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Review Article:

Zingiber officinale (Ginger): A Comprehensive Review of Its Therapeutic Potential

Reyam Oday Hatim [1], Zaid Muwafaq Younus [1], Mohannad Emad Qazzaz [1], Rima Atallah Hijazeen [2]

[1] *Department of Pharmacognosy and Medicinal Plants, College of Pharmacy, University of Mosul, Mosul, Iraq.*
[2] *Department of Biopharmaceutics and Clinical Pharmacy, Faculty of Pharmacy, University of Jordan, Amman 11942 Jordan.*

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Abstract

Background: Officially called (*Zingiber officinale Roscoe*), which is ginger, is a commonly used spice that is easily accessible. As a ginger spice, it contains various chemical constituents, including phenolic compounds, terpenes, polysaccharides, lipids, organic acids, and raw fibers. **Aim:** In this review, we describe the latest data on ginger's bioactive constituents, which incorporate ginger biochemicals and ginger bioactivities and their actions. The review will also discuss certain therapeutic applications of ginger in light of the current available literature. **Methods:** The reviewed data were abstracted utilizing scientific platforms, including Web of Science, Scopus, and Google Scholar. **Results:** The health benefits of ginger are primarily attributed to the phenolic compounds gingerols and shogaols. Ginger exhibits multiple biological activities, including antioxidant, anti-inflammatory, antimicrobial, anticancer, neuroprotective, and cardiovascular protective properties. Additionally, ginger has respiratory protective, anti-obesity, antidiabetic, as well as anti-nausea and antiemetic effects. **Conclusion:** According to this review, ginger has a great bioactive profile, and its active components have positive therapeutic effects.

1. Introduction

Ginger (Gn), scientifically known as *Zingiber officinale Roscoe*, belongs to the Zingiberaceae family and has been utilised for centuries both as a culinary spice and a herbal remedy (1). It is widely recognized for alleviating and managing common ailments such as headaches, colds, nausea, and vomiting. Ginger contains various bioactive compounds, primarily terpenes and phenolics, which have been extensively studied. Notably, ginger's diverse biological activities are largely attributed to its phenolic components, including gingerols, shogaols, and paradols (2).

Research in recent years has highlighted ginger's biological properties, particularly its anti-inflammatory, antimicrobial, antioxidant, and anti-cancer effects (3). Moreover, accumulating evidence supports ginger's preventive and therapeutic potential for various conditions, such as neurological disorders, overweightness, diabetes mellitus, cardiovascular disorders, chemotherapy-induced nausea and vomiting, and lung ailments (4). This review focuses on the active constituents and biological activities of Gn, with an emphasis on its underlying mechanisms of action.

Given its pharmacological and physiological potential, research exploring the health benefits of Gn has seen a dramatic increase. Numerous randomized clinical trials (RCTs) have been conducted to evaluate the therapeutic benefits of Gn, particularly in symptom relief. For example, many of these trials evaluated the effect of Gn supplements in reducing nausea, vomiting, and dysmenorrhea caused by chemotherapy in cancer patients. Additionally, numerous systematic reviews and meta-analyses (SR-MAs) have been conducted to evaluate the clinical efficacy of Gn. Clinical studies indicate that Gn supplementation may reduce inflammation and relieve joint pain, although a study found no significant impact on relief of pain or life

***Corresponding author:** *Zaid Muwafaq Younus, Department of Pharmacognosy and Medicinal Plants, College of Pharmacy, University of Mosul, Mosul, Iraq.*
Email: z.m.younus@uomosul.edu.iq

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quality (5). Two trials assessed ginger's effect on rheumatoid arthritis (RA), while others focused on knee osteoarthritis (OA). Treatment durations ranged from two weeks to three months, involving both the Gn and placebo groups. Two trials demonstrated that 750 mg of Gn powder, taken twice daily, reduced the expression of inflammation-related genes in RA patients who were also taking medications such as methotrexate, hydroxychloroquine, and prednisolone(6). A similar anti-inflammatory effect was seen in OA patients, where 1 g of Gn powder taken for three months decreased pro-inflammatory cytokine production (7). Additionally, in OA patients, Gn extract lowered NO and CRP levels after three months, with further reductions observed over 12 months (8).

2. Phytochemical composition of ginger

Members of the Zingiberaceae family, such as Gn (Zingiber officinale), are extensively utilized as culinary spices worldwide, particularly in many Asian countries (9). Gn is rich in active compounds, notably phenolic and terpene constituents. Among its phenolic compounds, gingerols, shogaols, and paradols are predominant. **Figure 1** shows the chemical forms of the key gingerols and shogaols present in Gn. Fresh Gn primarily contains polyphenols known as gingerols, including 6-gingerol, 8-gingerol, and 10-gingerol, which can convert into corresponding shogaols through heat processing or prolonged storage (10). Shogaols may further transform into paradols via hydrogenation. Additionally, Gn encompasses a broad range of other phenolic compounds, such as 6-dehydrogingerdione, zingerone, quercetin, and gingerenone-A.

The prominent essential oil constituents of Gn are β-bisabolene, α-curcumene, zingiberene, α-farnesene, and β-sesquiphellandrene. Moreover, Gn includes lipids, organic acids, polysaccharides, raw fibers. There is a comprehensive chemical analysis of over 400 unique compounds within ginger, marking its carbohydrates (50-70%), lipids (3-8%), several terpenes and phenolic compounds as dominant components (11).

Zingiberene, β-bisabolene, α-farnesene, β-sesquiphellandrene, and α-curcumene are classified as key terpene constituents while gingerol, paradols, and shogaol are phenolic compounds. Certain Gn varieties exhibit higher concentrations of gingerols (23-25%) and shogaols (18-25%). Additional constituents include amino acids, minerals, ash, proteins, phytosterols, and vitamins (such as vitamin A and nicotinic acid) (12). Terpenes like zingiberene and bisabolene contribute to the aromatic characteristics, while gingerols and shogaols account for its pungency.

Furthermore, compounds related to gingerol and shogaol (1-10%) have been identified in Gn rhizomes, including diarylheptanoids, 6-paradol, 1-dehydrogingerdione, 6-gingerdiol, 10-gingerdione, 4-gingerdiol, 6-gingerdiol, 8-gingerdiol, and 10-gingerdiol. The distinctive flavor and aroma of ginger are attributed to a mix of volatile oils, including shogaols and gingerols (13).

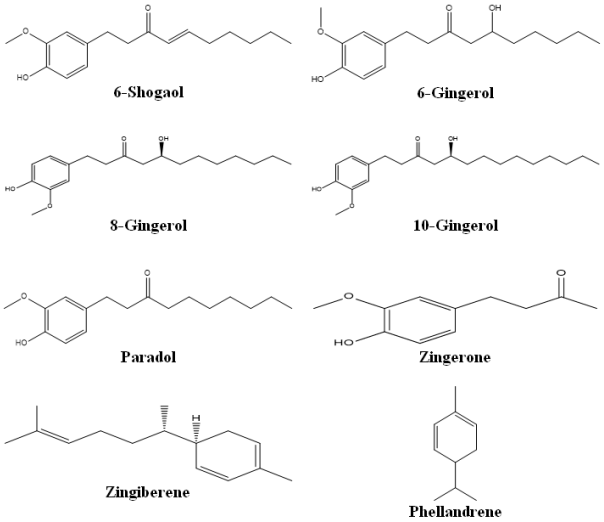

Figure 1. Chemical components of ginger (13)

Masuda and colleagues suggested that the scavenging power of gingerol and its relatives arises from the specific groups attached to their long carbon tails (13). Most of the over fifty compounds found in Gn oil are short-chain monoterpenes and slightly heavier sesquiterpenes (13).

3. Bioactivities of ginger

3.1. Antioxidant activity

The excessive production of free radicals, particularly reactive oxygen species (ROS), is recognized as a substantial factor in the numerous chronic diseases (14). Various natural constituents, including fruits, flowers, cereals, vegetables, and pharmacological plants have been shown to exhibit free radical scavenging properties (15). Research indicates that Gn also possesses strong antioxidant (antOx) activity (16). The antOx capacity of Gn has been estimated in vitro using the ferric-reducing antioxidant power (FRAP),2,2-diphenyl-1-picrylhydrazyl (DPPH), and 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays. Findings reveal that dried Gn exhibits the highest antOx activity, with phenolic content (5.2), and (2.4) times greater than moist and carbonized Gn, in a raw state (17). This is primarily associated with the polyphenolic content of each form.

Heating fresh Gn reduces moisture and results in dried Gn with elevated antOx activity. However, further heating to obtain carbonized Gn reduces antOx activity due to the conversion of gingerols into shogaols (18). Also, dried Gn powder fractions rich in polyphenols demonstrated high antOx activity in FRAP, oxygen radical absorbance capacity, and cellular antOx activity assays (19). A solvent used for constituents' extraction also influences the antOx potential. Ethanolic Gn extracts show significant Trolox-equivalent antOx capacity and ferric-reducing ability, while inorganic (aqueous) extracts display strong radical scavenging and metal-chelating activity (20). Additionally,

organic (hexane, methanolic, ethanolic, ethyl acetate) and aqueous Gn's extracts suppressed human LDL oxidation by Cu2+ at rates of 71%, 76%, 67%, 67%, and 43%, respectively (16). In the system of xanthine oxidase, aqueous and ethyl acetate extracts exhibited greater antOx effects compared to n-butanol, diethyl ether, and ethanol extracts (16). Numerous studies suggest Gn protects against oxidative stress (OS), with the mechanisms of antOx action examined in cellular system (16).

In chondrocytes of human, under OS induced by interleukin-1β (IL-1β), Gn extract showed antOx effects, enhancing the expression of antOx enzymes and reducing lipid peroxidation and reactive oxygen species generation (21). Gn's extract also decreased ROS levels in fibrosarcoma cells of human exposed to H2O2-induced OS (22). In stressed rat cardiac tissue, Gn extract lowered malondialdehyde (MDA) levels, an indicator of lipid peroxidation (21). Bioactive Gn constituents, such as 6-shogaol, exert antOx effects through the pathway named as Nrf2 signaling (22).

In human colon carcinoma cells, 6-shogaol increased the intracellular glutathione/glutathione disulfide (GSH/GSSG) ratio and upregulated some Nrf2 target genes like heme oxygenase-1 (HO-1), metallothionein 1 (MT1), aldo-keto reductase family 1 member B10 (AKR1B10), ferritin light chain (FTL), and gamma-glutamyltransferase domain containing protein 4 (GGTLA4) (22). 6-Shogaol additionally improved genes involved in synthesis of glutathione, like glutamate-cysteine ligase catalytic (GCLC) and modifier subunit (GCLM). This activation of Nrf2 was found to occur through cysteine residues alkylation on Kelch-like ECH-associated protein 1 (Keap1) (23).

Additionally, Gn phenylpropanoids were shown to stimulate Nrf2 activity, enhancing glutathione S-transferase P1 (GSTP1) and other Nrf2-responsive elements in foreskin fibroblasts (24). Gn oleoresin was tested in human mesenchymal stem cells for its protective effect against ionizing radiation-induced injury, and it lowered ROS levels by promoting Nrf2 translocation to the nucleus and upregulating HO-1 and NADPH quinone dehydrogenase 1 (NQO1) (23).

The antOx properties of Gn and its active compounds have also been investigated in animal models. For instance, 6-shogaol exhibited antOx effects in the colon of wild-type mice by inducing Nrf2 genes like GCLC, HO-1, and MT1, though these effects were absent in Nrf2-/- mice (23). In rats with diclofenac sodium-induced gastric ulcers, a butanol Gn extract prevented increases in MDA levels and decreases in catalase activity and glutathione levels (25). Additionally, 6-gingerol reduced MDA and H2O2 levels, enhanced antOx enzyme activity, and boosted glutathione in rats with chlorpyrifos-induced oxidative damage (23). Treatment with Gn extract also elevated serum testosterone and antOx levels and protected rat testes from cyclophosphamide-induced injury (26).

Collectively, both *in vivo* and *in vitro* studies demonstrate that Gn and its active components, such as 6-gingerol, oleoresin and 6-shogaol, own potent antOx activity. Activation of the Nrf2 signalling system appears to be essential for the antOx devices. It is worth noting, however, that while ROS overproduction is implicated in numerous diseases, the effectiveness of antOx may vary based on factors such as individual health conditions, lifestyle, diet, antOx solubility, dosage, and bioavailability, potentially explaining the limited efficacy of antOxs in real-world applications (**Figure 2**).

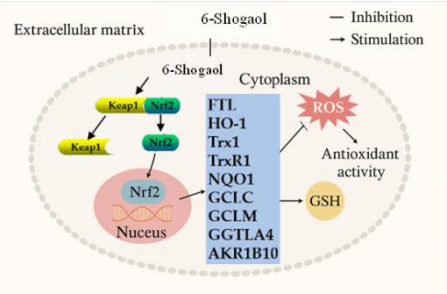

Figure 2: The plausible mechanism by which 6-shogaol can act as a potential antOx: 6-shogaol promotes the transportation of Nrf2 to the nucleus, enhancing the expression of Nrf2 target genes that are modified through the regulation of Keap1, which prevents the degradation of Nrf2 via proteasomes. Consequently, the amount of glutathione (GSH) increases while reactive oxygen species (ROS) diminish. Abbreviations: GCLC, glutamate-cysteine ligase catalytic subunit; Keap1, Kelch-like ECH-associated protein 1; HO-1, heme oxygenase-1; GCLM, glutamate-cysteine ligase modifier subunit; NQO1, AKR1B10, aldo-keto reductase family 1 member B10; NADPH-quinone oxidoreductase 1; TrxR1, thioredoxin reductase 1; ROS, reactive oxygen species; GSH, glutathione; GGTLA4, Gamma-glutamyltransferase-like activity 4; Nrf2, nuclear factor erythroid 2-related factor 2; Trx1, thioredoxin 1; FTL, ferritin light chain; ARE, antOx response element.

3.2. Anti-Inflammatory activity

Research indicates that Gn and its bioactive compounds exhibit significant anti-inflammatory (Antin) properties, which could improve the symptoms of diseases caused by inflammation, like colitis (27). The Antin effects of Gn are primarily related to the inhibition of pathways involving protein kinase B (Akt), phosphatidylinositol-3-kinase (PI3K), and nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB). 6-Shogaol, one of Gn's active components, has been disclosed to counteract tumor necrosis factor-alpha (TNF-α)-induced intestinal barrier dysfunction in the human intestinal cell system. It also prevents the upregulation of Claudin-2 and the disruption of Claudin-1 by suppressing the PI3K/Akt and NF-κB signaling pathways (27).

Additionally, 6-dehydroshogaol demonstrated greater potency than 6-shogaol and 6-gingerol in reducing the production of pro-inflammatory mediators, such as nitric oxide (NO) and prostaglandin E2 (PGE2), in mouse macrophage RAW 264.7 cells (27). Furthermore, Gn extract and zingerone inhibited NF-κB activation and reduced interleukin-1 beta (IL-1β) levels in the colons of mice, thereby alleviating 2,4,6-trinitrobenzene sulfonic acid-induced colitis (28).

Gn also offered protection against enteritis induced by anti-CD3 antibodies in mice, as it reduced TNF-α production along with NF-κB and Akt activation (28). Also,

nanoparticles resulting from Gn (GDNPs 2) were effective in preventing bowel inflammation by raising Antin cytokines, including IL-22 and IL-10, and reducing proinflammatory cytokines, like IL-1β, IL-6, and TNF-α, in rats with colitis (28). Nanoparticles carrying 6-shogaol result in to decrease in inflammatory bowel disease symptoms and promote wound healing in mice (29). Additionally, microRNAs within Gn exosome-like nanoparticles (GELN) improved inflammatory bowel disease symptoms in mice by promoting the creation of IL-22, which enhances the defence system (29). A fraction of Gn with a high ratio of 6-gingerol effectively stopped a rise in inflammatory factors, including nitric oxide, TNF-α, and myeloperoxidase, in the uterus, ovaries, and brain, of rats exposed to chlorpyrifos (29). In a study involving twenty-eight male runners, participants who ingested 500 mg of Gn exhibited reduced post-exercise elevations of pro-inflammatory cytokines, such as plasma TNF-α, IL-6, and IL-1β (30). Overall, Gn and its bioactive constituents have shown efficacy in reducing inflammatory symptoms, especially in cases of colitis. The mechanisms of Gn's Antin effects are thought to involve suppression of NF-κB and Akt activation, upregulation of Antin cytokines, and downregulation of pro-inflammatory cytokines. Notably, Gn -derived nanoparticles show promise in enhancing prevention and treatment strategies for colitis.

3.3. Antimicrobial activity

The rise in infectious diseases poses a significant public health concern, exacerbated by the growing problem of antimicrobial (AntiM) resistance. Numerous natural remedies have been utilized as AntiM agents that successfully work against various viral, bacterial, and fungal microorganisms (31). Research has shown that Gn can inhibit the proliferation of multidrug-resistant Pseudomonas aeruginosa by disrupting the integrity of the membrane (32). Gn extract has also been found to reduce biofilm formation by lowering the levels of bis-(3'-5')-cyclic dimeric guanosine monophosphate (c-di-GMP) in Pseudomonas aeruginosa PA14 (32).

Additionally, methanolic and crude extracts of Gn can downregulate the specific genes that could ultimately suppress glucan synthesis, adherence of Streptococcus mutans, and biofilm formation. These in vitro findings were consistent with results from an animal study, where a reduction in caries growth due to Streptococcus mutans was observed in rats (33). In another in vitro study, gingerenone-A and 6-shogaol demonstrated inhibitory effects on Staphylococcus aureus by reducing the activity of the bacterial enzyme 6-hydroxymethyl-7,8-dihydropterin pyrophosphokinase (33).

Gn essential oil, with its lipophilic properties, increases the permeability of fungal cell walls and membranes, leading to a loss of membrane integrity (33). Gn essential oil effectively inhibited the growth of Fusarium verticillioides by impairing ergosterol biosynthesis and affecting membrane integrity, as well as reducing fumonisin B1 and B2 production (34). It also showed the ability to suppress the growth of Aspergillus flavus, along with ergosterol and aflatoxin production (34).

The components gamma-terpinene and citral in Gn essential oil exhibit powerful antifungal effects against Aspergillus flavus, lowering the upregulation of genes interrelated to biosynthesis of aflatoxin (35). Fresh Gn has demonstrated efficacy in inhibiting plaque formation induced by human respiratory syncytial virus (HRSV) in cell lines of the respiratory tract, where it blocked viral internalization and attachment (35). In a clinical trial, Gn extract reduced hepatitis C virus (HCV) loads, levels of alpha-fetoprotein (AFP), and liver function markers, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), in Egyptian HCV patients (35).

In summary, Gn has shown inhibitory effects against various bacteria, fungi, and viruses, with mechanisms primarily involving inhibition of bacterial biofilm formation, ergosterol biosynthesis in fungi, and viral attachment and internalization.

3.4. Cytotoxicity

Cancer remains a leading cause of mortality (36). Research has shown that natural constituents possess antitumor properties (37). Recently, Gn has gained attention for its antineoplastic potential in various tumor types, including colorectal, prostate, cervical, and breast cancers (38). Gn's mechanisms involve inhibiting cancer cell proliferation and inducing apoptosis (**Figure 3**) (39). Several studies have shown that Gn and its active constituents suppress colorectal tumor progression. An in vitro research demonstrated that a polyphenol-rich extract of dried Gn inhibited gastric and colorectal tumor cell proliferation (39). Gn extract has also been shown to induce apoptosis in colorectal cancer cells by downregulating genes involved in the PI3K/Akt and Ras/ERK pathways, for example, ERK, Bcl-xL, Akt, and KRAS, and upregulating caspase 9 expression in HT-29 colorectal tumor cells (40).

In rats with colon cancer induced by 1,2-dimethylhydrazine, Gn extract-loaded alginate beads increased NADH dehydrogenase and succinate dehydrogenase activities (40). Furthermore, treatment with Gn-derived nanoparticles decreased cancer numbers and tumor loads in mice with colitis-associated tumor, alongside a reduction in proinflammatory cytokines and intestinal epithelial cell proliferation (40). In a clinical trial, Gn extract supplementation reduced proliferation markers, such as MIB-1 and telomerase reverse transcriptase, while increasing the expression of the pro-apoptotic gene Bax in the colonic mucosal membrane of patients with a high risk of colorectal malignancy (3).

Gn supplement also decreased cyclooxygenase-1 (COX-1) expression, suggesting its preventive potential in colorectal cancer (3). In prostate cancer research, Gn compounds such as 6-gingerol, 6-shogaol, 10-shogaol, and 10-gingerol have shown antitumor effects in human prostate malignancy by downregulating the expression of glutathione-S-transferase and multidrug resistance protein 1 (39). Binary combinations of Gn's bioactive constituents synergistically inhibited PC-3 prostate cancer cell

proliferation (41). In vivo studies have shown that natural Gn extract inhibited tumor growth in human prostate tumor xenografts in mice by 2.4-fold compared to a synthetic mixture of Gn components (41). 6-Shogaol was more effective than 6-gingerol and 6-paradol in inhibiting cell proliferation and stimulating apoptosis in prostate tumor, largely by suppressing STAT3 and NF-κB signaling and decreasing the expression of cyclin D1, survivin, c-Myc, and Bcl-2 while increasing expression of Bax (42).

Gn also reveals cytotoxic effects against other cancers, such as liver, pancreatic, cervical, and breast cancer. In vitro studies showed that 6-gingerol inhibited the proliferation of HeLa (human cervical cancer cells) and stimulated G0/G1 cell cycle arrest by reducing cyclin D1 and cyclin A levels. HeLa cells apoptosis was promoted by inhibiting mTOR signaling and upregulating caspase expression (42).

In a mouse model of breast cancer, Gn extract reduced tumor growth by activating AMPK and downregulating cyclin D1, while also increasing p53 expression and decreasing NF-κB in cancer cells (43). Also, 10-gingerol was effective in inhibiting the growth of breast carcinoma cells by inducing S-phase cell cycle arrest and leading to apoptosis (42). The Gn-derived Fluorescent carbon nanodots (C-dots) were found to successfully control cancer growth in nude mice. In vitro experiments showed that C-dots amplified ROS levels, upregulated p53 expression, and induced apoptosis in HepG2 cells in nude mice (43). Gn extract and 6-shogaol inhibited the proliferation of pancreatic tumor cells, inducing caspase-independent cell death and ROS-mediated, and reduced cancer cells' growth in pancreatic tumor models without significant negative consequences (43).

Other studies demonstrate that Gn has preventive in addition to therapeutic effects against various cancers, including colorectal, prostate, breast, cervical, liver, and pancreatic cancers. Its anticancer mechanisms predominantly involve apoptosis induction and inhibition of cancer cell proliferation.

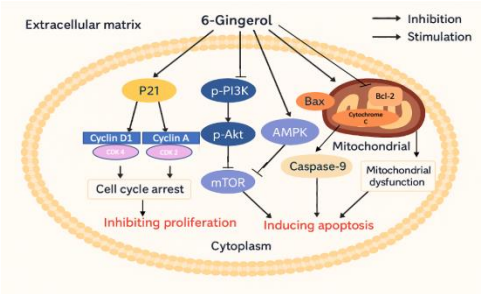

Figure 3. Signaling pathways relevant to the antitumor effects of 6-gingerol. CDK: Bcl-2: B-cell lymphoma 2; Cyclin-dependent kinase; Akt: Protein kinase B; AMPK: 5' adenosine monophosphate-activated protein kinase; mTOR: Mammalian target of rapamycin; Bax: Bcl-2-associated X protein; PI3K: Phosphoinositide 3-kinase

3.5. Neuroprotection

Older adults face a high risk of developing neurodegenerative conditions like Alzheimer's disease (AD) and Parkinson's disease (PD) (44). Recent studies indicate that Gn positively influences memory function and has anti-neuroinflammatory effects, which may be beneficial for managing and potentially preventing neurodegenerative diseases (45). Findings from studies using lipopolysaccharide-activated BV2 microglia cultures showed that 10-gingerol, a compound in fresh Gn Gn, plays a key role in anti-neuroinflammatory activity by inhibiting NF-κB activation, which reduces the levels of nitric oxide, TNF-α, IL-1β, and IL-6 (45).

Also, in the memory deficit model in mice induced by scopolamine, Gn extract improved cognitive function as assessed through object recognition testing. Further studies on mouse and rat glioma cells showed that Gn extract promotes synaptic function in the brain via the activation of extracellular signal-regulated kinase (46). Research has also shown that 6-shogaol in Gn exerts neuroprotective effects by stimulating scavenging free radicals, Nrf2, and raising levels of antOx molecules, in neuron-like rat pheochromocytoma PC12 cells (45). Furthermore, 6-dehydrogingerdione demonstrated cytoprotective effects in PC12 cells against neural cell injury induced by oxidative stress through effectively scavenging free radicals (45).

In an Alzheimer's disease mouse model produced by amyloid β1–42 plaques, fermented Gn improved memory by preserving neural cells in the hippocampus and increasing presynaptic and postsynaptic protein levels (46). In rats with AD, Gn extract exerted protective effects, with higher doses reducing latency associated with memory deficits and lowering NF-κB, MDA, and IL-1β levels (47).

Furthermore, 6-shogaol reduces inflammatory responses, increases nerve growth factor levels, and promotes synaptogenesis in the brain, which was found to decrease cognitive dysfunction in AD mice (47). In rat mesencephalic cells exposed to 1-methyl-4-phenylpyridinium, 6-shogaol increased the number of tyrosine hydroxylase-immunoreactive neurons while decreasing nitric oxide and TNF-α levels. In a PD model, treatment with 6-shogaol improved motor coordination and bradykinesia (44). The studies above confirm that Gn and its constituents, including 10-gingerol, 6-dehydrogingerdione, and 6-shogaol, exert neuroprotective consequences, largely through antOx and Antin mechanisms.

3.6. Cardiovascular Protection

Cardiovascular (CV) diseases are a leading cause of premature mortality (48). Hypertension and dyslipidemia are significant risk factors for CV diseases, including coronary heart disease and stroke (48). Multiple studies have shown that Gn lowers blood lipid levels and blood pressure, thereby reducing cardiovascular disease risk (49). In high-fat diet-fed rats, Gn extract reduced body weight and increased serum HDL-C, which is protective against coronary heart disease.

It also elevated liver mRNA levels of apolipoprotein A-1 and lecithin-cholesterol acyltransferase, which are involved in HDL formation (49). Also, Gn extract lowered LDL and total cholesterol (TC) levels in high-fat diet-fed rats, and combined with aerobic exercise, it further increased HDL levels. Moreover, Gn extract reduced plasma triglycerides

(TG), very low-density lipoprotein (VLDL), and TC, in high-fat diet-fed rats by promoting hepatic expression of PPARα and PPARγ (peroxisome proliferator-activated receptors), which play roles in preventing atherosclerosis (49).

The proliferation of vascular smooth muscle cells is associated with cardiovascular disease. In vitro, 6-shogaol suppressed cell proliferation by increasing cells in the G0/G1 phase and activating the HO-1 and Nrf2 pathways (49). Additionally, Gn reduced arginase and angiotensin-1 converting enzyme (ACE) activity while enhancing nitric oxide (NO) levels, a known vasodilator, resulting in decreased blood pressure in hypertensive rats (50). Also, some hypertension-related complications shown to be reduced by Gn through increasing adenosine levels and decreasing platelet adenosine deaminase activity, thereby preventing aggregation of platelet and promoting blood vessels dilatation in hypertensive rats (50). Gn extract also provided blood vessels protective effects by inhibiting cyclooxygenase and nitric oxide synthase in porcine coronary arteries (50). In a cross-sectional study, an increase in daily ginger intake was associated with reduced hypertension and coronary heart disease risk. Overall, Gn exhibits cardiovascular protective effects by reducing hypertension and improving lipid profiles, including enhancing HDL-C while lowering TC, LDL, TG, and VLDL (49).

3.7. Antidiabetic activity

A Serious metabolic disorder characterized by insulin insufficiency and/or resistance is called diabetes mellitus, leading to elevated blood glucose levels. Accelerated protein glycation resulted in the production of advanced glycation end products (AGEs) as a consequence of persistent hyperglycemia (51). Numerous studies have assessed the antidiabetic effects of Gn and its main bioactive compounds.

In vitro experiments demonstrated that both 6-shogaol and 6-gingerol inhibit diabetic complications by preventing AGE production through methylglyoxal (MGO) trapping, a precursor to AGEs (51). Additionally, 6-gingerol has been shown to lower plasma glucose levels in mice with obesity. It decreased N"-carboxymethyl-lysine, an AGE marker, by activating Nrf2 (51). Furthermore, 6-shogaol and 6-paradol improved glucose consumption by increasing phosphorylation of AMPK in C2C12 myotubes and 3T3-L1 adipocytes. Also, 6-paradol considerably lowered glucose levels in the blood in a high-fat diet mouse (52). Another study found that 6-gingerol facilitates glucose-stimulated insulin expression and improves glucose tolerance in type 2 diabetic mice by raising glucagon-like peptide 1. Moreover, 6-gingerol treatment activated glycogen synthase 1 and promoted glucose transporter type 4 (GLUT4) presence on cell membranes, thus enhancing glycogen storage in skeletal muscles (52). Gn consumption was associated with reduced fasting plasma glucose, glycated haemoglobin A1c (HbA1c), insulin, TG, and TC levels in type 2 diabetes patients (DM2) (52). In rats with metabolic syndrome, Gn extract improved insulin sensitivity, likely due to the enhancement of energy metabolism triggered by 6-gingerol. Additionally, Gn extract alleviated retinal microvascular damage in streptozotocin-induced diabetic rats by reducing TNF-α, vascular endothelial growth factor, and NF-κB levels in retinal tissue (52). In a placebo-controlled, randomized, double-blind trial, Gn consumption reduced insulin, TG, LDL levels, the homeostasis model assessment index, and increased the quantitative insulin sensitivity check index in DM2 patients (52). Studies suggest that Gn and its active constituents may protect against elevated blood glucose and its complications by reducing insulin levels while enhancing insulin sensitivity (52).

3.8. Beneficial impacts on respiratory conditions

Natural herbal therapies have long been used for respiratory disorders like asthma, and Gn is among these traditional treatments (53). Gn and its active constituents have demonstrated bronchodilation effects in various studies (53). In isolated human airway smooth muscle, Gn induced significant, rapid relaxation. Studies using guinea pig and human trachea models showed that 8-gingerol, 6-gingerol, and 6-shogaol rapidly relaxed precontracted smooth muscle of airway passages. In mice, 8-gingerol inhalation reduced airway resistance by limiting Ca2+ influx (54). Additionally, 8-gingerol, 6-gingerol, and 6-shogaol enhanced β-agonist-induced smooth muscle relaxation in human airways through phosphodiesterase 4D inhibition (55).

In ovalbumin-induced allergic asthma models, Gn also alleviated allergic asthma by diminishing the inflammation of the airway and suppressing T helper type 2-mediated immune responses (55). Moreover, Gn's water-extracted polysaccharides decreased citric acid-induced cough frequency in animal models. Gn oil and its active constituents, including eucalyptol and citral, reduced carbachol-induced tracheal contraction in rats (55). In patients with acute respiratory distress syndrome, a Gn - rich enteral diet improved air exchange and decreased the period of mechanical ventilation (56). The findings suggest that Gn and its active compounds, including eucalyptol, 8-gingerol, 6-gingerol, and 6-shogaol, provide defensive effects against some respiratory illnesses by inducing airway smooth muscle relaxation and reducing airway inflammation and resistance.

3.9. Other therapeutic activities of ginger

Beyond the activities discussed above, Gn has additional valuable effects, such as antiallergic and hepatoprotective activities (57). In a gentamicin-induced nephropathy rat, gingerol improved kidney function and decreased lipid peroxidation in a dose-dependent manner. It also elevated glutathione (GSH) levels and superoxide dismutase (SOD) activity (58). In radiation-induced kidney damage, Gn extract further mitigated biochemical and histological changes in rats through its antOx and Antin properties (58).

Histological analysis of liver tissues indicated that Gn essential oil reduced hepatic lipid accumulation in obese mice, protecting against steatohepatitis by enhancing

antOx defenses and reducing liver inflammation (59). In an alcohol-fed mouse model, Gn essential oil alleviated alcoholic fatty liver disease by lowering aspartate transaminase (AST), alanine transaminase (ALT), TG, and TC levels and boosting liver antOx enzymes like catalase and SOD (59).

There are currently no reports of Gn's liver toxicity. In a mouse model of ovalbumin (OVA)-induced allergic rhinitis, a Gn diet reduced sneezing and nasal rubbing severity, inhibited mast cell infiltration into the nasal mucosa, and decreased serum immunoglobulin E secretion. In vitro studies have shown that 6-gingerol alleviates allergic rhinitis by reducing cytokine production for T cell activation and inhibiting the activity of B cells and mast cells (60). Additionally, Gn reduced blood loss in women with heavy menstrual bleeding (61). In a double-blind, randomized clinical trial, Gn powder relieved common migraine attacks with fewer side effects compared to Depakene (62).

3.10. Analgesic and immunomodulating effect of ginger

By blocking the cyclooxygenase and lipoxygenase pathways, ginger has been shown to have analgesic effects by lowering the production of pro-inflammatory mediators such prostaglandins and leukotrienes. It is a promising natural substitute for nonsteroidal anti-inflammatory medicines (NSAIDs), as clinical investigations have shown that it effectively relieves pain related to osteoarthritis, dysmenorrhea, and muscle soreness (63). By controlling cytokine production, inhibiting pro-inflammatory indicators including TNF-α, IL-1β, and IL-6, and boosting antioxidant defenses, ginger has immunomodulatory effects. Ginger extracts can affect both innate and adaptive immune responses, according to experimental investigations, which helps to restore immunological balance and reduce inflammation (64).

4. Toxicity, safety, and dosage considerations of Ginger

Ginger (Zingiber officinale) is categorized as generally safe, with the U.S. FDA placing it on the "generally recognized as safe" (GRAS) roster; average adults may safely ingest up to 4 g daily (65). Ingestion exceeding 6 g may, however, induce mild gastrointestinal complaints such as heartburn, diarrhea, or reflux (65). Toxicologic investigations in rodents reveal minimal danger: rats given ginger powder up to 2000 mg/kg body weight exhibited neither mortality nor serious organ disturbance over sub-chronic and chronic intervals; only an exceedingly high regimen produced insignificant testicular weight decline. The herb's antiplatelet property may enhance bleeding tendency, prompting advisories against concomitant use with anticoagulants (notably warfarin), antiplatelet drugs, and agents affecting blood pressure or glucose levels (66). During gestation, randomized and cohort investigations employing daily doses of 500 to 1,000 mg display no pronounced teratogenic or chronic toxicity, albeit transient bowel discomfort and rare instances of miscarriage have been documented; collective evidence remains insufficient to endorse unrestricted use, recommending guarded oversight throughout pregnancy (66).

5. Conclusions

In summary, Gn is rich in diverse active constituents, including gingerols, shogaols, and paradols, which exhibit various beneficial properties, such as antOx, Antin, and AntiM effects. Gn shows promise as an ingredient for functional foods or nutraceuticals and may aid in the prevention and management of numerous health conditions, including CV diseases, diabetes mellitus, cancer, neurodegenerative diseases, obesity, emesis, nausea, and respiratory disorders. Future research should focus on isolating and precisely identifying additional bioactive compounds in Gn, investigating their biological activities, and elucidating the mechanisms underlying these effects. Importantly, rigorously designed clinical trials are essential to substantiate Gn's efficacy for treating these diseases in humans.

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الزنجبيل (*Zingiber officinale*): مراجعة شاملة لإمكاناته العلاجية

الخلاصة

المقدمة: يُعرف الزنجبيل رسميًا باسم(*Zingiber officinale Roscoe*) ، وهو من التوابل الشائعة الاستخدام وسهلة الحصول عليها. يحتوي الزنجبيل، كنوع من التوابل، على مكونات كيميائية متنوعة، بما في ذلك المركبات الفينولية، والتربينات، والسكريات المتعددة، والدهون، والأحماض العضوية، والألياف الخام. الهدف: في هذه المراجعة، نستعرض أحدث البيانات حول المكونات النشطة بيولوجيًا في الزنجبيل، والتي تشمل المواد الكيميائية الحيوية للزنجبيل ونشاطه الحيوي وتأثيراته. كما سنناقش المراجعة بعض التطبيقات العلاجية للزنجبيل في ضوء الدراسات العلمية المتاحة حاليًا. **المنهجية:** تم تلخيص البيانات التي تمت مراجعتها باستخدام منصات علمية، بما في ذلك Web of Science و Scopus و Google Scholar. **النتائج:** تُعزى الفوائد الصحية للزنجبيل بشكل رئيسي إلى المركبات الفينولية، الجنجرول والشوغول. يُظهر الزنجبيل خصائص بيولوجية متعددة، بما في ذلك خصائص مضادة للأكسدة، ومضادة للالتهابات، ومضادة للميكروبات، ومضادة للسرطان، ومضادة للأعصاب، ومضادة للقلب والأوعية الدموية. بالإضافة إلى ذلك، يتمتع الزنجبيل بتأثيرات وقائية للجهاز التنفسي، ومضادة للسمنة، ومضادة لمرض السكري، بالإضافة إلى تأثيرات مضادة للغثيان والقيء. **الخلاصة:** وفقًا لهذه المراجعة، يتمتع الزنجبيل بخصائص حيوية فعالة، ولمكوناته الفعالة تأثيرات علاجية إيجابية.

الكلمات المفتاحية: زنجبيل، مضاد للالتهابات، نشط حيويًا، مضاد للأكسدة، مضاد للميكروبات