Therapeutic Value of 6-Gingerol (1-[4′-hydroxy-3′-methoxyphenyl]-5-hydroxy-3-decanone): A review

ABSTRACT

Utilization of crude extracts separated from herbal medicine is getting more worthy and ideal, conceivably because of the expense of production, accessibility, and availability and to bring down harmfulness as much as possible. Various researches have shown that the regular use of particular soil products like fruits and vegetables can minimize the risk of a number of infections. Ginger is among the most sound and regularly devoured dietary sauces on the planet. One of the major impactful components of ginger, 6-gingerol, is suggested for the avoidance of malignancy and different maladies. As a spice and home grown medicine, the rhizome of Zingiber officinale (ginger) is devoured worldwide. It contains sharp phenolic compounds known as gingerols aggregately. The main pharmacologically-dynamic segment of ginger is 6-Gingerol. It is recognized to show a variety of organic actions including anti-cancer, anti-inflammation, and anti-oxidation.

6-Gingerol has been found to have anticancer exercises by means of its impact on an assortment of natural pathways associated with apoptosis, control of cell cycle, cytotoxic action, and restraint of angiogenesis. Consequently, because of its adequacy and control of different targets, just as its security for human use, 6-gingerol has gotten impressive enthusiasm as an expected helpful operator for the anticipation and additionally treatment of different maladies. Taken together, this review sums up the different *in vitro* and in vivo pharmacological aspects of 6-gingerol and the underlying mechanisms.

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Keywords: Ginger; 6-Gingerol; anticancer activity; anti-inflammatory activity; anti-oxidant activity.

1. INTRODUCTION

Utilization of crude extracts separated from herbal medicine is getting more worthy and ideal, conceivably because of the expense of production, accessibility, and availability and to bring down harmfulness as much as possible [1]. Wide assortment of phytochemicals is identified to be able to meddle with various types of sicknesses. Consequently, chemoprevention of illnesses by phytochemicals has become a prospering field of exploration over the previous decade [2]. The rhizome of ginger (Zingiber officinale) ~~(ginger)~~, family Zingiberaceae, is used worldwide as a spice and natural medication, and is grown in most tropical areas of the world [3]. Camphene, β-phellandrene, curcumene, cineole, geranyl acetic acid derivation, terpineol, borneol, geraniol, limonene, β-elemene, zingiberol, linalool, α-zingiberene, β-sesquiphellandrene, β-bisabolene, zingiberenol and α-Farnesene are volatile chemical constituents incorporate in ginger rhizomes. The non-volatile and impactful phytochemicals comprising in ginger are gingerols, shogaols, paradols and zingerone [4, 5].

Many ~~populace based~~populace-based investigations recommended that individuals in South East Asian nations have a much lower incidence ~~danger~~ of colon, gastrointestinal, prostate, breast, and other cancers than their western partners, and it is accepted that the phenolic substances from restorative plants, natural products, and vegetables in their eating regimen may assume a significant function in the protection [6]. Ginger contains sharp phenolic substances ~~all in all~~ known as gingerols. One of these, 6-gingerol (1-[4'- hydroxy-3'- methoxyphenyl]-5-hydroxy-3-decanone), is the major pharmacologically-dynamic segment of ginger [7, 8], and the dynamic aspect of the molecule is the aliphatic chain moiety containing a hydroxyl group (Figure 1) [9].

6-gingerol is the significant phenolic bioactive part separated from rhizome of ginger (Zingiber officinale) which is answerable for spicy taste of ginger. It has been revealed to show anti-proliferative effect against a wide scope of cells~~disease~~ by repressing different endurance pathways including NF-KB and β-catenine [10]. Like capsaicin, it has additionally increased intracellular accumulation of

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daunorubicin and rhodamine 123 by blocking the P-glycoprotein (p-gp) inhibition effect in multidrug-resistant human carcinoma KB-C2 cells. It improved the poisonousness of vinblastine in KB-C2 cells through P-glycoprotein (p-gp) restraint [11]. Nonetheless, the accessible reported data are not ~~isn't~~ adequate to clarify the mechanism of P-glycoprotein (p-gp) restraint by 6-gingerol.

6-Gingerol ~~(Figure 1)~~ has been accounted for to have an assortment of natural properties including anticancer, anti-oxidant, anti-inflammation, anti-platelet aggregation and antifungal [12-14].The object of this review is to give an extensive knowledge into the chemo preventive capability of 6-gingerol, including laboratory examines, epidemiological investigations, and even potential bearings for future research.

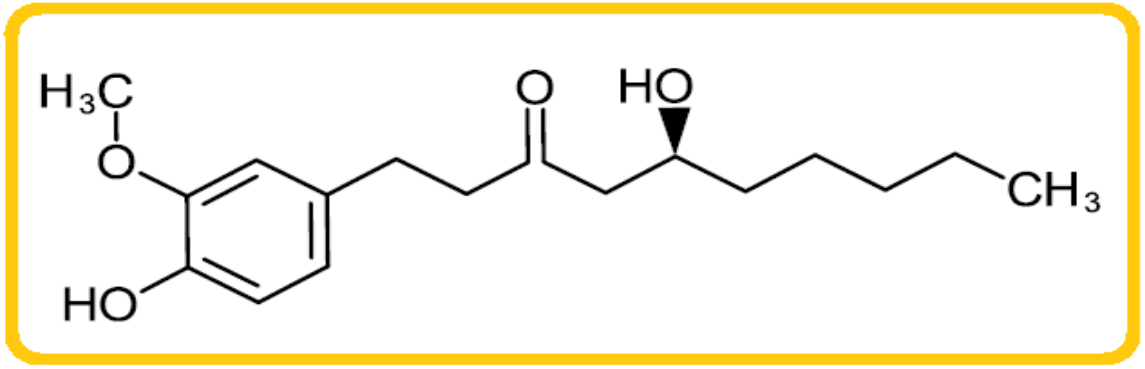

Fig. 1. The chemical structure of 6-gingerol (http://www.chemspider.com/Chemical-Structure.391126.html)

2.0 ANTICANCER EFFECT

On account of high demise rate related with cancer and high side effect of chemotherapy and radiation treatment, numerous patients look for alternative strategies for therapy. Plants have been utilized for treating infections since days of ancient time. More than 50% of current medications in clinical use are of plant source [15]. Ginger is esteemed for its spicy and therapeutic properties and it has been utilized as medication from ancient period and is termed as"maha aushadh", implies the promising medication. Currently the

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significance of ginger has been expanded as a result of its low poisonousness and its wide range of organic and pharmacological applications [15-20]. The different phytochemical composition present in ginger 6-gingerol is the most strong and pharmacologically active biomolecules and have anti-tumor and ant-proliferative properties. Because of this 6-gingerol is a target for anti-cancer drug development. The result of p~~P~~harmacological studies showed that ginger and its major pungent phytochemical compositions like 6-gingerol have chemo preventive and chemotherapeutic activities on many cancer cell lines and on animal models [21]. 6-Gingerol has been researched in numerous human carcinomas, including leukemia, breast, colon, pancreatic, prostate, gastric and liver malignant growths [22-25]. Nevertheless, the mechanisms by which it protects cancer are not surely known.

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2.1 Apoptosis (Program Cell Death)

6-Gingerol is known to facilitate its anticancer properties by encouraging apoptosis [26]. ~~It is recommended that a~~Apoptosis is interceded by two pathways, namely the death receptor (extrinsic) and mitochondrial (intrinsic) pathways [27]. Various mechanisms are associated with 6-gingerol incited apoptosis. Cyclin D1 is a proto-oncogene overexpressed in colorectal cancer, and may contribute a vital role in β-catenin signaling. Nonetheless, non-steroidal anti-inflammatory drug (NSAID) - gene-1 (NAG-1) is a cytokine with anti- tumorigenic properties [28, 29]. In gastric cells 6-gingerol encouraged TRAIL-incited apoptosis by expanding TRAIL-induced caspase-3/7 initiation [30]. In the previous researches, the results revealed that 6-gingerol can initiate apoptosis via the lysosomal-mitochondrial axis in human hepatoma G2 cells. Cathepsin D might be a positive facilitator of 6-gingerol induced apoptosis in HepG2 cells, acting upstream of cytochrome c discharge, and the apoptosis might be related with oxidative stress [31]. In the investigation of Nigam et al., the mouse skin carcinogenesis model was utilized. Topical treatment with 6-gingerol (2.5 μM/animal) was injected to the mouse 30 min earlier and post to benzo[a]pyrene (B[a]P) (5 μg/animal) for 8 months. It was seen that 6-gingerol had apoptotic potential in mouse skin tumors. The mechanism might be related with the modulation of p53 and inclusion of the mitochondrial signaling pathway [32].

2.2 Cytotoxic Activity and Inhibition of Angiogenesis

The cytotoxic effect of 6-gingerol is additionally identified with its anticancer capacities. Numerous investigations have detailed the cytotoxic impacts of 6-gingerol on various cancer cells *in vitro* and in vivo~~animals~~. It was found to show dose-dependent blocking impacts on human promyelocytic leukemia (HL-60) cell growth [33]. 6-Gingerol has revealed cytotoxic effect against huge lung carcinoma cell line (COR-L23), cervical cancer cell line (Hela), and human hepatoma G2 cells [34]. Additionally, 6-gingerol is widely metabolized in human lung cancer cells (H-1299), mouse lung cancer cells (CL-13), human colon cancer cells (HCT-116 and HT-29), and in mice. The significant metabolites were known as 6-gingerdiols, which could encourage cytotoxicity in these cancer cells [35]. 6-Gingerol is persuasive in forestalling carcinogenesis in numerous organs. A potential clarification for this outcome is that the compound may hinder angiogenesis. Angiogenesis is the development of new blood vessels from the previous endothelium, which is the major one in the physiological and pathological processes of tumor progression and metastasis [36]. In a past report, Eok-Cheon Kim et al. revealed that 6-gingerol had an inhibitory effect on~~against~~ angiogenesis~~city~~ *in vitro* and *in vivo*. It hindered the multiplication and tube formation of human endothelial cells in retort of vascular endothelial growth factor *in vitro* [37].

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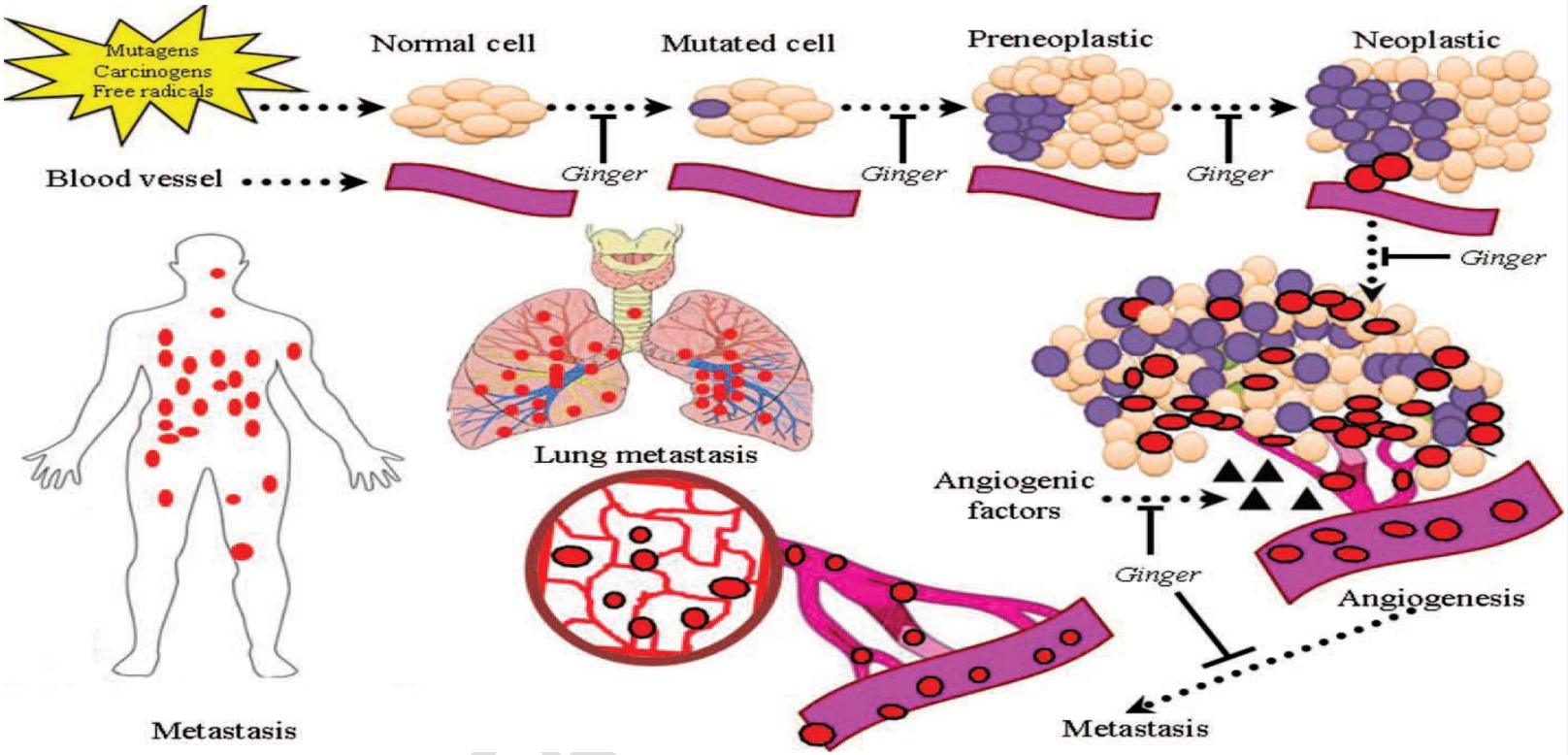

Fig. 2. Ginger hinders cancer progression, angiogenesis and metastasis [Ginger extract and 6-gingerol is reported to prevent the angiogenesis process by reducing the secretion of VEGF [38, 39]. 6-gingerol also blocked VEGF- and bFGF-induced proliferation [40] hindered the pulmonary metastasis [41] by declining the activities of MMP-2 or MMP-9. All these results cumulatively propose that 6-gingerolacts as a preventive agent for malignancy by selectively blocking angiogenesis, adhesion, invasion, motility and production of MMPs at the tumor site [42]. Zerumbone, is also showed to down-regulate the expression of CXCR4 in the HER2-overexpressing breast cancer cells which concurrently caused preventing ofCXCL12-induced invasion of breast and pancreatic cancer cells [43].

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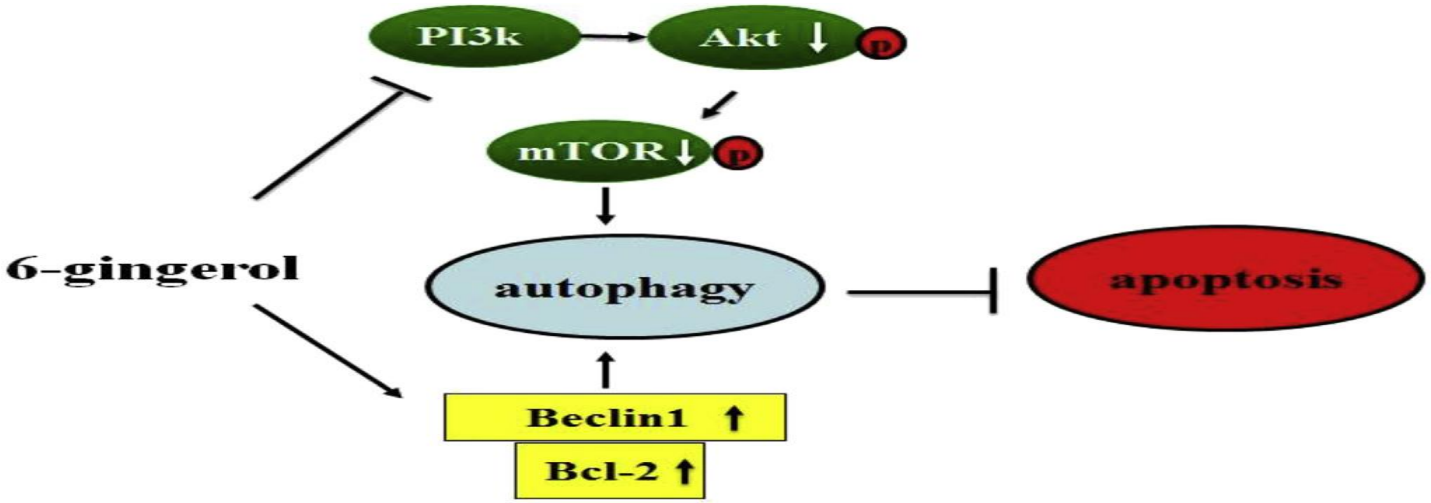

Fig.3. The projected pathway of 6-gingerol-induced autophagy in HUVECs. 6-gingerol can pledge an autophagic existence response against apoptosis. 6-gingerol encourages the activation of Beclin1, and hinders the PI3K/AKT/mTOR signaling pathway to promote autophagy. [44]

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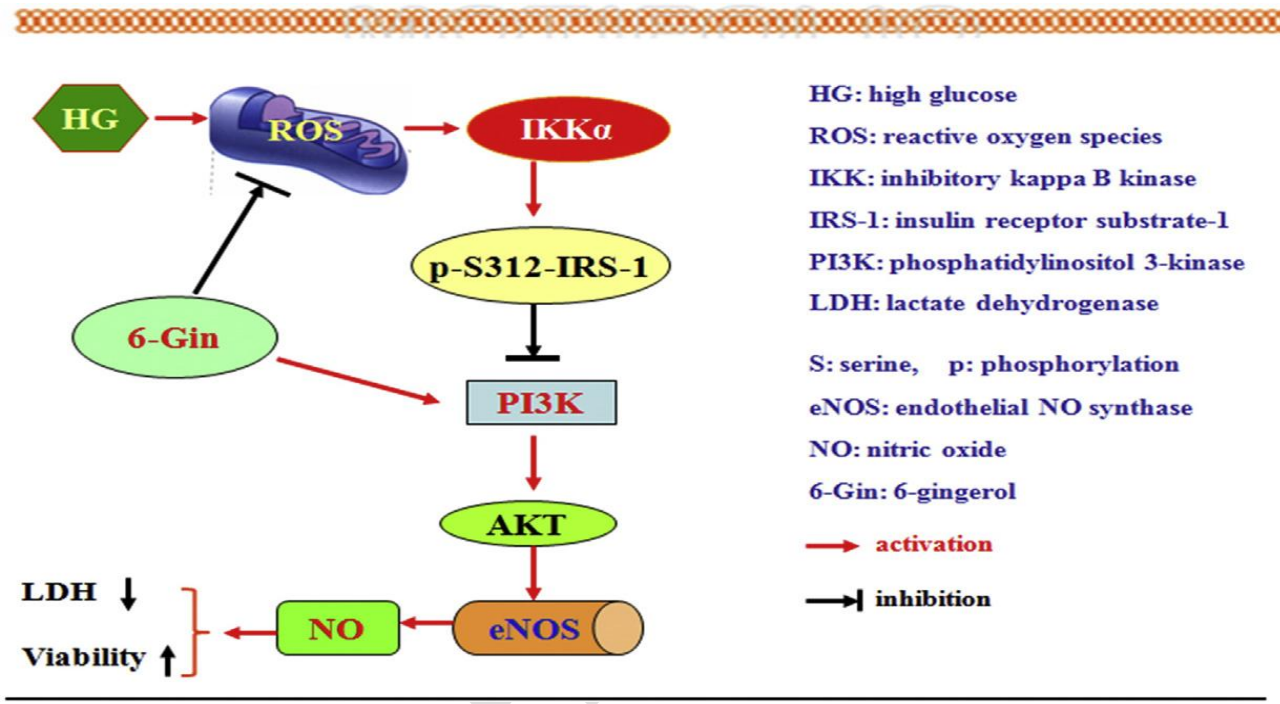

Fig.4. Schematic diagram for 6-Gingerol (6-Gin) putative action mechanism. Under the condition of HG, endothelial cells produce a lot of ROS in mitochondria, and ROS triggers IKK. Triggered IKK phosphorylates IRS-1 at serine 312. Phosphorylated IRS-1 hinders the PI3K-AKT-eNOS-NO pathway and eventually results in the injury of endothelial cells. 6-Gingerol plays protective roles in the injury of endothelial cells induced by HG by two means. One is by decreasing the ROS production and the other by activating the PI3K-AKT- eNOS pathway[45].

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3.0 ANTI-INFLAMMATORY EFFECT

Ginger is notable for its helpful use in inflammatory disorders [46], and 6-gingerol is one of the dynamic constituents accountable for these properties. The cytokines tumor necrosis factor, TNF-α, and interleukin (IL)-1β are an indication of as alert cytokines to start inflammatory cell enlistment by invigorating the expression of pro-inflammatory genes [47]. Besides, mitogen-activated protein kinase phosphatase-5 (MKP5) has a valuable role in facilitating the anti-inflammatory activities. It was stated for that TNF-α and IL-1β can upsurge p38-dependent nuclear factor kappa-β (NFkβ) activation and expression of the pro-inflammatory genes cyclooxygenase-2 (COX-2), IL-6 and IL-8 in normal prostatic epithelial cells. 6-Gingerol can up-regulate MKP5, and lessening cytokine-induced p38-dependent pro-inflammatory changes [48].

4.0 ANTIOXIDANT EFFECT

Since 6-gingerol is a natural anti-oxidant, it is suggested for the avoidance of numerous illnesses. The anti-oxidant effect properties of the phenolic compound might be identified with its capacity to give electrons and to go about as a free radical scavenger by the development of a stable phenoxyl radical [49]. The pretreatment of 6-Gingerol is important for the protection of Aβ-induced cytotoxicity and apoptotic cell demise. For the mechanism, 6-gingerol successfully diminished the level of reactive oxygen and additionally nitrogen species and returned anti-oxidant glutathione levels. The mRNA and protein expression of antioxidant enzymes such as γ-glutamylcysteine ligase (GCL) and heme oxygenase-1 (HO-1) were up-regulated by 6-gingerol [50].

This recommended that 6-gingerol lessened Aβ-induced oxidative cell demise fortifying the cellular antioxidant protective mechanism. Kuhad *et al.* revealed that 6-gingerol could act against cisplatin-induced oxidative stress and renal dysfunctions in rats. As a powerful antioxidant, meaningfully returned renal capacities, decreased lipid peroxidation and expanded the levels of glutathione and role of superoxide dismutase and catalase [51]. Also, 6-gingerol can diminish peroxidation of phospholipid liposomes within the sight of iron (III) and ascorbate [52]. Park et al. discovered that ROS are delivered during the phenotypic change of fibroblasts to myofibroblasts, a cycle that is engaged with the development of nasal polyps by prompting extracellular network (ECM)

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accumulation. In another investigation, sodium arsenite (iAs) was utilized to incite stress mediated impaired insulin signaling in mice. 6-Gingerol decreased raised blood glucose level and oxidative stress by expanding the degree of super oxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and GSH [53]. Consequently, 6-gingerol may become a significant natural antioxidant food additive.

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Table. 1. The Medicinal Value of 6-Gingerol in Human and Animal Health

Findings/outcomes	Study Type	Diseases	Pharmacological Actions	Reference
Significantly improved overall complete response rate in chemotherapy-induced nausea and vomiting.	Human Study *in vivo*	Cancer	Chemotherapeutic	54
Attenuates ischemia-reperfusion-induced cell apoptosis in human AC16 cardiomyocytes.	Human *In vitro*	Myocardial Ischemia	Anti-Apoptotic, Cardio protective	55
Prevent and treat the angiopathy resulting from diabetes mellitus.	Human *In vitro*	Diabetic Complications	Anti-inflammatory	56
Abates benzo[a]pyrene-induced colonic injury.	Animal study *in vivo*	Colonic injury	Anti-inflammatory	57
Alleviates inflammatory injury in DSS-induced ulcerative colitis.	Animal study *in vivo*	Ulcerative Colitis	Anti-inflammatory	58
Ameliorates age-related hepatic steatosis	Animal study *in vivo*	HepaticSteatosis	Antioxidants, Hepatoprotective	59
Attenuates LPS-induced neuroinflammation and cognitive impairment.	Animal study in vitro	Brain inflammation	Anti-inflammatory	60
Exerted protective influence against ulcerative colitis-induced testicular damage.	Animal study *in vivo*	Ulcerative Colitis	Anti-inflammatory	61
Exerts anti-inflammatory effects and protective properties on LTA-induced mastitis.	Animal study *in vivo*	Mastitis	Anti-inflammatory	62
A novel anti-inflammatory agent for the treatment of autoimmune diseases such as multiple sclerosis.	Animal study *in vivo*	Multiple Sclerosis	Anti-inflammatory	63
Induces cell-cycle G1-phase arrest through AKT-GSK 3β-cyclin D1 pathway in renal-cell carcinoma.	Animal study *in vitro*	Kidney cancer	Anti-proliferative	64
A potential therapeutic agent for the treatment of atherosclerosis.	Animal study *in vivo*	Atherosclerosis	Anti-atherogenic	65
Useful in the prevention and treatment of alzheimer's disease.	Animal study *in vivo*	Alzheimer's Disease,	Neuroprotective	66

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Protects heart by suppressing myocardial ischemia/reperfusion induced inflammation.	Animal study *in vivo*	Myocardial Ischemia	Cardio protective	67
Asthma-alleviating potential of 6-gingerol.	Animal study *in vivo*	Asthma	Anti-asthmatic	68
Exhibits potent anti-mycobacterial and immunomodulatory activity against tuberculosis.	*In vitro* study	Tuberculosis	Immunomodulatory	69
Potential use in treating inflammatory bone destruction associated with excessive prostaglandin E2 production.	*In vitro* study	Inflammation	Anti-inflammatory	70
Normalizes the expression of biomarkers related to hypertension.	*In vitro* study	Hypertension	Antihypertensive	71
6-Gingerol with 5-flourouracil and paclitaxel resulted in 83.2% and 52% inhibition of cervical cancer cells.	*In vitro* study	Cervical cancer	Chemotherapeutic	72
Exerts protective effects against ischemia reperfusion induced intestinal mucosa injury.	Animal study *in vivo*	Ischemia	Anti-oxidant	73
Protects cardiocytes H9c2 against hypoxia-induced injury by suppressing BNIP3 expression.	*In vitro* study	Hypoxia	Autophagy	74
Ameliorates isoproterenol -induced myocardial fibrosis.	*In vitro* study	Myocardial fibrosis	Anti-Fibrotic,	75
Ameliorates sepsis-induced liver injury through the Nrf2 pathway.	*In vitro* study	Sepsis	Hepatoprotective	76
Appears to be a safe and potent chemotherapeutic/chemo preventive compound. JAN 06, 2016	*In vitro* study	Cervical cancer	Chemopreventive	77
Effectively used for targeting the mitochondrial energy metabolism to manage gastric cancer cells.	*In vitro* study	Gastric cancer	Anti- proliferative ,	78
Modulate the anti-inflammatory responses triggered by V. cholera-induced infection.	*In vitro* study	Cholera	Anti-inflammatory	79
Enhances the cisplatin sensitivity of gastric cancer cells.	*In vitro* study	Gastric cancer	Chemotherapeutic	80
Enhances the radio sensitivity of gastric cancer cells.	*In vitro* study	Gastric cancer	Apoptotic, Radiosensitizer	81
Protective effects on chlorpyrifos induced toxicity in the brain and reproductive organs of rats.	Animal study *in vivo*	Pesticide Toxicity	Neuroprotective	82
Showed efficacy in the treatment of DSS-induced ulcerative colitis.	Animal study *in vivo*	Ulcerative Colitis	Anti-inflammatory	83
Ameliorates carbendazim-induced endocrine disruption.	Animal study *in vivo*	Endocrine imbalances	Endocrine Disrupting Chemicals (EDCs)	84

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5.0 CONCLUSION

Utilization of regular treatments, for example, phytochemical constituents, isolated from herbal medicine, to combat different kindes of diseases has pulled in the consideration of the scientific and medical communities because of their minimal side effects and lower cost. In this specific situation, 6-gingerol, a flavonoid anti-oxidant and the promising constituent of ginger, has been perceived and utilized as an elective medication in treating various diseases, alone or in blend with other chemotherapeutic medications. It shows significant anti-oxidant not only this but also it has anti-inflammatory activities that could be utilized in forestalling and treating diseases. Ginger is among the most sound and regularly devoured dietary sauces on the planet. One of the major impactful components of ginger, 6-gingerol, is suggested for the avoidance of malignancy and different maladies.

Past work, summed up above has exhibited numerous systems engaged with the effect of 6-gingerol. Nonetheless, a large portion of the investigations with this compound have been made *in vitro* and with laboratory animals. In this way, additional investigations on determining the effect of 6-gingerol ought to embrace human intervention trails. Nevertheless, further mechanistic work is needed to explain the molecular mechanism underlying the impacts of 6-gingerol on gene expression, the signaling pathway, and efficacious protein included. In general, 6-gingerol can be a significant complementary medication for protection and therapy of various types of disease, attributable to its natural origin, safety, and its cost effectiveness relative to synthetic drugs. And also 6-gingerol could along these lines give a valuable part of dietary or pharmacological treatment for additional drug formulation to create novel and powerful clinical competitors.

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DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable

ETHICAL APPROVAL

It is not applicable

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