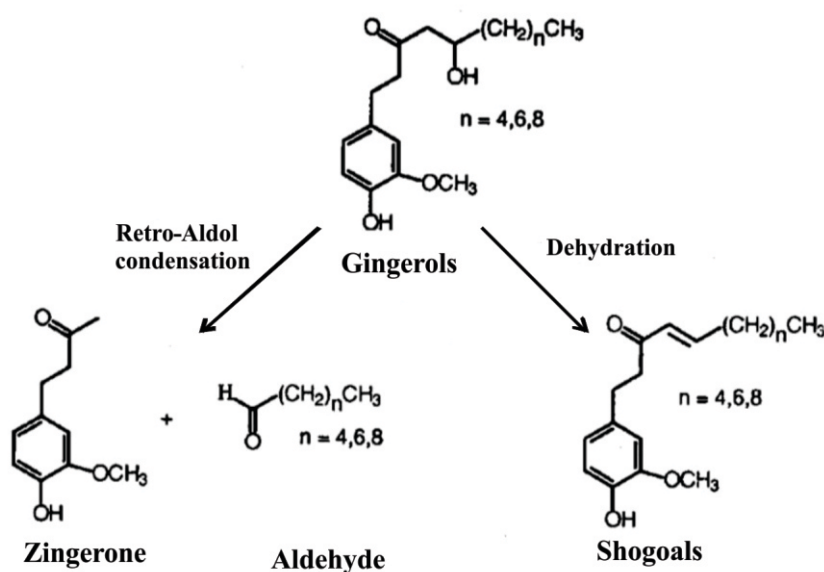


Figure 4: Conversion of gingerol in to zingerone and shogoal

PHYTOCHEMISTRY AND PHARMACOLOGICAL ACTIVITIES OF ACTIVE INGREDIENTS

Gingerol

Gingerols, so called “pungent principles” are the active constituent of fresh ginger and responsible for taste of ginger. It is normally found as pungent yellow oil, but also can form a low melting crystalline solid. Ginger contains 1.0-3.0% volatile oils and a number of pungent compounds^[21]. Several gingerols of various chain lengths (n3 to n12) are present in ginger in which most abundant being [6]-gingerol (Figure 3).

Pharmacological activities of Gingerols

[6]-gingerol administered by intraperitoneal injection has been used to induce a hypothermic state in rats^[22]. It enhances glucose uptake in L6 myotubes by activation of AMP-activated protein kinase (AMPK) in response to Ca^{2+} ions^[23]. [6]-gingerol seems to be effective in an animal model of rheumatoid arthritis^[24]. [6]- and [10]-gingerol are effective in the suppression of transformation, hyperproliferation and inflammation of the cells that initiate and promote carcinogenesis, angiogenesis and metastasis^[25]. Gingerols have been investigated *in vitro* for its antitumor effect on bowels^[26], breast tissues^[27], ovaries^[28] and pancreas^[29] with significant positive results. Gingerol and its analogs have a favorable toxicity towards a range of cancer cell lines

including ovarian^[28], colorectal^[30], colon^[31], breast^[32], blood and lung cancer^[33]. Gingerol and its analogs showed significant inhibition of platelet aggregation and lipid peroxidation induced by prostaglandin synthetase enzyme^[34,35].

Leukotriene B4 (LTB4) is a potent chemoattractant that is synthesized by enzyme leukotriene A4 hydrolase (LTA4H) in oxidative metabolism of arachidonic acid to induce a forceful inflammatory response^[36] (Figure 5). LTB4 has been implicated to play a prominent inductive role in carcinogenesis, where LTA4H acts as an attractive target for chemoprevention and cancer therapy^[37]. Suppression of LTA4H provided new direct evidence showing that LTA4H is implicated in the independent growth of cancer cells. Besides catalyzing the production of LTB4, LTA4H also possesses aminopeptidase activity^[38], which exhibits high levels of protein expression in certain types of cancer cells^[39]. [6]-gingerol directly binds with LTA4H and inhibits LTA4H enzymatic activity in HCT116 and HT29 cancer cells. The aminopeptidase activity of LTA4H was also potently suppressed by [10]-gingerol. These results indicate that LTA4H might be a highly desirable target for the prevention of proliferation of cancer cells.

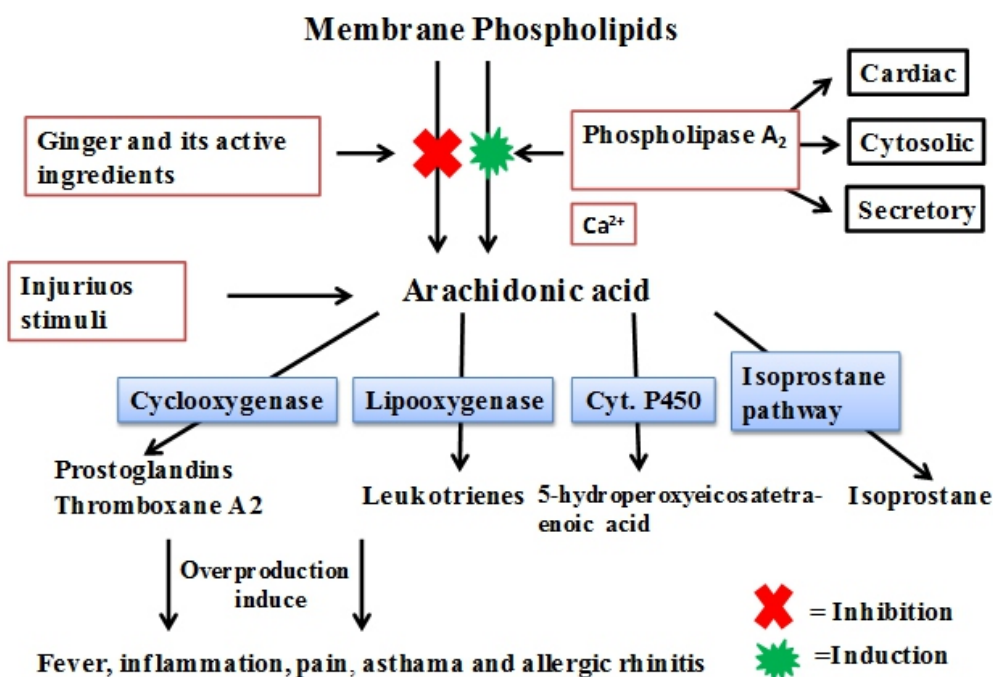


Figure 5: Arachidonic acid induces production of various inflammatory mediators in response to injurious stimuli.

Further research is defensible to test [6]-gingerol in animal studies as a potential anticancer plant bioactive in treatment of cancer. According to Lee and Surh^[40] [6]-gingerol induced apoptosis in human promyelocytic leukaemia (HL-60) cells by caspase mediated pathway and melanogenesis in skin cells by cAMP signaling (Figure 6). *In vitro*, [6]-gingerol inhibited both the vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), angiogenesis promoters that induced proliferation of human endothelial cells and caused cell-cycle arrest in the G1 phase^[41]. [6]-gingerol activated fas-associated protein with death domain (FADD), an adaptor protein that bridges members of the tumor necrosis factor

receptor superfamily, such as the fas-receptor, to procaspases 8 and 9 to form the death inducing signaling complex during apoptosis (Figure 6). Melanin is photo-protective which may contribute to UV-induced skin damage by generating free radicals upon UV radiation. Binding of α -melanocyte stimulating hormone (α MSH) to melanocortin-1 receptor (MC1R) induces the expression of tyrosinase gene for melanin synthesis. [6]-gingerol induced the binding of α MSH to MC1R receptor and promotes the synthesis of melanin to protect from skin cancer^[41] (Figure 6).

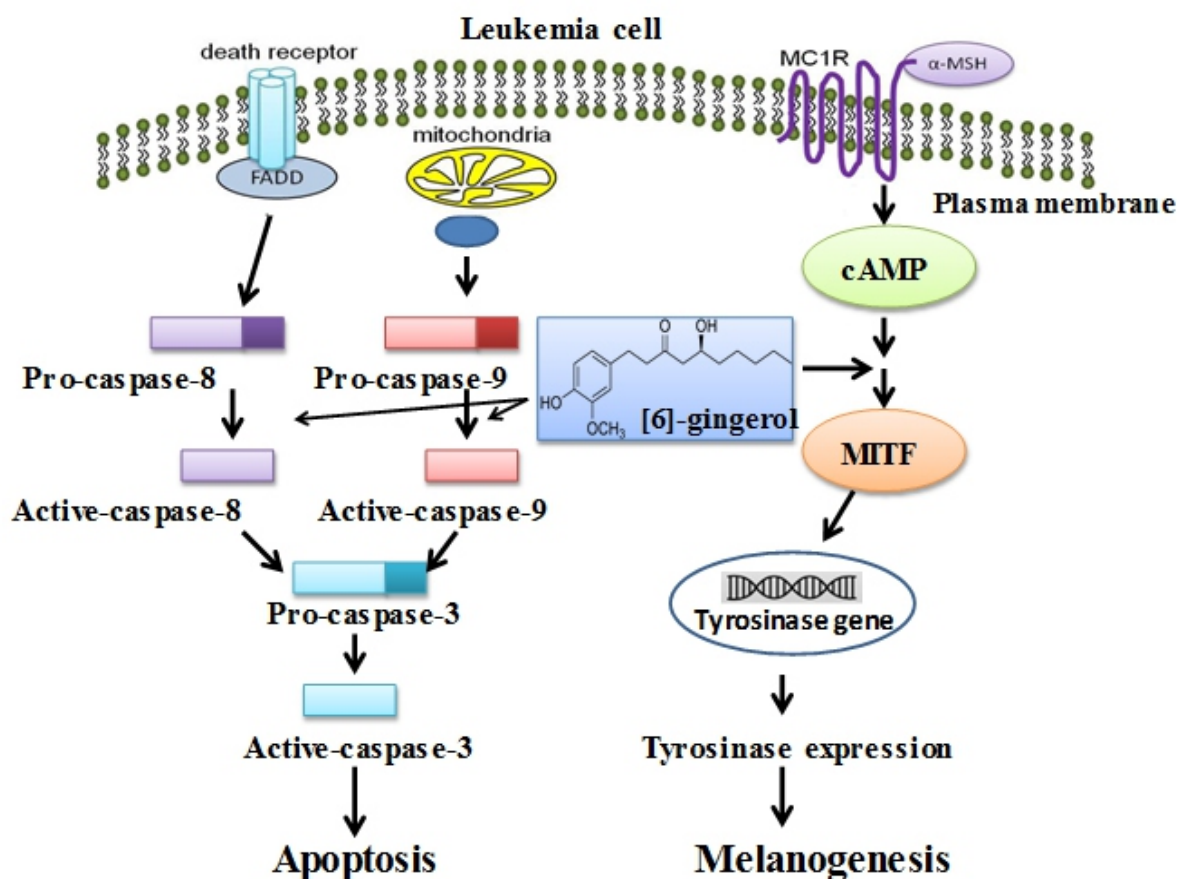


Figure 6: Apoptotic and melanogenesis pathway of [6]-gingerol.

FADD: fas-associated protein with Death Domain; MITF: microphthalmia associated transcription factor; MC1R: melanocortin-1 receptor; α MSH: α -melanocyte stimulating hormone.

Cyclin D1 is a protein required for progression through the G1 phase of the cell cycle. During the G1 phase, it is synthesized rapidly and accumulates in the nucleus and is degraded as the cell enters the S phase. Cyclin D1 is a regulatory subunit of

cyclin-dependent kinases CDK4 and CDK6. The protein dimerizes with CDK4/6 to regulate the G1/S phase transition and entry into the S-phase. Cyclin D1 has been found to be overexpressed in breast carcinoma. Cyclin D1 overexpression has

been shown to correlate with early cancer onset and tumor progression^[42] and it can lead to oncogenesis by increasing independent growth and angiogenesis via VEGF production. Cyclin D1 overexpression can also down-regulate fas expression, leading to increased chemotherapeutic resistance and protection from apoptosis. NSAID activated gene-1 (NAG-1), is a cytokine associated

with pro-apoptotic and anti-tumorigenic properties^[42]. According to Seong et al.^[43] [6]-gingerol influences cyclin D1 and NAG-1 expression and inhibits the growth of human colorectal cancer cells *in vitro*. The study suggests that [6]-gingerol stimulates apoptosis through up regulation of NAG-1 and G1/S cell cycle arrest through down regulation of cyclins CDKs (Figure 7).

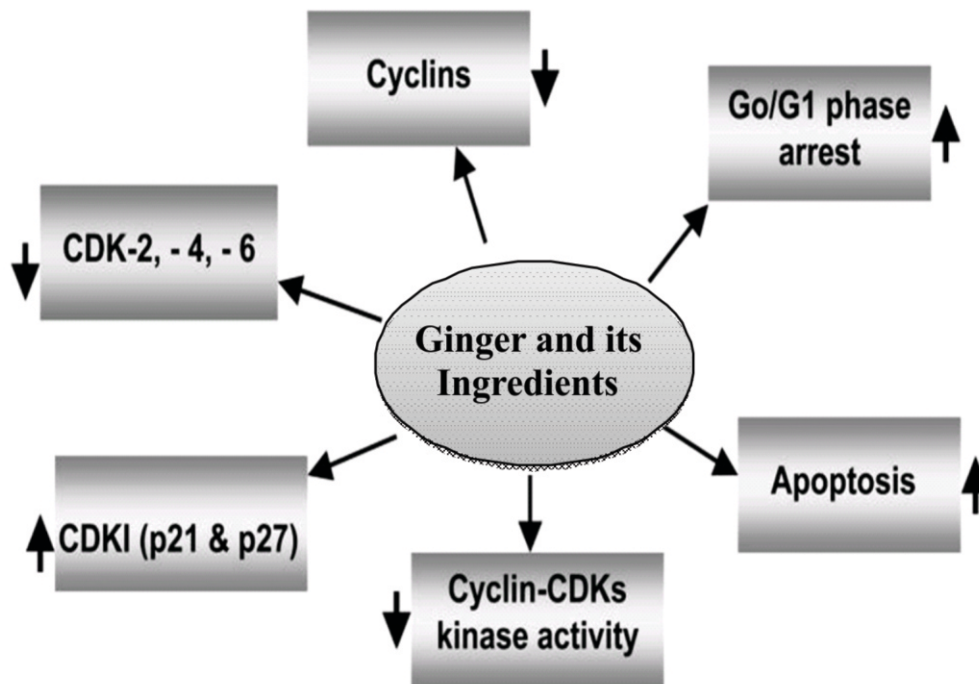


Figure 7: Molecular targets of cell cycle regulation in cancer cells by ginger and its active ingredients under *in vitro* and *in vivo* conditions (↑) indicates enhancement and (↓) indicate a reduction in the levels or inhibition of the activity of the target molecules.

In case of [10]-gingerol, its effect on HL-60 cells is better than [6]-gingerol^[44]. The modifying potential of [10]-gingerol on the process of colon carcinogenesis induced by 1, 2-dimethylhydrazine (DMH) was investigated in male Wistar rats by Dias et al.^[45]. The effect of [10]-gingerol on initiation and post-initiation stages of DMH-induced colon carcinogenesis in male Wistar rats was also studied by Manju and Nalini^[46]. These studies showed a lower incidence of cancer in [10]-gingerol treated cells in comparison to DMH induced colon cancer cells.

ER is a major Ca^{2+} store house in majority of cells^[47]. Various proteins and lipids are synthesized and modified in the ER^[48]. Disturbance of ER Ca^{2+} homeostasis creates protein misfolding or

oxidative stress which may lead to cell death^[49]. The acute incubation of [10]-gingerol maintained Ca^{2+} homeostasis and inhibited the cytotoxicity of cancer cells^[50, 51] (Figure 8). A rise in Ca^{2+} induced by reactive oxygen species (ROS) may activate Ca^{2+} -dependent enzymes such as proteases, nucleases and phospholipases to facilitate mitochondrial oxidative stress^[52]. [10]-gingerol may affect cell physiology significantly by changing Ca^{2+} signaling and stimulating Ca^{2+} coupled bioactive molecules. [10]-gingerol can induce the activity of ER Ca^{2+} -ATPase which is cytotoxic to the colorectal cancer cell^[53]. [10]-gingerol is cytotoxic to other several types of human cancer cell lines, for example A549, SK-OV-3, SK-MEL-2, and HCT15^[54].

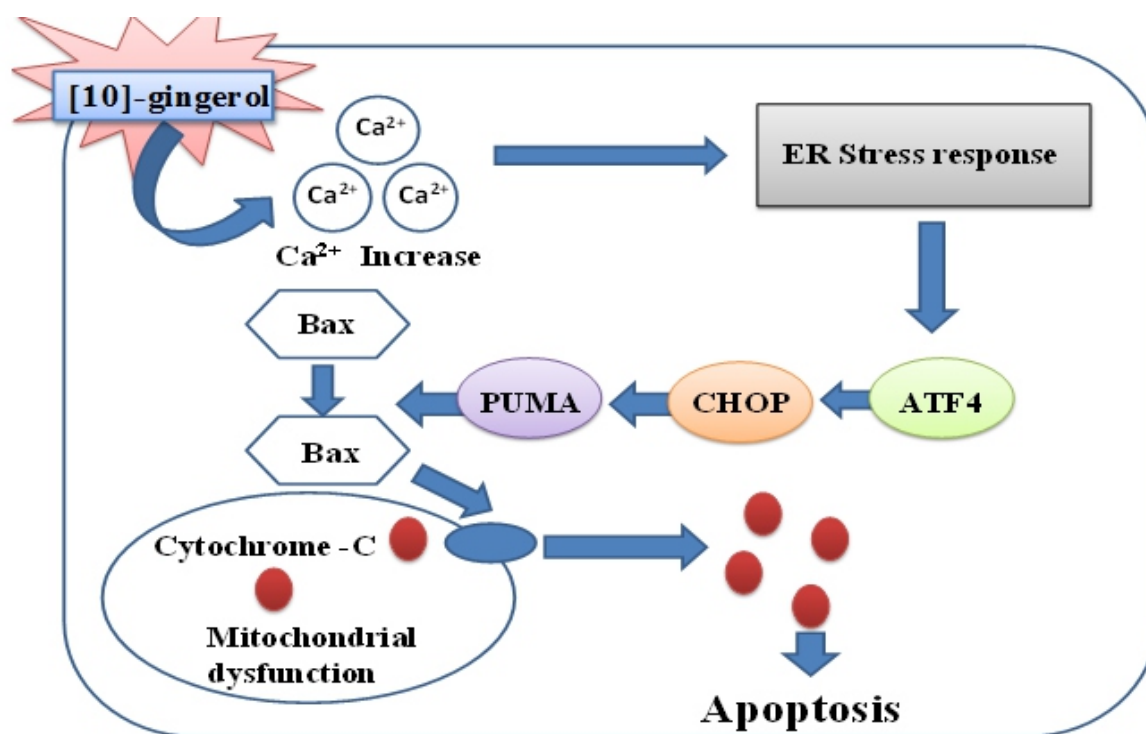


Figure 8: Cytochrome-c mediated mitochondrial apoptotic pathway of [10]-gingerol.

PUMA: p53 upregulated modulator of apoptosis; CHOP: C/EBP homologous protein (transcription factor); ATF4: activating transcription factor 4; Bax: bcl2 associated x protein.

Zingerone

Zingerone is nontoxic and pungent component of ginger with various pharmacological activities. Zingerone is absent in fresh ginger but cooking or heating transforms gingerol to zingerone^[55]. Zingerone is present in a significant amount of about 9.25% in dry ginger. Use of high profile liquid chromatography has shown that the contents of zingerone is usually low in fresh ginger while on drying and roasting the amount of zingerone increases significantly^[55]. Chemically, zingerone is vanillyl acetone which is a member of phenolic alkanone group^[56] (Figure 3). Various pharmacological properties of zingerone have been reported such as antioxidant, antimicrobial, anti-inflammatory and anticancer^[57,58,59,60]

Pharmacological activities of Zingerone

Zingerone has the ability to degrade free radicals generated by radiolysis of various food products^[61]. Zingerone inhibits an enzyme, xanthine oxidase, which is mainly involved in the generation of superoxide radicals. The observation that zingerone minimizes oxidation of lipids undoubtedly signifies its role as a good antioxidant.

It was supported by the fact that zingerone suppresses ferric ascorbate induced lipid peroxidation in rat brain^[61]. Zingerone has been reported to protect *in vitro* DNA damage against stannous chloride induced ROS oxidative damage^[57]. Zingerone provides direct adaptogenic effect by preventing oxidative stress on smooth muscles of intestine^[62]. Further, zingerone administration was found to reduce the mitochondrial injury and induce the expression of some pro-apoptotic proteins like bax (bcl 2-associated x protein), apaf-1 (apoptotic protease activating factor 1) and caspases 3-9 (cysteine dependent aspartate proteases)^[63]. Induced expression of bax proteins induces apoptosis, while bcl-2 protein (B-cell lymphoma-2) protects cells from apoptosis^[64, 65]. Recent studies have shown that zingerone by virtue of its antioxidant activity protects the heart of rats against the isoproterenol (slow heart rate mediator) induced myocardial infarction^[66,67].

According to Vinothkumar et al.^[59] zingerone contains anticancer potential. It has been proved that supplementation with zingerone in DMH treated rats led to a significant decrease in tumor incidence with simultaneous modulation in

the levels of tissue lipid peroxidation. Oxidation is also the main cause for the pathogenesis of various inflammatory conditions including neuronal cell injury, hemorrhage and septic shock^[68]. Zingerone treatment has potential of being used as a potent drug for treatment of inflammatory diseases like Alzheimer's and atherosclerosis^[63]. One of the important neuronal diseases called Parkinson's disease can be prevented by use of this potent byproduct of ginger, due to its leading antioxidant properties^[69]. This was elucidated when zingerone was shown to reduce the formation of striatal dopamine (neuro inhibitor) and its various metabolites^[70]. More studies were done to observe the antioxidant properties of zingerone by studying its effect on peroxisome proliferator activated receptors (PPAR) and nuclear factor-kB (NF-kB). Zingerone was found to suppress activity of both inflammatory inducer PPAR and NF-kB in Wistar rats by interleukin signaling pathway^[71, 72]. Zingerone also acts as a hepatoprotective agent as a result of its ability to scavenge free radicals in mice. A recent study revealed hepatoprotective activity of zingerone against CCl₄ induced hepatic injury in mice^[73].

Acute diarrhea is a leading cause for mortality in both young and adult individuals mostly due to high loss of fluids from a diarrhoeic patient. Zingerone is likely the active compound responsible for the antidiarrhoeal activity of ginger^[74, 75]. Zingerone also exerts an inhibitory effect on colonic motility by directly acting on smooth muscles of colon^[76].

Zingerone is known to have antagonistic function against the serotonin receptors of central and peripheral nervous systems similar to gingerols. It acts as a noncompetitive antagonist to 5-HT₃ receptors in visceral afferent neurons^[77]. As such it can be used to treat cytotoxic chemotherapy induced nausea and vomiting^[78].

Overweight is the fifth leading cause for deaths^[79]. Reported studies have revealed that the zingerone has potent lipolytic activity. Zingerone has been reported to be effective in enhancing basal lipolysis and isoprenaline induced lipolysis in adipocytes^[80]. The mechanism responsible for its lipolytic action is mediated by increasing the activity of norepinephrine sensitive lipases^[81].

Shogaol

Shogaol is dehydrated products of gingerol (Figure 3). It has been reported that shogaols are minor components in fresh ginger and the ratio of

[6]-shogaol to [6]-gingerol is approximately 1:1 in dried ginger^[82, 83]. Interestingly, some studies have demonstrated that [6]-shogaol might be more biologically active ingredient than [6]-gingerol^[84, 85]. Bhattarai et al.^[86] reported that [6]-gingerol can be degraded to [6]-shogaol at high temperature and acidic condition.

Pharmacological activities of shogaols

Shogaols have gained interest because of recent discoveries revealing their higher anticancer potencies over gingerols. It is reported that [6]-, [8]- and [10]-gingerols had little to no effect but [6]-shogaol significantly inhibited the growth of A-2780 ovarian cancer cells^[28]. Kim et al.^[87] reported that [6]-shogaol exhibited much stronger growth inhibitory effects on A-549 human lung cancer cells, SK-OV-3 human ovarian cancer cells, SKMEL-2 human skin cancer cells and HCT-15 human colon cancer cells than [6]-, [8]- and [10]-gingerols. [6]-, [8]- and [10]-shogaols exhibited much higher antiproliferative potential in comparison to [6]-, [8]- and [10]-gingerols against H-1299 human lung cancer cells with IC₅₀ values of 8 μM for [6]-shogaol and 150 μM for [6]-gingerol^[82]. [6]-shogaol was also more effective than [6]-gingerol in inhibiting 12-O-tetradecanoylphorbol-13-acetate (TPA) induced tumor promotion in mice^[83, 94].

[6]-shogaol has been shown to induce mitotic arrest and reduce viability of gastric cancer cells^[88]. Aberrant mitosis followed by apoptosis has also been found to be induced by [6]-shogaol in HCT-116 colon cancer cells^[89]. [6]-shogaol induces apoptosis via oxidative stress pathway in a caspase dependent mechanism^[75, 90] (Figure 9) similar to [6]-gingerol and zingerone.

Multiple targets and pathways are associated with [6]-shogaol mediated cancer cell death, for example extracellular signal regulate N-terminal Kinase, p38 MAPK, phosphatidyl inositol 3-kinase/Akt and cell cycle checkpoint proteins cdk1, cyclin B and cdc25C^[91, 88] (Figure 8). It has also been reported to induce autophagy in HNSCLC A-549 breast cancer cells via inhibition of the AKT/mTOR signaling (an intracellular signaling pathway important in regulating the cell cycle) pathway^[91, 92]. Microtubule is a possible target of [6]-shogaol as it interacts with the sulphhydryl groups of cysteine in tubulin through its side chain containing α, β unsaturated carbonyl moiety^[93] and inhibits the cell proliferation.

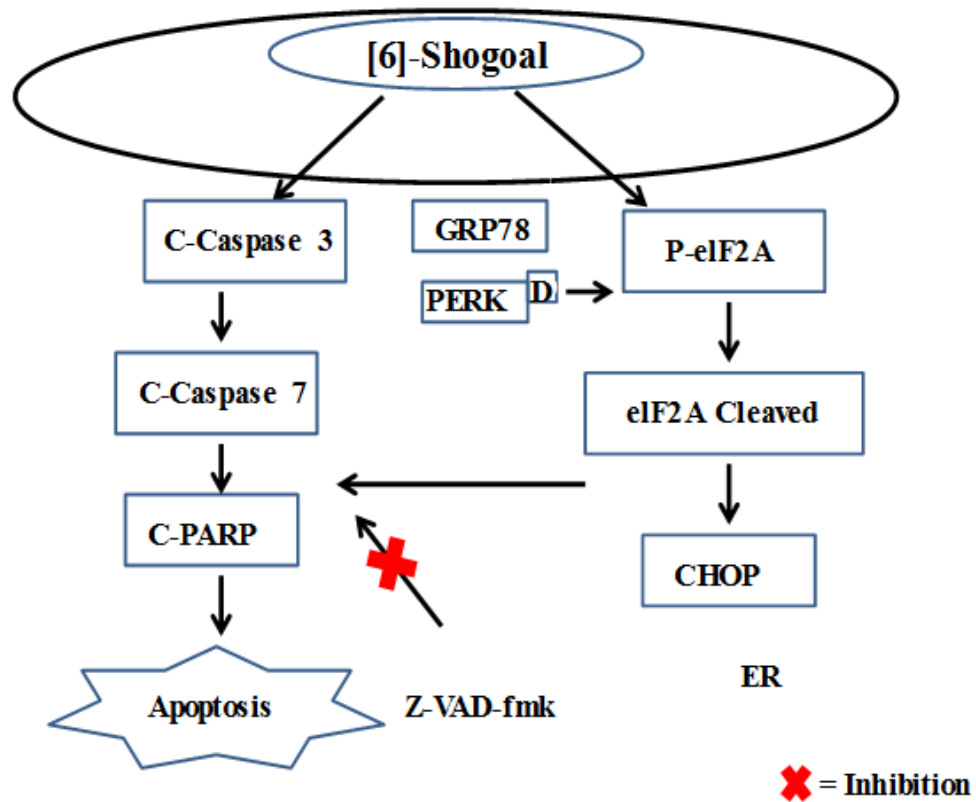


Figure 9: [6]-shogaol induces apoptosis in human leukemia cell through caspase mediated cleavage of elongation factor eIF2a.

PARP: poly ADP ribose polymerase; CHOP: C/EBP homologous protein; Z-VAD-FMK: carbobenzoxy-valyl-alanyl-aspartyl-[O-methyl]-fluoromethylketone; PERK: Protein kinase (PKR)-like ER Kinase; GRP78: Glucose regulated protein 78; ER: Endoplasmic reticulum.

Saha et al.^[94] reported that [6]-shogaol produces significant anticancer activity against human and mouse prostate cancer cells by inhibiting cell survival and inducing apoptosis through reduction of signal transducer and activator of transcription 3 (STAT3) and NF- κ B activity. Collectively, the current results suggest that [6]-shogaol may have a role to play as a chemopreventive and/or therapeutic agent for prostate cancer. All reported anticancer studies place [6]-shogaol as a promising agent to be studied further in view of its future therapeutic potential in cancer therapy.

[6]-shogaol has shown significant anti-inflammatory properties in a Complete Freund's adjuvant (an effective stimulator of cell-mediated immunity that activates T helper cells for production of certain immunoglobulins) model of mono-arthritic rats^[95]. Reduction of macrophage infiltration in the knee joint was a significant finding in that study: macrophages are therefore considered to be targets for the anti-inflammatory

effects of [6]-shogaol. Sabina et al.^[96] suggested that [6]-shogaol can be regarded as a useful tool for the treatment of acute gouty arthritis.

Frequent use of NSAIDs like aspirin, indomethacin and reserpine may cause gastric ulcer and hypothermic restraint stress. Yamhara et al.^[97] has proven that [6]-shogaol is a cytoprotective and anti-ulcerogenic agent. Production of nitric oxide (NO) molecules is an important cytotoxic function that macrophages use to resolve infection by several intracellular protozoal and bacterial parasites. The inducible form of the NO synthase enzyme (iNOS) produces large amounts of reactive nitrogen molecules by oxidizing the terminal guanidino nitrogen of L-arginine. Since reactive nitrogen molecules can damage host tissues as well as the invading microbes, the activation of NO production by macrophages is a tightly regulated process. [6]-shogaol was shown to be potent inhibitors of nitric oxide (NO) synthase in activated macrophages and reduced formation of ulcer^[98].

[10]-shogaol, the only non-pungent compound among the shogaols, has the ability to induce G2/M arrest and abnormal mitotic cell death that is associated with tubulin aggregation^[99].

Paradol

[6]-paradol, a pungent anti-inflammatory vanilloid is derived from rhizome of ginger and also from the seeds of *Aframomum melegueta*. This compound can be obtained from gingerol by successive dehydration and hydrogenation^[100]. Paradol has been shown to exhibit many pharmacological effects and contains different analogs similar to gingerol and shogaol^[101] (Figure 3). Paradol has been identified as the active ingredients of ginger and is responsible for the antioxidant activity and its characteristic pungent taste^[102,103].

Pharmacological activities of paradol

[6]-paradol showed anti-carcinogenic, anti-edematous and DNA protective activities in mouse induced by TPA^[103] inhibitor and also has ability to induce apoptosis in cultured HL-60 cells^[52] similar to [6]-gingerol and [6]-shogaol. Bode and co-workers^[104] reported that [6]-paradol exerts its primary inhibitory effect on cell proliferation through the induction of apoptosis^[105] (Figure 10). [6]-paradol and other structurally related derivatives induced apoptosis in oral squamous carcinoma cell line in a dose dependent manner through a caspase-3-dependent mechanism^[106]. Antitumor promotion effects of [6]-paradol and [6]-dehydroparadol were as efficient as that of

curcumin, one of the well-investigated chemopreventive agents^[107]. Some studies proved the *in vitro* antitumor effects of [6]-paradol and its homologues^[26,90] (Figure 10).

[8]-paradol and their synthetic analogues showed chemopreventive and anti-inflammatory activity by inhibiting COX-2 (Cyclooxygenase-2) enzyme activity in a dose dependent manner^[108]. It has been reported that some of the paradol derivatives have a wide spectrum of antimicrobial^[109] and anti-tumor activities^[103].

Paradol and its derivatives are effective in controlling the extent of colorectal, gastric, ovarian, liver, skin, breast and prostate cancers^[26,51]. According to Keum et al.^[103], the *in vitro* anti-tumor effects of ginger are mainly because of [6]-gingerol, [6]-shogaol, [6]-paradol and its analogs. [6]-paradol has been reported to possess a strong anti-inflammatory activity to suppress the TNF- α (Tumor necrosis factor- α) production in TPA treated female mice and rats^[110]. The activation of the TNF- α gene causes the release of pro-inflammatory cytokines, and this would activate the transcriptional factor NF- κ B. Activation of NF- κ B would activate the expression of other inflammatory cytokine inducing enzymes such as COX-2, lipooxygenase-2 (LOX-2) and iNOS, which would lead to inflammation and age related diseases. [6]-paradol has a strong analgesic and anti-platelet aggregation potential than aspirin due to strong inhibiting activity of COX-1 and COX-2 enzymes^[111] (Figure 10).

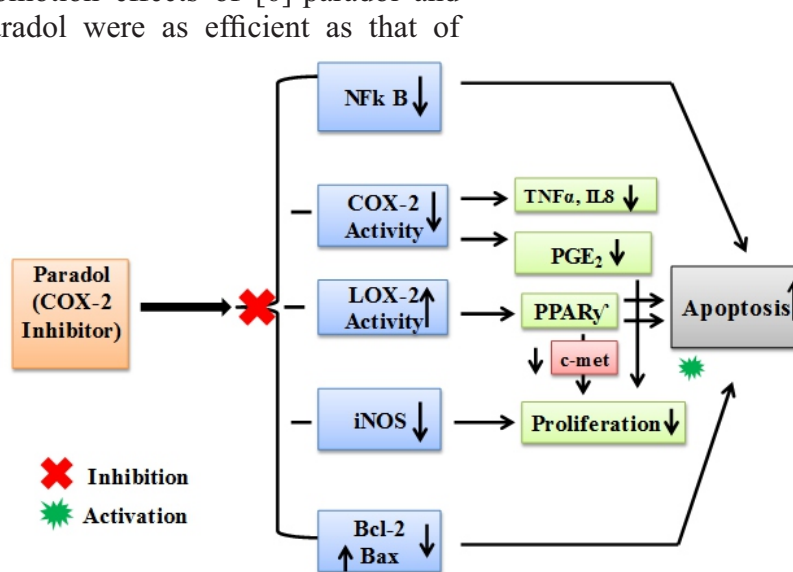


Figure 10: Molecular mechanism of anti-inflammatory activity of paradol, COX: cyclooxygenase; LOX: lipooxygenase; iNOS: inducible nitric oxide synthase; PGE2: Prostaglandin E2; PPAR γ : peroxisome proliferator-activated receptors γ ; c-met: protein with tyrosine kinase activity.

Zingiberene

Zingiberene is a volatile compound extracted from rhizome of ginger^[112, 113]. Zingiberene is a monocyclic sesquiterpene that is the predominant constituent of the ginger oil^[114] (Figure 3). It contributes up to 35% of the essential oils in ginger rhizomes^[115]. Zingiberene is a compound that gives ginger its distinct flavoring and causes the fragrance of the spice. Zingiberene is formed in the isoprenoid pathway by catalytic activity of enzyme zingiberene synthase^[116].

Pharmacological activities of Zingiberene

Zingiberene possesses antioxidant activity as well as significant anti-inflammatory and antinociceptive property. Zingiberene scavenged superoxide, DPPH radical, hydroxyl radicals and inhibited tissue lipid peroxidation *in vitro*^[117]. Intraperitoneal administration of zingiberene was found to inhibit TPA induced superoxide radicals elicited by macrophages. Oral administration of zingiberene for one month significantly increased superoxide dismutase, glutathione-S-transferase and glutathione reductase enzyme levels in blood and liver of mice. Zingiberene produced significant reduction in carrageenan and dextran induced acute inflammation and formalin induced chronic inflammation^[117]. Immunomodulatory properties of zingiberene have been demonstrated by Nogueira de Melo^[118]. The experiment carried out

by Sharma et al.^[119] on arthritic rats has suggested that zingiberene contains significant anti-rheumatic property.

Chronic pain is a symptom of many long term medical conditions, including cancer, arthritis and nerve damage after traumatic injury, and neuropathy associated with chronic conditions such as diabetes. Zingiberene was clinically effective hypo- analgesic agents (pain killer) against knee osteoarthritis pain than NSAIDs. Mechanisms of action include modulation of leukotriene and prostaglandin synthesis and inhibition of NF- κ B^[172].

Zingiberene inhibits the viability of breast cancer cells through caspase mediated pathway, as well as down regulates Hsp90 and its related proteins. Zingiberene also decreased protein levels of cell cycle check proteins such as cyclin D1, cdk-2, cdk-4 and bcl-2 level while it increased the level bax to regulate the apoptotic pathway (Figure 7). In addition, zingiberene inhibited *in vitro* angiogenesis and proliferation of cancer cells by inhibiting VEGF. It also significantly reduced the expression of various oncoproteins and repressed the activity of telomerase that are expressed in breast cancer cells^[120]. Hence, zingiberene is a component of essential oil of ginger with various anti-cancer properties and inhibits hallmark (telomerase) of breast cancer cells *in vivo*.

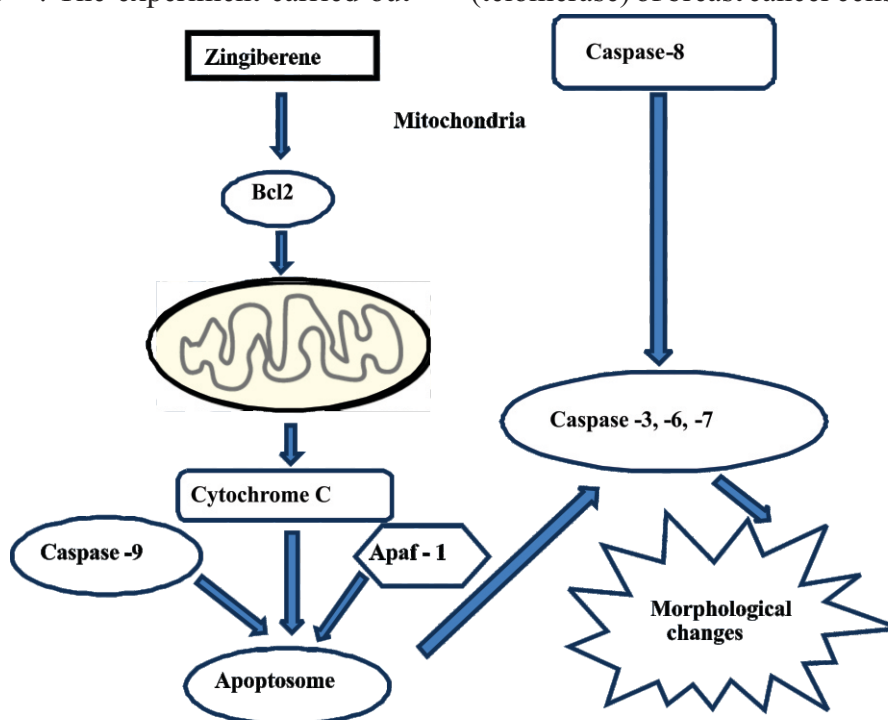


Figure 11: Caspase mediated mitochondrial apoptosis activity of Zingiberene. Apaf-1: Apoptotic protease activating factor 1.

It has shown significant hypoglycemic activity in Albino rats and reduced the sugar level in rats administered with zingiberene over period of twenty-one days. Till twenty-one days, treatment with zingiberene in rats significantly reduced the total serum cholesterol level (136.46 to 109.46 mg/dl) and significantly increased the serum high density lipoproteins-cholesterol (41.82 to 65.42 ± 1.54mg/dl) while low density lipoproteins-cholesterol and triglycerides level decreased^[121]. Suekawa et al.^[122] showed analgesic and antipyretic properties of zingiberene oil extracts in a range of laboratory animals at the dose of 200 mg/kg body weight.

Zingiberene could be employed as natural food preservatives, preventing lipid peroxidation (at concentration levels 20-100 µg/ml), which could cause food spoilage. It showed significant inhibitory activity against pathogenic bacteria and fungi, with MIC values ranging from 20 to 120 µg/ml^[123]. Zingiberene was found to possess antiviral property^[124]. It exhibited high levels of virucidal activity against acyclovir-sensitive strain KOS and acyclovir-resistant HSV-1 clinical isolates and reduced plaque formation significantly^[125]. The specific antimicrobial and anti-radiation properties of zingiberene make them highly appreciated raw materials to be used in the cosmetic industry^[126,127].

CONCLUSION

Current mode of treatment based on synthetic drugs shows various adverse side effects. A safe, effective and inexpensive product is needed to control the diseases progression via modulation of metabolic pathways. Ginger and its active ingredients reduce the chance of various diseases by suppression of NF-kB, COX-2, LOX (inflammation mediators) and induction of apoptosis and tumor suppressor genes. Ginger and their active ingredients create hopefulness towards the novel therapeutic strategies against various diseases. Future research should focus on clinical trials to investigate its effectiveness and their exact role in modulation of metabolic pathways. This review provides necessary information about the enormous pharmacological properties of ginger and its active ingredients to researchers to help them understand the mechanism of action of these compounds, which may be used to fill the much-needed gaps in advanced research that may be helpful to protect human beings from several diseases.

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