



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

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Authors' contributions

This work was carried out in collaboration among all authors. Author GTB is the first and corresponding author designed the review and wrote the first draft of the manuscript. Authors BAT, PH and FMN managed the literature searches and critically revised the intellectual content. All authors read and approved the final manuscript.

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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 to bring down harmful effects 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 commonly 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 and 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 effects 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

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security for human use, 6-gingerol has gained impressive enthusiasm as an expected helpful operator for the anticipation and additionally treatment for different maladies. Taken together, this review sums up the different *in vitro* and *in vivo* pharmacological aspects of 6-gingerol and their underlying mechanisms.

Keywords: Anticancer activity; anti-inflammatory activity; anti-oxidant activity; ginger; 6-Gingerol.

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 harmful effects as much as possible [1]. The presence of 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*), 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 incorporated in ginger rhizomes. The non-volatile and impactful phytochemicals comprising in ginger are gingerols, shogaols, paradols and zingerone [4,5]. Many investigations recommended that individuals in South East Asian nations have a much lower incidence of colon, gastrointestinal, prostate, breast and other cancers than their western partners. Thus, 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 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 (Fig. 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 effects against a wide scope of cells by repressing different endurance pathways

including NF-KB and β -catenine [10]. Like capsaicin, it has additionally increased intracellular accumulation of daunorubicin and rhodamine 123 by blocking the P-glycoprotein (p-gp) inhibition effect in multidrug-resistant human carcinoma KB-C2 cells. It has improved the poisonousness of vinblastine in KB-C2 cells through P-glycoprotein (p-gp) restraint [11]. Nonetheless, the accessible reported data are not adequate to clarify the mechanism of P-glycoprotein (p-gp) restraint by 6-gingerol.

6-Gingerol has been accounted for having an assortment of remedial properties including anticancer, anti-oxidant, anti-inflammation, anti-platelet aggregation and antifungal properties [12-14]. The objective 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. On an account of high demise rate related with cancer and high side effects of chemotherapy and radiation treatment, numerous patients look for alternative strategies for therapy. Plant sources 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 significance of ginger has been expanded as a result of its low poisonousness and its wide range of organic and pharmacological applications [15-20].

2. ANTICANCER EFFECTS

The different phytochemical composition present in ginger 6-gingerol is the most strong and pharmacologically active biomolecules and have anti-tumor and anti-proliferative properties. Due to this reason, 6-gingerol is a preferred target for anti-cancer drug development studies. The result of Pharmacological studies reported that the 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 6-gingerol protects from cancer are not yet known.

2.1 Apoptosis (Program Cell Death)

6-Gingerol is known to facilitate its anticancer properties by encouraging apoptosis [26]. 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 to 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 result 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 and team, the mouse skin carcinogenesis model was utilized. Topical treatment with 6-gingerol (2.5 μ M/animal) was injected to the mouse 30 min earlier and post to benzo[a]pyrene (B[a]P) (5 μ g/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]. Fig. 2. describes the projected pathway of 6-gingerol-

induced autophagy in HUVECs with the reported evidences on its action against apoptosis.

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 about the cytotoxic impacts of 6-gingerol on various cancer cells *in vitro* and *in vivo*. It was found to show dose-dependent blocking impacts on human promyelocytic leukemia (HL-60) cell growth [33]. 6-Gingerol has revealed cytotoxic effects 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 by Eok-Cheon Kim and coworkers revealed that the 6-gingerol had an inhibitory effect on angiogenesis *in vitro* and *in vivo*. It is evidenced by hinderance of the multiplication and tube formation of human endothelial cells in retort of vascular endothelial growth factor *in vitro* [37]. Fig. 3 depicts about the action of 6-gingerol hindering the cancer progression, angiogenesis and metastasis with the supporting reports.

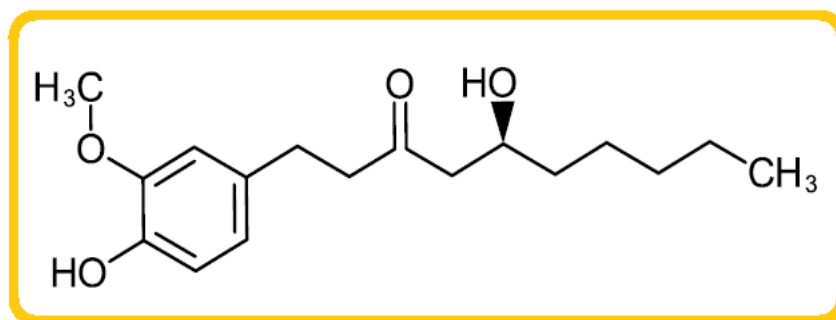


Fig. 1. The chemical structure of 6-gingerol (<http://www.chemspider.com/Chemical-Structure.391126.html>)

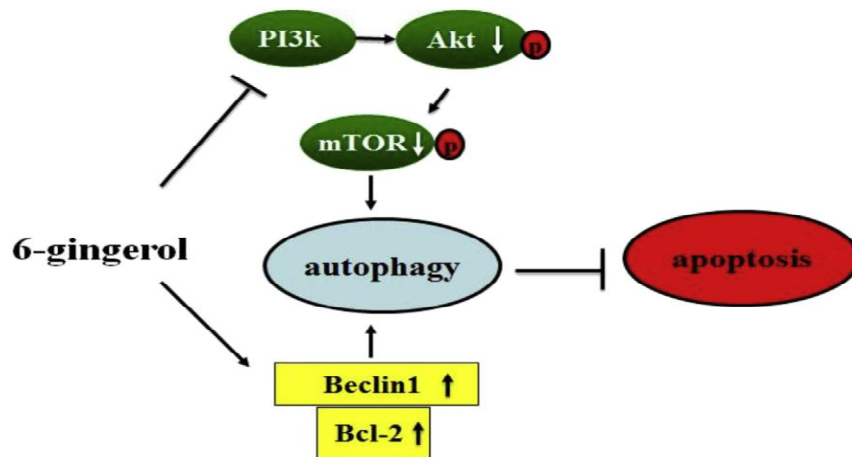


Fig. 2.The projected pathway of 6-gingerol-induced autophagy in HUVECs. 6-gingerol can pledge an autophagic existence response against apoptosis. 6-gingerol encourages the activation of Beclin1, and hinders the PI3K/AKT/mTOR signaling pathway to promote autophagy [38-39]

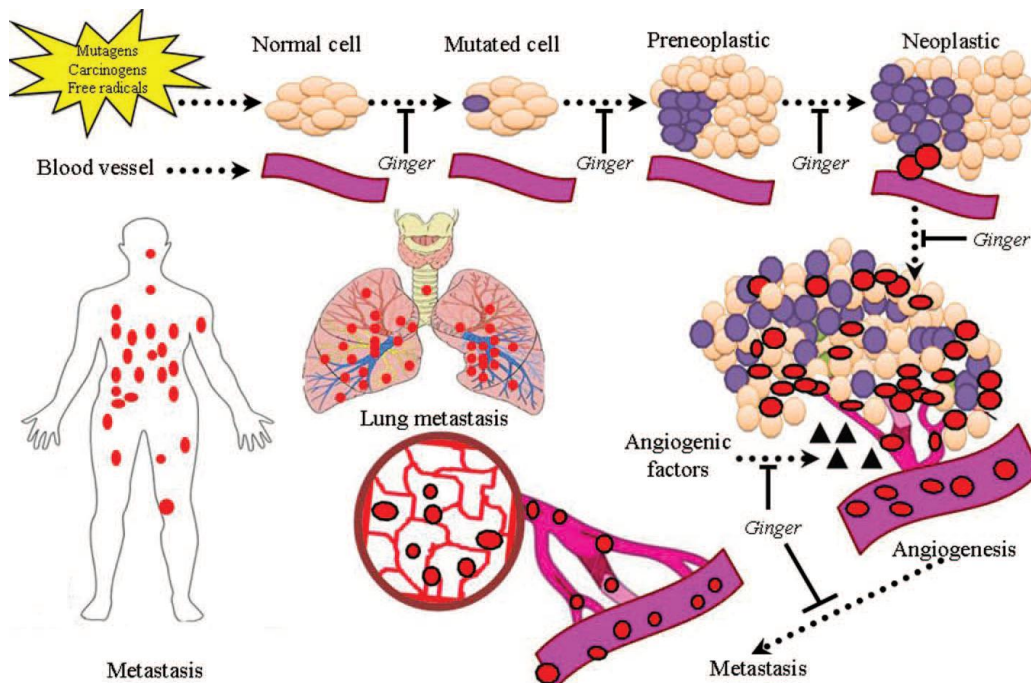


Fig.3.Depiction of 6-gingerol hindering cancer progression, angiogenesis and metastasis [40-44]. Ginger extract and 6-gingerol is reported to prevent the angiogenesis process by reducing the secretion of VEGF [40,41]. 6-Gingerol also reported about blocking VEGF- and bFGF-induced proliferation [42], hindering the pulmonary metastasis [43] by declining the activities of MMP-2 or MMP-9. All these results cumulatively propose that 6-gingerol acts as a preventive agent for malignancy by selectively blocking angiogenesis, adhesion, invasion, motility and production of MMPs at the tumor site [44]. Sung and his colleagues have reported that Zerumbone has also shown to down-regulate the expression of CXCR4 in the HER2-overexpressing breast cancer cells which concurrently caused preventing of CXCL12-induced invasion of breast and pancreatic cancer cells [38]

Table1. The medicinal values of 6-gingerol in human and animal health as per published literature

Findings/outcomes	Study Type	Date of publication	Diseases	Pharmacological Actions	Reference
Significantly improved overall complete response rate in chemotherapy-induced nausea and vomiting.	Human Study <i>In vivo</i>	Mar 31, 2017	Cancer	Chemotherapeutic	54
Attenuates ischemia-reperfusion-induced cell apoptosis in human AC16 cardiomyocytes.	Human <i>In vitro</i>	Dec 31, 2018	Myocardial Ischemia	Anti-Apoptotic, Cardio protective	55
Prevent and treat the angiopathy resulting from diabetes mellitus.	Human <i>In vitro</i>	Aug 31, 2017	Diabetic Complications	Anti-inflammatory	56
Abates benzo[a]pyrene-induced colonic injury.	Animal study <i>In vivo</i>	Apr 17, 2019	Colonic injury	Anti-inflammatory	57
Alleviates inflammatory injury in DSS-induced ulcerative colitis.	Animal study <i>In vivo</i>	Jul 13,2020	Ulcerative Colitis	Anti-inflammatory	58
Ameliorates age-related hepatic steatosis	Animal study <i>In vivo</i>	Dec31,2018	HepaticSteatosis	Antioxidants, Hepatoprotective	59
Attenuates LPS-induced neuroinflammation and cognitive impairment.	Animal <i>in vitro</i>	Oct 31,2018	Brain inflammation	Anti-inflammatory	60
Exerted protective influence against ulcerative colitis-induced testicular damage.	Animal study <i>In vivo</i>	Dec31,2016	Ulcerative Colitis	Anti-inflammatory	61
Exerts anti-inflammatory effects and protective properties on LTA-induced mastitis.	Animal study <i>In vivo</i>	May 25,2020	Mastitis	Anti-inflammatory	62
A novel anti-inflammatory agent for the treatment of autoimmune diseases such as multiple sclerosis.	Animal study <i>In vivo</i>	Jul16,2019	Multiple Sclerosis	Anti-inflammatory	63
Induces cell-cycle G1-phase arrest through AKT-GSK 3 β -cyclin D1 pathway in renal-cell carcinoma.	Animal <i>in vitro</i>	Dec 11, 2019	Kidney cancer	Anti-proliferative	64
A potential therapeutic agent for the treatment of atherosclerosis.	Animal study <i>In vivo</i>	March 30,2018	Atherosclerosis	Anti-atherogenic	65
Useful in the prevention and treatment of alzheimer's disease.	Animal study <i>In vivo</i>	March 25, 2015	Alzheimer's Disease,	Neuroprotective	66
Protects heart by suppressing myocardial ischemia/reperfusion induced inflammation.	Animal study <i>In vivo</i>	Dec31,2017	Myocardial Ischemia	Cardio protective	67
Asthma-alleviating potential of 6-gingerol.	Animal study <i>In vivo</i>	Dec31,2018	Asthma	Anti-asthmatic	68
Exhibits potent anti-mycobacterial and immunomodulatory activity against tuberculosis.	<i>In vitro</i> study	Jul17,2020	Tuberculosis	Immunomodulatory	69
Potential use in treating inflammatory bone destruction associated with excessive prostaglandin E2 production.	<i>In vitro</i> study	Jul15,2018	Inflammation	Anti-inflammatory	70
Normalizes the expression of biomarkers related to hypertension.	<i>In vitro</i> study	Dec31,2017	Hypertension	Antihypertensive	71
6-Gingerol with 5-flourouracil and paclitaxel resulted in 83.2% and 52% inhibition of cervical cancer cells.	<i>In vitro</i> study	Feb26, 2017	Cervical cancer	Chemotherapeutic	72
Exerts protective effects against ischemia reperfusion induced intestinal mucosa injury.	Animal study <i>In vivo</i>	Feb03, 2017	Ischemia	Anti-oxidant	73
Protects cardiocytes H9c2 against hypoxia-induced injury by suppressing BNIP3 expression.	<i>In vitro</i> study	Nov30,2019	Hypoxia	Autophagy	74
Ameliorates isoproterenol -induced myocardial fibrosis.	<i>In vitro</i> study	Jun30, 2020	Myocardial fibrosis	Anti-Fibrotic,	75
Ameliorates sepsis-induced liver injury through the Nrf2 pathway.	<i>In vitro</i> study	Jan20, 2020	Sepsis	Hepatoprotective	76
Appears to be a safe and potent chemotherapeutic/chemo	<i>In vitro</i> study	Jan06, 2016	Cervical cancer	Chemopreventive	77

Findings/outcomes	Study Type	Date of publication	Diseases	Pharmacological Actions	Reference
preventive compound. JAN 06, 2016					
Effectively used for targeting the mitochondrial energy metabolism to manage gastric cancer cells.	<i>In vitro</i> study	Aug07,2018	Gastric cancer	Anti- proliferative ,	78
Modulate the anti-inflammatory responses triggered by V. cholera-induced infection.	<i>In vitro</i> study	Mar17,2016	Cholera	Anti-inflammatory	79
Enhances the cisplatin sensitivity of gastric cancer cells.	<i>In vitro</i> study	Feb26, 2019	Gastric cancer	Chemotherapeutic	80
Enhances the radio sensitivity of gastric cancer cells.	<i>In vitro</i> study	Apr30,2018	Gastric cancer	Apoptotic, Radiosensitizer	81
Protective effects on chlorpyrifos induced toxicity in the brain and reproductive organs of rats.	Animal study <i>In vivo</i>	May24,2017	Pesticide Toxicity	Neuroprotective	82
Showed efficacy in the treatment of DSS-induced ulcerative colitis.	Animal study <i>In vivo</i>	Mar31,2020	Ulcerative Colitis	Anti-inflammatory	83
Ameliorates carbendazim-induced endocrine disruption.	Animal study <i>In vivo</i>	Aug21,2016	Endocrine imbalances	Endocrine Disrupting Chemicals (EDCs)	84

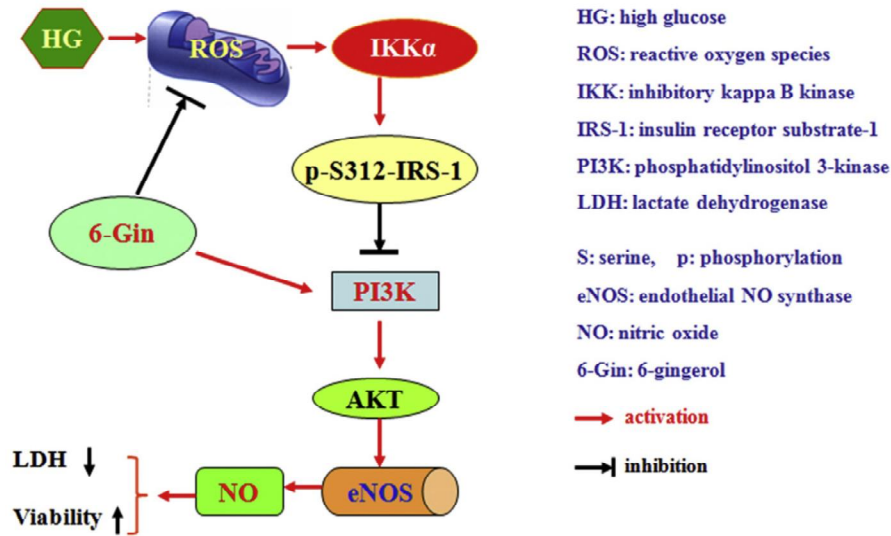


Fig. 4. Schematic diagram for 6-gingerol (6-Gin) putative action mechanism. Under the condition of High Glucose, endothelial cells produce a lot of Reactive Oxygen Species (ROS) in mitochondria and ROS triggers IKK. Triggered IKK phosphorylates IRS-1 at serine 312. Phosphorylated IRS-1 hinders the PI3K-AKT-eNOS-NO 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 is by activating the PI3K-AKT- eNOS pathway [45]

3. 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)-1 β are an indication of alerting 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 is reported that TNF- α and IL-1 β can upsurge p38-dependent nuclear factor kappa- β (NF κ B) activation and expression of the pro-inflammatory genes cyclooxygenase-2 (COX-2), IL-6 and IL-8 are in normal prostatic epithelial cells. 6-Gingerol can up-regulate MKP5 and lessen cytokine-induced p38-dependent pro-inflammatory changes [48].

4. ANTIOXIDANT EFFECT

The natural antioxidant property of 6-gingerol suggests that it avoids 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]. Figure 4 summarizes the mechanism of protection by 6-gingerol for putative action against injury to the cells. The pretreatment of 6-Gingerol is important for the protection of A β -induced cytotoxicity and apoptotic cell demise. For this mechanism, 6-gingerol has successfully diminished the level of reactive oxygen and additionally nitrogen species and returned the 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 A β -induced oxidative cell demise fortifying the cellular antioxidant protective mechanism. Kuhad and his team portrayed that 6-gingerol could act against cisplatin-induced oxidative stress and renal dysfunctions in rats. As a powerful antioxidant, it meaningfully returned renal capacities, decreased lipid peroxidation and expanded the levels of glutathione and role of superoxide dismutase and catalase [51]. Also, 6-gingerol could diminish peroxidation of phospholipid liposomes within the sight of iron (III) and ascorbate [52]. Park and his coworkers

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) accumulation. In another investigation, sodium arsenite (iAs) was utilized to incite stress mediated impaired insulin signaling in mice. 6-Gingerol impacted by decreasing the 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. The description of the research results reported by various research studies on the effect of 6-gingerol both *in vitro* and *in vivo* are tabulated in Table 1 [54-84].

5. CONCLUSION

Utilization of regular treatments, for example, phytochemical constituents, isolated from herbal medicine, to combat different kinds 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 antioxidant and the promising constituent of ginger, has been perceived and utilized as an elective medication in treating various diseases, alone or in blending with other chemotherapeutic medications. Besides showing significant antioxidant activity, it has anti-inflammatory activities also which could be utilized in forestalling and treating diseases. Ginger is among the most commonly 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. In summation of the past studies, enormous effects of 6-gingerol has been exhibited in curing various maladies. 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 dissection studies underlying the impacts of 6-gingerol on gene expression, the signaling pathway, and involvement of efficacious protein. With all these authentic information available on 6-gingerol, it can be a significant complementary medication for health protection and significant therapy for various types of diseases, attributable

to its natural origin, safety and its cost effectiveness relative to synthetic drugs. 6-gingerol could also be a valuable part of dietary or pharmacological treatment for additional drug formulation to create novel and powerful clinical competitors.

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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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