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REVIEW ARTICLE

Pharmacological activity and biochemical interaction of zingerone: a flavour additive in spice food

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Abstract

Zingerone (4-(4-Hydroxy-3-methoxyphenyl)-2-butanone) is one of the non-volatile and nontoxic compounds of ginger. It is also called vanillylacetone with a crystalline solid form which is sparingly soluble in water and more soluble in ether. The contribution of this compound in ginger is about 9.25%. The chemical structure is made of a phenolic ring with methoxy group attached to benzene ring. Gingerol can be heated to form zingerone by retroaldol reaction. It has been reported that zingerone has multiple pharmacological activities. It is effective against diarrhoea causing enterotoxigenic bacteria that leads to infant death. It is also used against intestinal gastric, oxidative stress, weak immunity, obesity. During its activity against cancer, it governs the expression of different cell cycle protein and TGF-β1 expression. Antioxidant response is controlled by inducing the activity of ROS neutralising enzymes like superoxide dismutase, catalase and glutathione reductase. It can also reduce various inflammations by restricting the activity of interleukins. This review summarizes the multiple pharmacology activities of zingerone against various important diseases like cancers, tumors, inflammations, oxidative conditions, microbial infections, biofilm formations, thrombosis and other diseases. In addition, the molecular regulation of these pharmacological responses by zingerone is also critically discussed.

Keywords

anticancer, anti-inflammation, antioxidant, ginger, zingerone

Introduction

Ginger (*Zingiber officinale* Roscoe) is well known for its medicinal properties and its use in spices. It contains various minerals and vitamins which are the basic need of human diet. Ginger is a traditional medicine, having immense active ingredients used for the treatment of numerous diseases (1, 2). Ginger has antidiabetic, anti-inflammatory, anticancer, analgesic, hepatoprotective efficacy (3). According to the literature, more than 60 active volatile and non-volatile compounds have already been reported in leaves and rhizome of ginger. The major volatile components found in rhizome essential oil of ginger are zingiberene, curcumene and farnesene b-sesquiphellandrene (4, 5). The non-volatile compounds present in the rhizome of *Z. officinale* are gingerols, shogaols, paradols and zingerone (4-6). The contribution of zingerone in ginger is about 9.25% (2). Zingerone is also found in the floral parts of *Bulbophyllum* sp. like *Bulbophyllum patens* and *B. baileyi* (7, 8). In *B. patens*, zingerone was found to be highest that is 930 ppm

in the labellum while other parts like sepals, petals and column were having 167 ppm, 95 ppm, 51 ppm respectively (7).

However, zingerone is an important medicinal active compound and is predominantly found in ginger. It bears a strong, spicy, pungent odour reminiscent of ginger (9). It also known as vanillylacetone and its IUPAC name is 4-(4-hydroxy-3-methoxyphenyl)-2-butanone ($C_{11}H_{14}O_3$) (10) (Fig. 1). It is a non-volatile constituent which is naturally

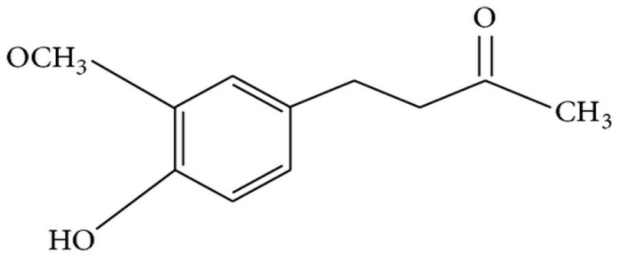

Fig. 1. Chemical structure of zingerone

produced directly during drying of ginger and also indirectly by thermal degradation of gingerols or shogaols (2). Gingerol is heated to produce zingerone and aldehyde in retro aldol reaction (Fig. 2). In addition, zingerone is an

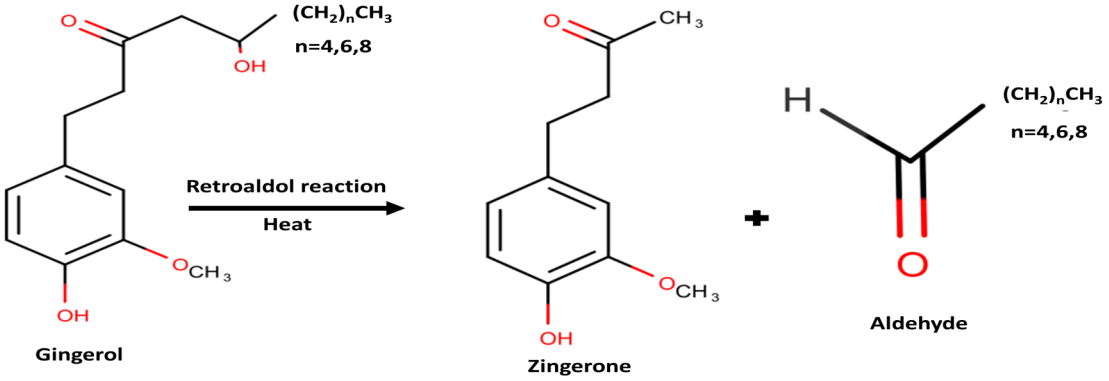

Fig. 2. Conversion of gingerol to zingerone.

important compound present in ginger oleoresin and it is very difficult to extract. However, few extraction methods are developed to extract this compound from ginger oleoresin. In a study, it was identified as major compound in ethanol extraction of ginger oleoresin by using ultrasound at a frequency of 42 kHz and at a temperature of 60 °C (11). In another study, the supercritical CO_2 extraction method was optimized to 25 MPa pressure, 45 °C temperature and 150 min time for extraction of zingerone in ginger oleoresin (12). This compound can also be synthesized artificially (13, 14). Initially, under basic conditions both vanillin and acetone are allowed for aldol condensation to form dehydrozingerone. Then the dehydrozingerone is hydrogenated to form zingerone (14). In addition, five quinoline derivatives of zingerone such as 4-((2,4-Dimethylquinolin-3-yl) methyl)-2-methoxyphenol, 2-Methoxy-4-((2-methyl-4-phenylquinolin-3-yl) methyl)phenol, 2-Methoxy-4-((2-methyl-6-nitro-4-phenylquinolin-3-yl) methyl)phenol, 4-((6-Chloro-2-methyl-4-phenylquinolin-3-yl) methyl)-2-methoxyphenol and 4-((6-Amino-2-methyl-4-phenylquinolin-3-yl) methyl)-2-methoxyphenol were synthesized (15).

In 2017, the total global burden of health was more than 2.4 billion (16). This includes more than 362 million of cardiovascular diseased patients, 230 million of cancer diseases, 133 million of diabetes and endocrine diseases, 84 million of digestive diseases and 40 million of liver diseases (16). However, these non-communicable diseases contribute more than 1.4 billion to the global health burden (16). Although several synthetic drugs are available against these diseases, herbal medicines are very effective without any side effect. Zingerone is a non-volatile constituent of ginger and is found to be a promising herbal medicine against multiple health disorders (17) (Fig. 3, Table 1). Zingerone treatment can reduce cancer, tumor, inflammation, cardiac diseases, thrombosis, obesity, diabetes and many other diseases (17-22). It also plays important role against platelet aggregation in blood (22). In cancer, use of this active compound can inhibit the expression of transforming growth factor-beta 1 (TGF-β1) to control the cancer metastasis. It also regulates the Bax, Bcl2 and cyclin d proteins to manage cancer diseases. During anti-inflammatory activities, nuclear factor-κB (NF-κB) expression regulated by zingerone and the activities of interleukins are also reduced. Apoptosis also gets inhibited by use of this compound which regulates the caspases enzyme activities. It has also high antioxidant properties and induce the activity of ROS scavenging enzymes to control ROS production during stress (21). It has been also reported that zingerone treatment can reduce colon cancer and hepatocellular cancer and also effective against tumors by inhibiting cell cycle proteins (23-25). Several important pharmacological activities like anticancer, antitumor, antioxidant, anti-inflammatory of zingerone are discussed in this review.

Biological importance

As zingerone is one the important compound of ginger, it retains various types of medicinal and pharmacological properties. Zingerone is also a nontoxic compound. It has no side effects and is obtained from natural sources.

Anticancer and Antitumor activities

Zingerone derived from ginger has anticancer properties against colon cancer, hepatocellular carcinoma and tumor

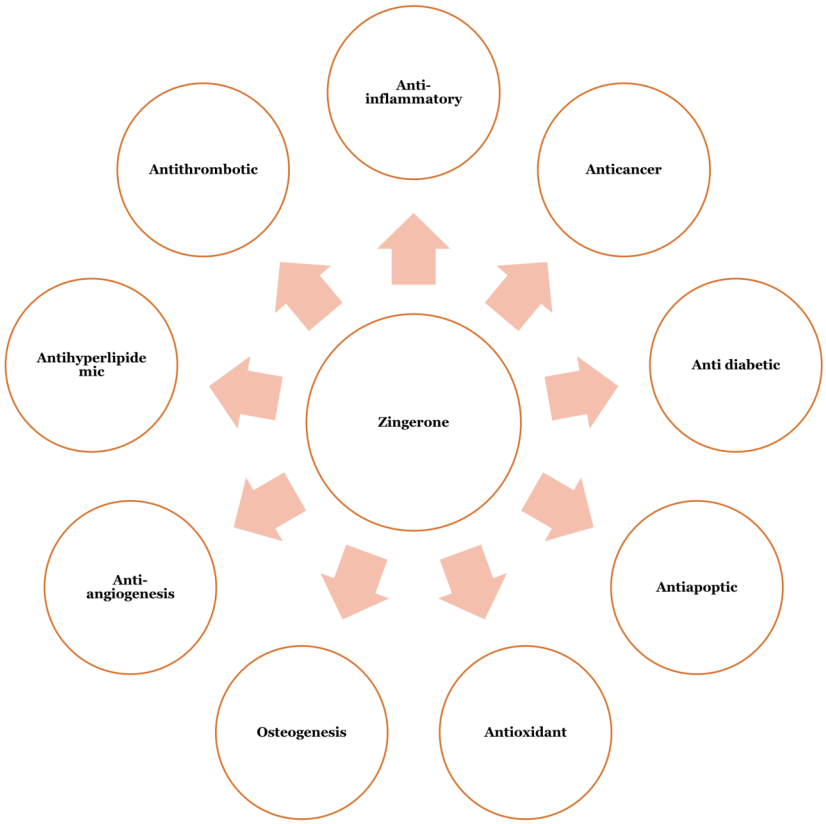

Fig. 3. Biological importance of zingerone

development (20, 23, 25). 2 mM of zingerone dissolved with dimethyl sulfoxide (DMSO) prevents the rapid divisions of cancer cells by inhibiting the expression of cyclin D1 (24). Cyclin D1 is a cell cycle check point protein, required at G1 phase of cell cycle. The G1 phase components undergo S phase, G2 phase and M phase to complete a cell division (Fig. 4). Cyclin-dependent kinase (CDK) inhibitor p21 inhibits the cell cycle protein complexes like cyclin-cdk2, cdk1, cdk4/6 and stops cell cycle at S and G1 phase during Ultraviolet B (UVB) induce cell damage. However, 40 mg/kg of this compound has the capacity to reduce the production of p21 and allow the cell to complete cell cycle during division (25). The derivative of this compounds is found effective against hepatocellular carcinoma (HCC) and its metastasis as well as found to act on TGF-β1, which regulates epithelial mesenchymal transition (EMT) for metastasis (Fig. 4) of HCC (18). Further, its nanoparticles (10 mg/kg) have efficiency to reduce cell proliferation in tumor cells and enhance the pharmacological properties of the compound (26). In cancer cells, the zingerone nanoparticles increase DNA damage, which subsequently leads cancer cells to apoptosis. It acts over hepatocellular cancer cells and lead them to apoptosis by cascades of caspase signalling pathways. Caspase 3 activity is induced by this compound and it cleaves poly (ADP-ribose) polymerase (PARP) which is mainly responsible for death of cancer cells (24, 26). The effect of zingerone (40 mg/kg) against chemical induced colon cancer is tested in rat model (25). The colon cancer is reduced by inhibiting the formation of aberrant crypt foci (ACF) in colon tissue (25). ACF are abnormal tubular glands reside in the colon and rectum, which further leads to colon cancer (27). Tumor development is controlled by angiogenesis and this compound is also found effective against tumor angiogenesis. Matrix metalloproteinases (MMPs) are required for degradation of basement membrane during angiogenesis. The tumor cells treated with zingerone further retire angiogenesis by decreasing the MMP-2 and MMP-9 activities (20).

Antioxidant activities

Zingerone has an efficient role against reactive oxygen species (ROS), peroxides and free radicals. The antioxidant activities generally inhibit xanthine oxidase activity as xanthine oxidase is recruited ROS production (17). The ROS includes singlet oxygen ($^1O_2$), hydroxyl radical ($^{\bullet}OH$), superoxide anion (O_2^{-}), hydroxyperoxyl ($HO_2^{\bullet}$), peroxyl ($ROO^{\bullet}$), alkoxyl ($RO^{\bullet}$), ozone (O_3), hypochlorous acid (HOCl), peroxynitrite ($ONOO^{-}$), hydrogen peroxide (H_2O_2) (28). It triggers the activity of ROS detoxifying enzymes like superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), glutathione reductase (GR) and glutathione peroxidase (GPx) (17-19). Structurally zingerone contains hydroxyl groups in the aromatic rings and double bonds between C_3 and C_4 carbon (29). This may support the antioxidant properties of zingerone. Alloxan is an organic compound induce diabetes by destroying insulin producing beta cells in pancreas and also produce ROS simultaneously. Zingerone is found effective to reduce the ROS level produced by alloxan by increasing the activities of SOD, CAT, GSH and GPx as compare to untreated diabetic rats (30). In exposure to radiations, various ROS products are also generated which can be controlled by zingerone (31). Zingerone is known to produce more numbers of scavenging enzymes when treated to radiation exposed cells. Apoptosis can be prevented by the application of zingerone. Two important proteins Bcl-2 and Bax crosstalk play important role in regulation of apoptosis. Bcl-2 is an anti apoptic protein and Bax is a pro apoptic protein. Bax protein gets activated in response to ROS production and leads to apoptosis. However, application of zingerone increases the efficiency of Bcl-2 which subsequently acts over Bax (Fig. 4) and inhibit apoptosis (29). An elevated amount of ROS is produced during ischemia–reperfusion injury in neuron mitochondrial cells. This leads to apoptosis of neuron cells by involving intrinsic pathway of programmed cell death (iPCD) (29, 32). The application of zingerone (50 mg and 100 mg/kg) also lower the expression of Apaf -1 and Bax proteins in the neural cell during ischemia–reperfusion injury (32). Nitrite and peroxynitrite anions are nitrogen reactive compounds formed during oxidative stress. These are the product of reaction between nitric oxide (NO) and oxygen. By the use of zingerone (25 µg/ml) it competes with oxygen and is attached to NO to prevent the formation of nitrogen reactive compounds (29). Cisplatin is a compound used in chemotherapy, produces various types side effects. Cisplatin treated organisms mainly suffer from nephrotoxicity

Table 1. Biological activities of Zingerone

Sl. No.	Biological activities	Sample/organism	Effective amount of Zingerone	References
1.	Anticancer, Antioxidant, Anti-hyperproliferative	Rat (Colon)	100 mg/kg	(23)
2.	Anticancer	Human (Neuroblastoma cells)	2 mM (Dissolved with dimethyl sulfoxide)	(24)
3.	Antitumor	Mouse (Renca cells)	10 mg/kg	(26)
4.	Antitumor	Human (Hepatoma cells)	50 uM (nano sized (1.4 nm)) (Dissolved with ethanol)	(26)
5.	Antitumor	Mouse (Renca cells)	20 mg/kg	(20)
6.	Anti-inflammation	Rat	200 mg/kg	(52)
7.	Anti-inflammation	Rat (Liver)	100 mg/kg	(53)
8.	Anti-inflammation, Anti-fibrotic	Rat (Liver)	20 mg/kg	(54)
9.	Anti-inflammation, Antioxidant, Anti-hyperlipidemic	Rat (Hepatic cells)	20 mg/kg	(19)
10.	Anti-inflammation	Rat (kidneys)	8 mg/kg	(44)
11.	Anti-inflammation	Mouse (Liver)	100 mg/kg	(43)
12.	Anti-inflammation	Mouse	0.72 mg/kg	(36)
13.	Anti-inflammation	Mouse (Colon)	100 mg/kg	(42)
14.	Anti-inflammation, Antioxidant, Antiapoptic	Rat	25 mg/kg	(55)
15.	Antioxidant, Antihyperlipidemic, Antithrombotic	Rat (Heart)	6 mg/kg	(48, 49)
16.	Antioxidant, Anticancer	Rat (Colon)	40 mg/kg	(25)
17.	Anti-Fxa and Anti platelet	Human (Umbilical vein endothelial cells)	50 uM (Dissolved with dimethyl sulfoxide)	(22)
18.	Antiapoptic	Rat (Heart)	6 mg/kg	(50)
19.	Antiangiogenic	Mouse (Renca cells)	20 mg/kg	(20)
20	Antiapoptic	Human (Lymphocytes)	10 ug/ml	(31)
21	Antioxidant	Human (Lymphocytes)	10 ug/ml (treatment for more than 1hr)	(31)

disease, which reduces the antioxidant enzymes and increases malondialdehyde (MDA) production by lipid peroxidation. Zingerone in an amount of 50 mg/kg restores the activity of CAT and GPx. It also reduces MDA production (33). Zingerone (500 ug/ml) showed its protective effect against *in vitro* DNA damage induced by stannous chloride (34). Streptozotocin/high fat diet (STZ/HFD) causes type-2 diabetes and increase ROS production in Wistar rat. ROS level decrease by zingerone as antioxidant enzymes increase their own activities (35). Ethanol, the so-called alcohol can increase ROS production in living cells by reducing the scavenging enzyme activities (19).

Anti-inflammatory activities

Proinflammatory cytokines such as interleukins (IL1-b, IL-6, IL-2) and tumor necrosis factor alpha (TNF-α) are increased during chemical induced diabetes. IL1-b, IL-6, IL-2 and TNF-α have an important role in malfunctioning the β cells of pancreas during diabetes (30). These inflammatory cytokines are found to decrease in diabetes rats by the treatment of zingerone. It is in amount of 50 mg/kg successfully reduced the cisplatin induced inflammation by limiting TNF -α production (Fig. 4) in Wistar rats (33). UVB is very harmful radiation mainly responsible for epithelial cell damage and show inflammation by increasing the level of cytokines in keratinocyte stem cells (KSCs) (36). During UVB exposure, the elevated TNF-α employs inflammatory cells which secrete elastases and collagenases. They further lead to aging or skin damage (36-39). NF-κB pathway is one of the important signalling pathways to show inflammation by the cell under stress. Lipopolysaccharides produce proinflammatory cytokines in living organisms. Lipopolysaccharides induced acute systemic inflammation is controlled by zingerone. Zingerone reduce the production of p65 proteins in the cells which suffer from acute systemic inflammation (40). P65 protein is attached with p50 protein to form a protein dimer in NF-κB signalling pathway. This protein dimer is transferred to nucleus from cytosol after the proteosomal degradation of phosphorylated IκBα, which subsequently initiate transcription of proinflammatory cytokines to show inflammation (41). Inflammatory bowel disease (IBD) is one the important cause of colitis. NF-κB and IL- 1β are important proteins expressed during 2,4,6-trinitrobenzene sulphonic acid (TNBS) induced colitis. The microarray study for gene expression showed that ginger and zingerone (100 mg/kg) application reduce the expression of NF-κB and IL-1β in TNBS induced colitis (42). Ethanol consumption also shows inflammatory response in hepatic cells through NF-κB and leads to hepatoxicity. Zingerone (20 mg/kg) treatment increase the number of anti-inflammatory Nrf-2 (basic leucine zipper (bZIP) protein) protein and decrease NF-κB expression which reflects reduction in hepatotoxicity by zingerone (19). The probable mechanism behind zingerone (100 mg/kg) mediated anti-inflammatory therapy is inhibition of inflammatory genes expression like toll like receptor 4 (TLR4), RelA, NF-kB2, TNF-α, iNOS, COX-2 (43). Peroxisome proliferator-activated receptors (PPARs) is associated with various types of biological activities like increasing cell proliferation, glucose and lipid metabolism, insulin sensitivity, tissue remodelling and inflammations. PPARs activities is increased by zingerone (8 mg/kg), which further supress NF-kB and prevent inflammation (44).

Antilipidemic activities

Alcohol was also involved to increase lipids like cholesterol, triglycerides, free fatty acids, phospholipids and low-density lipoproteins. Zingerone has an emerging role in antihyperlipidemic and antiapoptotic properties (45). The elevated expression of TNF-α and IL-6 is reduced by zingerone. Triglyceride and cholesterol levels are decreased by zingerone. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4 (NOX 4) is upregulated by zingerone to prevent diabetic nephropathy (46).

Other biological activities

In a report of 2015, it was found that about 15.9 million of people suffers from myocardial infarction (47). The pre-treated rats with zingerone showed prevention mechanism against isoproterenol induced myocardial infarction. This result concludes that zingerone is effective to protect heart from myocardial infarction disease (48, 49). The apoptosis responsive genes like Fas-receptor, caspase-8, caspase-9 and caspase-3 are found down regulated due to zingerone in myocardial infarction. Bcl-2 and Bcl-xL are upregulated whereas Bax and Bad genes are down regulated in zingerone treated myocardial infarction tissue (induced by isoproterenol) (50). Zingerone also decreases biofilm formation and subsequently enhances ciprofloxacin activity in *Pseudomonas aeruginosa* (43).

Osteoblast differentiation is the process leading to osteogenesis and boosted by zingerone in the mesenchymal stem cells. mRNA Runx2, involved differentiation is enhanced by zingerone treatment. Zingerone may deposit calcium, which is responsible for osteogenesis (51).

Apart from this, zingerone has also the efficiency to act as antithrombosis agent. Thrombosis generally takes place by conversion of FX to FXa, which further converts prothrombin to thrombin and sequentially again converts fibrinogen to fibrin. In addition to fibrin deposition, Platelets activated and aggregated to clot blood. But zingerone inhibits FXa formation and platelet aggregation (22).

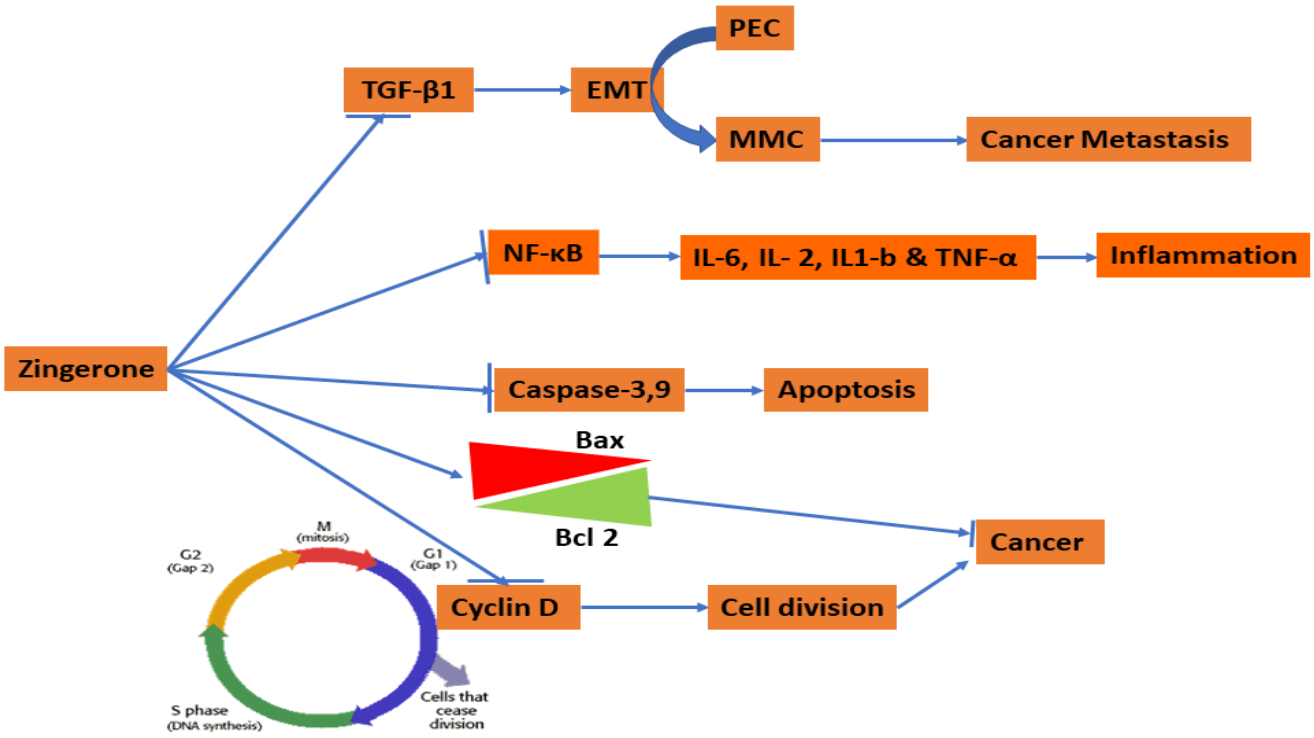

Fig. 4. Zingerone is involved in signalling pathways against various diseases.
Cancer metastasis is controlled by zingerone by inhibiting TGF-β1. EMT is controlled by TGF-β1 and is responsible for converting PEC to MMC, which further lead to cancer metastasis. Zingerone regulates NF-kB signalling in inflammation. Apoptosis and cancer are also regulated by zingerone. Zingerone induce Bcl 2 expression and supress Bax expression to inhibit cancer. Cell cycle check point protein complexes are inhibited by zingerone during cancer development. TGF-β1 (Transforming growth factor-beta 1), EMT (Epithelial mesenchymal transition), PEC (Polarized epithelial cells), MMC (Motile mesenchymal cells), NF-kB (Nuclear factor kappa beta), IL (Interleukin), TNF (Tumor necrosis factor).

Conclusion

Zingerone is used against diseases like myocardial infarction, hepatic cancer, colon cancer, neurological disorders and many other diseases. It has many important pharmacological activities like antioxidant, anticancer, antiinflammation, antithrombotic and various other activities. Zingerone is also found to regulate important genes like TGF-β, NF-κB, TNF-α and cytokines like interleukins in the signalling pathway. But the actual mechanism involved is still unknown. Extensive studies are required to elucidate the exact mechanism of this compound in various disease responses. More studies can be also focused on the biological activities of zingerone after cooking in comparison to its crude form. This review will further help in potential drug discoveries

from ginger plant using zingerone. However, the contributions of zingerone to the pharma as well as medicinal industries can be very high for multiple therapies. In addition, this compound in nanoform showed effective activities than its crude form. As so many studies on its dietary supplements for various pharmacological activities have been reported, it can be adopted by pharma companies to develop novel drug molecules. The multiple bioactivities of zingerone will also further definitely help scientific communities to get depth knowledge on it and its importance in various health sectors.

Author's contribution

BCS did the literature survey and wrote the manuscript. SS helped in reviewing and editing the manuscript. SN helped in reviewing and editing the manuscript. BK gave the concept, designed the work, reviewed and edited the manuscript.

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Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical issues: None.

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