REVIEW ARTICLE Agricultural Science Digest, Volume 42 Issue 5: 528-533 (October 2022)

Pharmacological Aspects of 6-Gingerol: A Review

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10.18805/ag.D-5387

ABSTRACT

Habitual consumption of raw fruits as well as vegetables can trim down the threat of many diseases. Ginger is consumed globally as a cuisine and herbal medicine. It is rich in pungent phenolic phytochemical substances together called gingerols. 6-Gingerol (1-[4'-hydroxy-3'-methoxyphenyl]-5-hydroxy-3- decanone) is the chief pharmacologically-active moiety of ginger. Molecularly, gingerol is a relative of capsaicin and piperine, the compounds which are alkaloids, though the bioactive pathways are unconnected. It is normally found as pungent yellow oil in the ginger rhizome, but can also form a low-melting crystalline solid. Previous studies have suggested ample of therapeutic activities including anticancer, anti-inflammation and anti-oxidation. 6-Gingerol has been found to possess anticancer activities *via* its effect on a variety of biological pathways involved in apoptosis, cell cycle regulation, cytotoxic activity and inhibition of angiogenesis. Thus, due to its efficacy and regulation of multiple targets, as well as its safety for human use, 6-gingerol has received considerable interest as a potential therapeutic agent for the prevention and/or treatment of various diseases. Overall, this review encapsulates different therapeutic and pharmacological facets of 6-gingerol along with its possible mechanism of action.

Key words: Anti-cancer, Antioxidant, Gingerol, Rhizome, Therapeutic.

Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) is a rhizomatous perennial herb, widely used around the world in foods as a spice (Mishra *et al*., 2012). Rhizomes are aromatic, thick lobed, pale yellowish. Chemical constituents of ginger rhizomes include volatiles (camphene, β-phellandrene, curcumene, cineole, geranyl acetate, terpineol, borneol, geraniol, limonene, β-elemene, zingiberol, linalool, α-zingiberene, β-sesquiphellandrene, β-bisabolene, zingiberenol and α-farnesene) and non-volatile pungent phytochemicals consisting of the biologically active components, gingerols, shogaols, paradols and zingerone (Mao *et al*., 2019; Govindrajan, 1982). [6]-gingerol (Fig 1) is a phenolic phytochemical compound found in fresh ginger, the active part of the molecule being the aliphatic chain moiety containing a hydroxyl group (Prasad and Tyagi, 2015; Yang *et al*., 2010). Ginger also contains other analogues such as [8]-gingerol, [10]-gingerol and [12]-gingerol (Park *et al*., 2008). The major pharmacological activity of ginger appears to be due to gingerol and shogaol (Mao, 2019). Both *in vivo* and *in vitro* studies have demonstrated antioxidant, anti-inflammatory (Zhang *et al*., 2016), neuroprotective (Ho *et al*., 2013), anti-fungal (Ficker *et al*., 2003) and gastroprotective activities in gingerol.

Previous research have exhibited that gingerols are effective against wide range of cancers such as leukemia (Wei *et al*., 2005), prostate (Salehie *et al*., 2019), breast (Lee *et al*., 2008) skin (Bode *et al*., 2001) ovarian (Rhode *et al*., 2007), lung (Semwal *et al*., 2015), pancreatic (Park *et al*., 2006) and colorectal (Lee *et al*., 2008). Furthermore gingerols have been shown to facilitate healthy glucose regulation for diabetics (El-Bassossy *et al*., 2016; Son *et al*., 2015).

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How to cite this article: Chauhan, N. (2022). Pharmacological Aspects of 6-Gingerol: A Review. Agricultural Science Digest. 42(5): 528-533. DOI: 10.18805/ag.D-5387.

Submitted: 24-05-2021 **Accepted:** 25-10-2021 **Online:** 02-12-2021

Pharmacological activities

Anticancer activity

Experimental outcomes over mice models have significantly proved that [6]-gingerol compounds exhibit apoptosis in cancer and transformed cells lines by interfering with the mitochondrial membrane potential (Salehie *et al*., 2019). Various experimental findings prove a mechanism related with the interruption of G1 phase cell cycle proteins to stop the division of cancer cells (Lee *et al*., 2008; Park *et al*., 2006; Salehie *et al*., 2019). Gingerol has a potential to stop cellular proliferation through inhibiting the translation pathway of Cyclin mediated proteins that is essential for replication of cell during G1 and G2 phase of cell cycle (Mao *et al*., 2019). It has a power to decrease inducible nitric oxide synthase (iNOS) action and a cytokine that is tumor necrosis factor alpha (TNF-alpha) expression through suppressing cytokine I-kappaB alpha (IkappaBalpha) phosphorylation mechanism, through nuclear factor kappa B (NF-kappaB) nuclear translocation. Additional antiproliferative action of [6]-gingerol exhibits the release of Cytochrome c, Caspases factor activated system and enhanced apoptotic protease-

activating factor-1 (Apaf-1) that are responsible for apoptosis (Oyagbemi *et al*., 2010).

• Apoptosis

6-Gingerol has potent anticancer action by inducing apoptosis (Nigam *et al*., 2010) by two different pathways, first one is the extrinsic pathway (death receptor) and second one is intrinsic (mitochondrial) pathway (Pan *et al*., 2008). 6-Gingerol has a power to suppress cyclin D1 gene expression (protooncogene) and also induce NAG-1 (antitumorigenic) expression through PKC pathway and glycogen synthase kinase (GSK)-3β enzymatic pathways in human colorectal cancer cell lines. At the transcriptional level (mRNA production), the action of the cyclin D1 factor promoter activity signifies that the -163/+130 region is the binding site for cyclin D1 inhibition by 6-gingerol. At the translational level (protein production), 6-gingerol affected cyclin D1 expression by means of post-translational modification at golgi apparatus (Lee *et al*., 2008). Furthermore, 6-gingerol has potent apoptotic power in mouse skin tumors cells by modulating p53 pathway and mitochondrial signaling pathway (Nigam *et al*., 2010).

• Cell cycle

A complete cell division includes 4 phases, the G1, DNA synthesis (S phase) G2 phases and of nuclear division (M phase). The cell division is regulated by a number of enzymes *i.e*. serine/threonine kinases, the cyclin-dependent kinases proteins (CDKs). 6-gingerol has a potential of cell division arrest and cell death of mutant p53-expressing cancer cells of pancreas (Park *et al*., 2006) by reducing cyclin A and CDK gene expression, that leads to reduced level of retinoblastoma (Rb) phosphorylation, followed by jamming the S phase entry. The cell division was inhibited by action of 6-gingerol through cell division arrest at the starting period of G1 phase. In a study of the effect of 6-gingerol on the proliferation of rat ascites hepatoma AH109A cells, it was found to inhibit both the proliferation and invasion of hepatoma cells in a dose-dependent manner. The results suggested that the suppression of hepatoma cell proliferation by 6-gingerol could be due to cell cycle arrest and apoptosis induction. It was also indicated that the anti-oxidative property of 6-gingerol could be involved in its anti-invasive effect upon hepatoma cells (Yagihashi *et al*., 2008). 6-gingerol exhibits a power of inducing significant arrest at a level of G2/M phase of the human colon cancer cell (Lin *et al*., 2012).

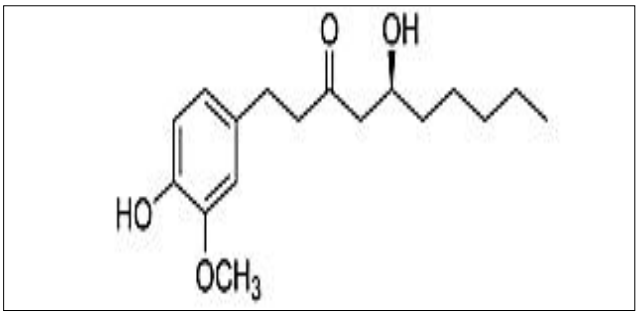

Fig 1: Chemical structure of 6-gingerol.

• Cytotoxic activity

6-Gingerol has property to exhibit dose-dependent inhibitory action on human leukemia (HL-60) cell division (Wang *et al*., 2003). 6-Gingerol also exhibits cytotoxic activity against human hepatoma G2 cells, cervical cancer cell line (Hela) and lung carcinoma cell line (COR-L23) (Pawa, 2012). The chief metabolites were recognized as 6-gingerdiols, which might induce cytotoxicity activities in various cancer cells (Lv *et al*., 2012).

• Anti-angiogenic activity

Angiogenesis is the formation of new blood vessels from the preexisting endothelium, which is fundamental in the physiological and pathological processes of tumor progression and metastasis (Hanahan and Folkman, 1996). It was found that 6-gingerol had anti-angiogenic activity *in vitro* and *in vivo*. It inhibited the tube formation and proliferation of human endothelial blood cells in reaction to vascular endothelial growth proteins *in vitro* (Kim *et al*., 2005).

Anti-hyperglycemic

Gingerols enhanced over production of glutathione (toxin scavenger) molecules that help to control diabetes (Tamrakar *et al*., 2009). Anti-hyperglycemic action was experimentally observed in severely diabetic and obese albino mice. Gingerols improved glucose uptake directly into cells without insulin. They also enhanced power of glucose tolerance and surprisingly lowered the fasting glucose amount (Son *et al*., 2015) along with lipoprotein cholesterol level (Tamrakar *et al*., 2009) thus ensuring their metabolic benefits. In diabetes mellitus, the anti-inflammatory effects of gingerol also exhibit suppression of the cardio-arrhythmia risks by lowering dissolved blood glucose amount that leads to decrease in the osmotic pressure of blood as seen *in vivo* (El-Bassossy *et al*., 2016). In another finding, sodium arsenite (iAs) induced stress mediated impaired insulin signaling pathway in mice. 6-Gingerol decreased the elevated blood glucose amount and also oxidative stress by increasing the concentration of super oxide dismutase (SOD), catalase enzyme, glutathione peroxidase activity (GPx) and GSH (Chakraborty *et al*., 2012).

Antioxidant

Gingerol action is antagonistic to oxygen radicals and exhibit antioxidant activity (Dugasani *et al*., 2010). The antioxidant activities of the phenolic molecule are due to its ability to donate electrons to free radical and form a stable phenoxyl radical (Mishra *et al*., 2012). 6-gingerol considerably decreases the DNA strand breaks and also micronucleosome formation caused by patulin activity (PAT). Gingerol has good protective action on nuclear DNA damage induced by H_2O_2. Moreover, 6-gingerol efficiently concealed PAT-induced intracellular RAS factor formation and the 8-OHdG level. The GSH level decline/genotoxicity induced by PAT in HepG2 cells was also attenuated by 6-gingerol pretreatment

(Bhattarai *et al*., 2001). Similarly, ROS production (increased by transforming growth factor TGF-β-1 stimulation) was decreased by 6-gingerol (Yamahara *et al*., 1989). In this study, myofibroblast differentiation, collagen production and phosphorylation of Smad2/3 were also prevented by 6-gingerol. These results suggested that 6-gingerol may have some antioxidant effect in inhibiting the production of the extracellular matrix in the development of nasal polyps. As a potent antioxidant, 6-gingerol significantly restored renal functions, reduced lipid peroxidation and increased the levels of glutathione and activities of superoxide dismutase and catalase (Lumb, 1993).

• Anti-alzheimer

β-Amyloid (Aβ) molecules have typical activity of neuropathological marker for diagnosing Alzheimer's disease (AD) (Lim *et al*., 2014). They exhibit apoptosis in neural cells *via* oxidative and/or nitrosative stress (overproduction of nitric oxide). 6-Gingerol pretreatment prevented Aβ molecule-induced cytotoxicity action and apoptotic (natural) cell death (Huh *et al*., 2018). Action of 6-gingerol is to decrease the level of highly reactive oxygen and/or nitrogen molecule and restore natural antioxidant glutathione levels. The mRNA production and protein action of antioxidant enzymes such as heme oxygenase-1 (HO-1) and γ-glutamylcysteine ligase (GCL) were up-regulated by 6-gingerol (Mao *et al*., 2019). These findings confirmed that 6- gingerol attenuated Aβ molecule-induced oxidative cell death by invigorating the cellular antioxidant defensive system. According to outcomes from this research the protective action against DNA fragmentation and deterioration of mitochondrial transmembrane potential of cells indicates a potent neuroprotective effect of gingerol (Lee *et al*., 2011). It also proved that gingerol up-regulates glutathione production in neurons, through anti-oxidative action which reduces the chance of Alzheimer's in human neuroblastoma cells and mouse hippocampal cells (Lee *et al*., 2011).

• Food preservative

6-gingerol can prevent peroxidation of liposomes (phospholipid) in the presence of iron (III) ion and ascorbate molecule (Aeschbach *et al*., 1994). Therefore, 6-gingerol might develop into a vital natural antioxidant food additive.

Anticoagulant

Ginger has been shown to inhibit platelet aggregation and to decrease platelet thromboxane production *in vitro*. Gingerol analogues, (8)-shogaol and (8)-paradol exhibited antiplatelet activities (Nurtjahja-Tjendraputra *et al*., 2003).

Antiemetic

The components in ginger that are responsible for the antiemetic effect are thought to be the gingerols, shogaols and galanolactone, a diterpenoid of ginger (Rahmani *et al*., 2014). Animal model and *in vitro* studies have demonstrated that ginger extract possesses antiserotoninergic and 5- HT3 receptor antagonism effects, which play an important role in the etiology of postoperative nausea and vomiting (Lumb *et al*., 1993). The exact mechanism responsible for the anti-emetic effects of ginger is unknown; however, the ginger phytochemicals, especially 6-gingerol, 8-gingerol, 10-gingerol and 6-shogaol, may function as a 5-hydroxytryptamine (5-HT3) antagonist, NK1 antagonist, antihistaminic and possess prokinetic effects (Haniadka *et al*., 2012).

Anti-inflammatory

Ginger has a long history of being used for its anti-inflammatory activity and many of its constituents have been identified as having anti-inflammatory properties (Zhang *et al*., 2016; Zhang *et al*., 2013). Gingerol, shogaol and other structurally-related substances in ginger have been found to inhibit prostaglandin and leukotriene biosynthesis by suppressing 5-lipoxygenase or prostaglandin synthetase. In addition, they can also inhibit synthesis of pro-inflammatory cytokines such as IL-1, TNF-α and IL-8 (Tjendraputra *et al*., 2001; Verma *et al*., 2004). The cytokines TNF-α and interleukin (IL)-1β are responsible for initiating inflammatory cell recruitment by stimulation of the expression of pro-inflammatory genes (Apte and Voronov, 2002). Mitogen-activated protein kinase phosphatase-5 (MKP5) also mediates the anti-inflammatory activities. 6-Gingerol is capable of upregulating MKP5 and decreasing cytokine-induced p38-dependent pro-inflammatory changes (Nonn *et al*., 2007).

• Antiarthritic effect

6-gingerol-enriched products have shown improvement in joint inflammation in an experimental arthritis model due to their anti-inflammatory property. A well characterized crude ginger extract was compared with a fraction containing [6] -gingerol and their derivatives to inhibit joint swelling in an animal model of rheumatoid arthritis, streptococcal cell wall-induced arthritis. The crude dichloromethane extract, containing essential oils and more polar compounds, was more efficacious, when normalized to [6]-gingerol content, in preventing, both joint inflammation and destruction. Non-gingerol components enhance the antiarthritic effects of the more widely studied [6]-gingerol (Funk *et al*., 2009). It was also demonstrated that 6-gingerol has a therapeutic effect in osteoarthritis *via* protection against oxidative stress and down-regulation of pro-inflammatory mediators *in vitro* and *in vivo* (Abusarah *et al*., 2017).

Cardiovascular

In vitro research outcomes indicate that gingerols and the related shogaols are having cardio depressant action at very low doses and cardiotonic activities at higher doses. All (6)-shogaol, (6)- gingerol and the gingerdiones, having potent enzymatic inhibition of prostaglandin, thromboxane and leukotriene biosynthesis. (Mishra *et al*., 2012). In a study using a cell-based calcium mobilization assay [6]-Gingerol was identified as a novel angiotensin II type 1 receptor antagonist, with an IC50 value of 8.173 μM. It was found

that [6]-gingerol could inhibit angiotensin II type 1 receptor activation, which somewhat explained the cardioprotective effects of ginger (Liu *et al*., 2013).

Anti-hypercholesterolemic

Several studies in animal models have proved the lipid and cholesterol lowering activity of ginger. Gingerol being the principal active component of ginger was investigated for its effect on cholesterol metabolism in different studies. In a study the cholesterol-lowering activity of gingerol- and shogaol-enriched ginger extract (GSE) was analyzed in thirty hamsters. It was found that plasma total cholesterol, liver cholesterol and aorta atherosclerotic plaque were dose-dependently decreased with increasing amounts of GSE added into diets. The fecal sterol analysis showed dietary GSE increased the excretion of both neutral and acidic sterols in a dose-dependent manner *via* up-regulation of hepatic CYP7A1 and down-regulation of mRNA of intestinal NPC1L1, ACAT2 and MTP (Lei *et al*., 2014). In another recent study of liver cells it was observed that 6-gingerol could significantly reduce cellular total and free cholesterol levels and also increase LDL uptake and LDLR-binding activity in HepG2 cells by modulation of cholesterol metabolism-related genes and proteins in the liver (Li *et al*., 2018).

Anti ulcer

When the anti-ulcer effect of ginger constituents on HCl/ethanol-induced gastric lesions in rats was examine, gingerol, at 100 mg/kg significantly inhibited gastric lesions by 54.5% (Yamahara *et al*., 1988). Both 6-gingerol and 6-shogaol reduced aspirin induced ulcer formation, mucosal iNOS and plasma TNF-α and IL-1β levels in experimental rats by reducing mucosal iNOS activity and the plasma levels of inflammatory cytokines (Wang *et al*., 2011).

Antimicrobial activity

Pseudomonas aeruginosa is a well-known pathogenic bacterium that forms biofilms and produces virulence factors *via* quorum sensing (QS). 6-gingerol reduces biofilm formation and virulence by antagonistically binding to *P. aeruginosa* QS receptors (Kim *et al*., 2015).

Miscellaneous

Previous data have shown antitussive and immuno modulatory property of 6-gingerol (Suekawa *et al*., 1984). It further proved to induce weight loss. Foods as well as herbal drinks having ginger as chief constituent remarkably affect metabolic targets including fat oxidation, satiety and thermogenesis (Westerterp-Plantenga *et al*., 2006). It restores “affirmative energy poise” and avert obesity. Furthermore, gingerol possess radio protective activity. *In vitro*, pre-treatment with [6]-gingerol reduced electromagnetic UV-B waves-induced intracellular highly reactive oxygen molecules concentration, leading to activation of caspase 3, -8, -9 proteins and Fas gene expression. It also reduced electromagnetic UVB waves-induced allele expression and leads to transactivation of COX-2. Movement of NF-κB factor from cytoplasm to nucleoplasm in HaCaT cells was repressed by [6]-gingerol *via* suppression of factor IκBα phosphorylation (ser-32). Evaluation by EMSAs and immune histocompatability chemistry exhibited that topical application of [6]-gingerol (30 μM) prior to UVB irradiation (5 kJ/m^2) of hairless mice, also inhibited the activation of COX-2 mRNA and protein, as well as NF-κB factor translocation (Kim *et al*., 2007). Norethandrolone and oxandrolone were investigated for their genotoxic effect on human lymphocyte chromosomes using chromosomal aberrations, crossing over and sister chromatid exchanges and subsequently Genistein and [6]-gingerol were used as antigenotoxic agents to improve the genotoxicity induced by the non polar action of steroids. Norethandrolone and oxandrolone were evaluated at 5, 10, 20, 30 and 40 μM, concentration respectively and were found to be appreciably genotoxic at 30 and 40 μM. Genistein and [6]-gingerol proved to be evenly successful in reducing genotoxic damage at appropriate doses (Beg *et al*., 2008).

CONCLUSION

Ginger is among the most healthy and frequently utilized dietary nutritive condiments in the world. One of the chief pungent rudiments of ginger, 6-gingerol, is recommended for the prevention of cancer and other diseases. Previous work, summarized above has demonstrated multiple mechanisms involved in the activities of 6-gingerol. However, most of the studies with this compound have been made *in vitro* and with laboratory animals. So, additional researches on evaluating the activities of 6- gingerol are supposed to perfectly include human intervention trial. However, further mechanistic work is required to elucidate the molecular mechanisms primarily the effects of 6-gingerol on gene expression, the signaling pathway and effectual proteins involved. Overall, 6-gingerol could thus provide a useful component of dietary or pharmacological treatment for further drug-synthesis to develop novel and potent clinical candidates. In the future, more bioactive compounds in ginger might be isolated and undoubtedly recognized and their biological activities and associated mechanisms of action should be further investigated. Notably, well-designed clinical trials of ginger and its various bioactive compounds are warranted to prove its efficacy against these diseases in human beings.

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