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A review of nutritional implications of bioactive compounds of Ginger (*Zingiber officinale* Roscoe), their biological activities and nano-formulations

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REVIEW ARTICLE

Abstract

Ginger is a rhizome of the family *Zingiberaceae* and is one of the most commonly used spices in food and beverages worldwide. The pharmacological activities of ginger, including antioxidant, anti-inflammatory, anticancer, and protective effects against pain and gastrointestinal tract disorders, are primarily attributed to its phenolic compounds. However, knowledge about the mechanisms of toxicity, absorption, molecular targets, and dose–response relationship of ginger in human clinical studies is still elusive. The aim of this review is to give an overview of the current literature in the context of bioactive compounds and biological activities of ginger. Furthermore, recent findings regarding the absorption, tissue distribution, and nano-formulations of ginger bioactive compounds are discussed. The current *in vitro* and *in vivo* studies identified and validated ginger extracts and bioactive compounds, including gingerols, zingiberene, shogaols, and zingerone. Despite the data available regarding the pharmacological uses of ginger together with a deep mechanistic approach about the pharmacokinetic, pharmacodynamic and dose-response studies in humans is yet to be provided. Studies on the absorption, bioavailability, adverse reactions, and safe doses of the bioactive compounds of ginger will additionally improve its therapeutic applications. Nonetheless, the use of nano-formulations of bioactive compounds of ginger will be a more effective strategy in drug delivery. These novel evidences may bring ginger to the forefront of nutraceuticals for the treatment and/or prevention of various human health disorders.

Keywords: absorption; bioactive compounds; biological activities; ginger; nano-formulations

Introduction

Ginger (scientific name: *Zingiber officinale* Roscoe) is a perennial and yellow flowering plant, belonging to the *Zingiberaceae* family. Ginger plant has tuberous roots, named as rhizomes, which have pungent taste and aromatic odor. Ginger is primarily used for culinary purposes as a flavoring agent mostly in dried, fresh, powdered, and preserved food and/or pickles (Peng *et al.,* 2017). More importantly, ginger has received much attention from researchers because of its therapeutic potential to modulate the activities of several enzymes. Ginger is also used in traditional medicines such as Unani system, Ayurvedic and Chinese medicines since ancient times to treat different ailments, including sprains and muscular aches, rheumatoid arthritis, nausea, sore throat, indigestion and constipation, fever, infectious diseases, helminthiasis and cancer (Ali *et al.,* 2008). Nowadays, ginger plant is grown in tropical regions such as Africa, Asia, Europe and America, and has gained an increasing interest because of its medicinal properties (Srinivasan, 2017) and research, including identification and isolation of its bioactive constituents (as shown in Figure 1) and its pharmacological, phytochemical and toxicological properties.

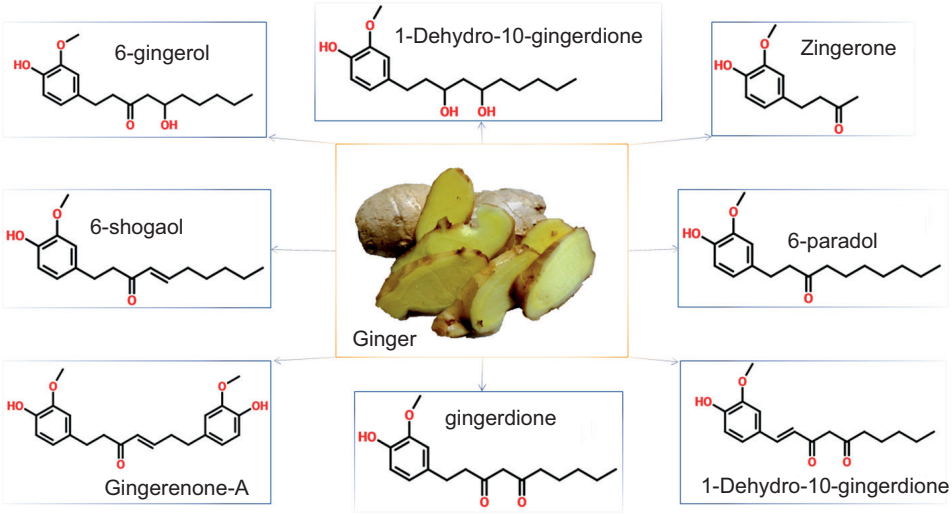

Figure 1. Ginger rhizome and chemical structure of some of its bioactive compounds.

Bioactive compounds in ginger

Chemical analysis of ginger revealed that if contains more than 400 compounds. The major constituents of ginger are lipids (3–8%), carbohydrates (50–70%), phenolic compounds and terpenes (Grzanna *et al.,* 2005). The nutraceutical properties of ginger are attributed to its bioactive constituents, primarily, phenolic compounds and terpenes. Some of these compounds belonging to classes such as shogaols, gingerols, paradols, zingerone and zigiberenes have been reported to possess potential to modulate biological activities. Shogaol (18–25%) and gingerols (23–25%) are found in higher quantities compared to other compounds. Besides these, water, raw fiber, protein, ash, phytosterols, minerals and some vitamins are also present (Ali *et al.,* 2008). Gingerols account for the taste of ginger. However, shogaols are formed at high temperature, for instance, during cooking, and provide spicy–sweet aroma. These active compounds have many biological activities through the modulation of enzyme activities in living systems (Shukla and Singh, 2007; Srinivasan, 2017). Therefore, in this review, the pharmacological activities (as shown in Figure 2) associated with the bioactive compounds, their absorption and distribution, with a special focus on enhancing its bioavailability through nano-formulations are discussed.

Biological Activities of Ginger

Antioxidant activities

Studies have reported that reactive oxygen species (ROS) play a crucial role in the growth of different chronic diseases (Poprac *et al.,* 2017). The antioxidant activity of spices could be due to one or more of the following reasons: (1) suppressing of lipid peroxidation; (2) Inhibition of enzymes of arachidonate metabolism: 5-lipoxygenase and 2-cyclooxygenase enzymes; (3) free radical scavenging; (4) stimulating the activities of endogenous antioxidant enzymes; (5) enhancing antioxidant molecules in tissues; (6) inhibition of the activity of inducible nitric oxide synthase and (7) inhibition of low-density lipoprotein (LDL) oxidation (Srinivasan 2014). Similarly, ginger has been reported to possess antioxidant activities, and has demonstrated a crucial role in scavenging superoxide anion and hydroxyl radicals (Ji *et al.,* 2017; Mao *et al.,* 2019). It has been analyzed that the trend varies with the content of phenolics found in ginger. For example, dried ginger has higher phenolic contents and indicates stronger antioxidant activities compared to stir-fried ginger and its other forms (dried ginger > stir-fried ginger > carbonized ginger > fresh ginger). On heating, the antioxidant activity decreases due to the conversion of gingerols into shogaols (Li *et al.,* 2016). The type of solvents used for extraction could have an effect on the phenolic contents, and subsequently affect the antioxidant activity of ginger (Yeh *et al.,* 2014). For instance, an aqueous extract and an ethyl acetate extract had higher antioxidant potential than diethyl ether, *n*-butanol and ethanol extracts (Nile and Park, 2015). The underlying mechanism of ginger's antioxidant potential were investigated, and it was found that ginger extract reduced the generation of ROS and lipid peroxidation and stimulated the expression of several antioxidant enzymes (Hosseinzadeh *et al.,* 2017). In addition, ginger extract activated the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway and its downstream genes, which, in turn, provide defense against oxidative stress and free radicals (Peng *et al.,* 2015). The bioactive compound of ginger, 6-shogaol, up-regulated Nrf2 target genes and enhanced intracellular glutathione/glutathione

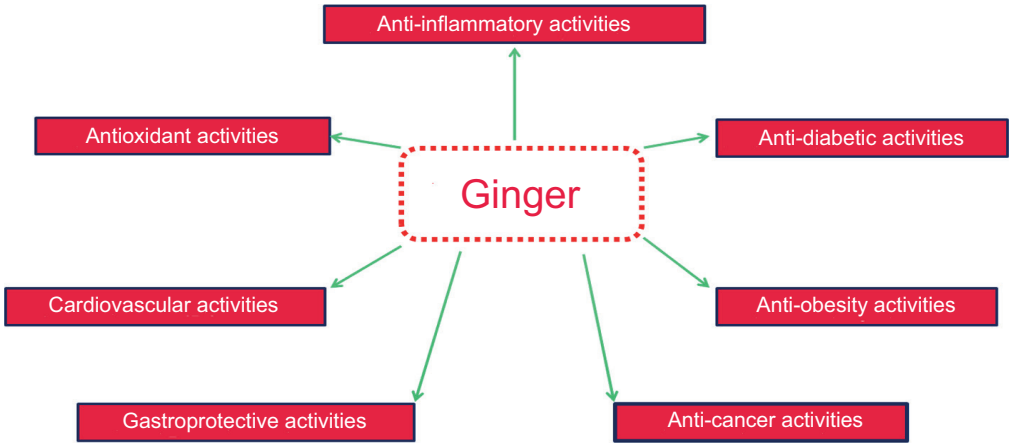

Figure 2. Schematic diagram showing multiple biological activities exhibited by ginger.

disulfide (GSH/GSSG), metallothionein 1 (MT1), heme oxygenase-1 (HO-1), aldo-keto reductase family 1 member B10 (AKR1B10), γ-glutamyl transferase-like activity 4 (GGTLA4), glutamate-cysteine ligase catalytic subunit (GCLC), glutamate-cysteine ligase modifier subunit (GCLM) and ferritin light chain (FTL) (Chen *et al.,* 2014). 6-Shogaol, 6-dehydroshogaol and 1-dehydro-6-gingerdione inhibited the synthesis of nitric oxide (NO) in macrophages (Li *et al.,* 2011). A previous study demonstrated that gingerol reduced the peroxidation of phospholipid liposomes in the presence of ascorbate and ferric ions (Fe^{3+}) (Aeschbach *et al.,* 1994). Another study reported the antioxidant effects of ginger in cerebellum, cerebral cortex, hypothalamus and hippocampus in diabetic mice (Shanmugam *et al.,* 2011). It is worthy to mention here that there are several factors, such as individual differences, health conditions, other dietary factors, the lifestyles of people, solubility, route, dosage, and solubility, that could affect the bioavailability and bioaccessibility of antioxidants, which are probably associated with the efficacy of antioxidants in the real world.

Digestive stimulant and gastroprotective activities

Ginger exerts potential protective effects on the gastrointestinal membrane and lowers the chances of mucosal injury (Prakash and Srinivasan, 2010a). It has been reported that dietary ginger altered the permeability and fluidity of the intestinal membrane, resulting in increased absorptive surface of the small intestine with an increase in microvilli length (Prakash and Srinivasan, 2010b). It was demonstrated that dietary ginger (0.05%) fed for 8 weeks significantly altered the ultrastructural morphology in Wistar mice. Besides, ginger enhanced the activity of enzymes such as leucine aminopeptidase, g-glutamyl transpeptidase and glycyl-glycine dipeptidase, accompanied by a decrease in the ratio of cholesterol and phospholipid in the small intestinal mucosa. Ginger also increased the absorption of zinc, iron, β-carotene and calcium in the intestines (Prakash and Srinivasan, 2013). In another study, higher intestinal absorption of micronutrients has been noted in ginger-fed animals. This may be presumably associated with alteration in permeation characteristics, including increased absorptive surface and antioxidant status in the intestines (Veda and Srinivasan, 2011). Despite providing increased surface area for absorption, ginger acts as a sialagogue, stimulates the production of saliva and thus enhances the swallowing process (Platel and Srinivasan, 2004). Ginger stimulated bile acid secretion from the liver (Bhat *et al.,* 1985), leading to the absorption and digestion of dietary fat. Dietary ginger significantly increased the activity of several digestive enzymes, for example, amylase, proteases (chymotrypsin, trypsin and carboxy peptidase) and pancreas' lipase (Platel and Srinivasan, 2000). Enzymes such as disaccharides are also stimulated by ginger, and food transit time is reduced due to facilitated digestion and increased intestinal motility (Platel and Srinivasan, 1996). Among spices, ginger ranks at the top level based on its pharmacological evidence (Platel and Srinivasan, 2004), and is used for alleviating the gastrointestinal tract (GIT) disorders in traditional medicines (Afzal *et al.,* 2001). Moreover, ginger's free phenolic and hydrolyzed phenolic fractions inhibited growth of *Helicobacter pylori* and gastric cell proton potassium ATPase activity. It has been suggested that these two steps are associated with the inhibition of ulcers (Siddaraju and Dharmesh, 2007).

Anti-inflammatory activities

Currently, gastric ulcer and adverse effects have been observed due to extensive use of nonsteroidal anti-inflammatory drugs. In general, the anti-inflammatory mechanism of ginger and its active compounds has been probably associated with the suppression of protein kinase B (Akt) and nuclear factor *kappa B* (NF-κB)

pathway, up-regulation of anti-inflammatory cytokines and inhibition of pro-inflammatory cytokines. A previous study demonstrated that ginger suppressed pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), Interlukin (IL)-1 and IL-8 (Pan *et al.,* 2008). Another study established that ginger oil (33 mg/kg, orally) for 26 days significantly alleviated joint swelling in mice during chronic adjuvant arthritis (Sharma *et al.,* 1994). Ginger extract administered at a dose of 100 mg/kg body weight suppressed the elevated expression TNF-α in mice (Habib *et al.,* 2008). Besides, ginger inhibited both cyclooxygenase and 5-lipoygenase *in vitro* and *in vivo* (Kiuchi *et al.,* 1992; Mustafa *et al.,* 1993), and reduced the expression of inflammatory genes (Ho *et al.,* 2013; Tripathi *et al.,* 2008) through the suppression of *NF-κB* gene expression (Kim *et al.,* 2004; Oyagbemi *et al.,* 2010; Takada *et al.,* 2005). In addition, 6-shogaol suppressed Claudin-1 and Claudin-2 through PI3K/Akt and NF-κB pathway and inhibited TNF-α-induced intestinal barrier dysfunction in human cell models (Luettig *et al.,* 2016). It has been noted that 6-dehydroshogaol proved to be more effective than 6-gingerol and 6-shogaol in reducing prostaglandin E2 (PGE2) and nitric oxide (NO) in mouse macrophage RAW 264.7 cell line (Zhang *et al.,* 2013). Moreover, 6-gingerol decreased the expression of inflammatory markers such as NO, TNF-α and myeloperoxidase in the ovaries, uterus and brain of mice treated with chlorpyrifos (Abolaji *et al.,* 2017). Capsules containing ginger powder (500 mg) alleviated the increased levels of plasma IL-1β, IL-6 and TNF-α after running exercise in 28 male endurance runners (Zehsaz *et al.,* 2014). The anti-inflammatory effects of ginger and its bioactive constituents, such as zingerone, 6-, 8-, 10-gingerol and 6-shogaol proved effective against lipopolysaccharide (LPS)-induced inflammation *in vivo* and *in vitro* (Hsiang *et al.,* 2015). These studies revealed that ginger and its bioactive compounds act as a broad spectrum anti-inflammatory agents through suppression of inflammatory cells infiltrates, NF-κB, IL-1β and other pro-inflammatory cytokines.

Anti-obesity activity

Previous research has reported that obesity is a risk factor for cardiovascular diseases, hypertension and diabetes (Misawa *et al.,* 2015). Recently, ginger has gained an increasing interest in the prevention and management of obesity (Ebrahimzadeh Attari *et al.,* 2018). In 3T3-L1 preadipocyte cells, gingerenone A attenuated diet-induced obesity through modulation of fatty acid metabolism via up-regulation of 5' AMP-activated protein kinase (AMPK) *in vivo*, and exhibited an effective inhibitory effect on lipid accumulation and adipogenesis compared to 6-shogaol and gingerols (Ebrahimzadeh Attari *et al.,* 2018). In cultured skeletal muscle myotubes, 6-gingerol and 6-shogaol enhanced the catabolism of cellular fatty acid through activation of peroxisome proliferator-activated receptor δ (PPARδ)-dependent gene expression (Misawa *et al.,* 2015). In high-fat diet mice, both orlistat and ginger decreased lipid profile and body weight. However, ginger proved effective than orlistat by reducing the level of high-density lipoprotein cholesterol (HDL-C) (Mahmoud and Elnour, 2013). In addition, in a double blind, randomized and placebo-controlled study, daily intake of 2 g of ginger powder decreased body mass index (BMI) in obese women (Ebrahimzadeh Attari *et al.,* 2016). A study reported that ginger oleoresin interfered with cholesterol absorption (Gujral *et al.,* 1978). It was demonstrated that fecal cholesterol increased and liver and serum cholesterol levels decreased compared to control group in mice fed with 1% cholesterol diet along with 0.5% ginger oleoresin for 20 days (Gujral *et al.,* 1978). In hypercholesterolemic mice, aqueous ginger infusion significantly reduced serum total cholesterol, triglycerides and LDL-cholesterol (ElRokh el *et al.,* 2010). However, dietary ginger (0.04% dry powder) did not reduce cholesterol in hypercholesterolemic mice (Sambaiah and Srinivasan, 1991). It is important to observe that dietary ginger stimulated the absorption and digestion of dietary fat by enhancing the activity of pancreatic lipase and secretion of bile salts (Prakash and Srinivasan, 2012). It has been observed that gingerol significantly reduced glucose and insulin resistance, body weight gain, expression of inflammatory markers and activity of enzymes of cholesterol biosynthesis, which results in the prevention of *high-fat diet* (HFD)-induced hyperlipidemia through modulating the expression of enzymes associated with cholesterol homeostasis (Brahma Naidu *et al.,* 2016). Thus, ginger helps in management of weight through suppression of body cholesterol and reducing accumulation of lipids.

Anti-diabetic activity

Diabetes mellitus caused by insulin deficiency is a severe metabolic disorder that results in hyperglycemia. Numerous studies have evaluated the antidiabetic potential of ginger and its bioactive compounds. In an *in vitro* study, 6-gingerol and 6-shogaol prevented diabetic complications by inhibiting advanced glycation end products (AGEs) by trapping methylglyoxal (MGO) (Zhu *et al.,* 2015). In addition, 6-gingerol decreased the level of plasma glucose and insulin in mice through Nrf2 activation (Sampath *et al.,* 2017).

In C2C12 myotubes and 3T3-L1 adipocytes, 6-shogaol and 6-paradol promoted glucose utilization via AMPK phosphorylation. Besides, 6-paradol decreased the level of glucose in the blood of mice fed with high-fat diet (Wei *et al.,* 2017). Another study reported that 6-gingerol

alleviated glucose tolerance through activation of glucagon-like peptide-1 (GLP-1) in type 2 diabetic mice and facilitated glucose-mediated secretion of insulin. It has been found that 6-gingerol enhanced cell membrane presentation of glucose transporter type 4 (GLUT4) and activated glycogen synthase 1, resulting in enhancing storage of glycogen in skeletal muscles (Samad *et al.,* 2017). Moreover, consumption of ginger could decrease the levels of glycated hemoglobin A (HbA1C), plasma glucose, insulin, total cholesterol (TC) and triglyceride (TG) in patients with type 2 diabetes mellitus (Arablou *et al.,* 2014).

In mice, ginger extract promoted insulin sensitivity during metabolic syndrome, which might be associated with improvement in energy metabolism by the active component, 6-gingerol (Li *et al.,* 2014). Apart from direct protective effects on diabetes mellitus, ginger demonstrated protective effects against diabetes mellitus-induced secondary complications of the kidney, eye, liver and neural system (Li *et al.,* 2012). Studies have established that ginger and its bioactive compounds possess potential therapeutic properties that could protect from diabetes mellitus. The main mechanism of action could be one of the following: (1) ginger maintains blood glucose homeostasis by promoting glucose uptake in insulin responsive peripheral tissues, (2) ginger enhances insulin sensitivity and release and/or (3) it improves lipid metabolism and inhibits enzymes in carbohydrate metabolism. These mechanisms provide evidence for the future studies to evaluate these steps in the clinical investigations of ginger and its bioactive compounds for treating diabetes mellitus.

Cardiovascular and blood protective activities

Ginger has the potential to treat cardiovascular diseases and has preventive effects on the blood. It is well documented that high blood cholesterol is primarily associated with cardiovascular diseases. Studies reported that cardiovascular diseases cause 17.9 million premature deaths annually (Du *et al.,* 2016). Hypertension and dyslipidemia are well known risk factors for stroke, coronary heart disease and cardiovascular diseases (Khosravani *et al.,* 2016).

Several studies have investigated the cardiovascular protective properties of ginger and indicated that ginger treatment primarily decreased blood pressure and level of blood lipids (Natalia *et al.,* 2017). In high-fat diet-fed mice, ginger extract increased the level of serum HDL-C and reduced body weight, thus protecting against coronary heart disease. Besides, the levels of lecithin-cholesterol acyltransferase and apolipoprotein A-1 mRNA were increased in the liver, associated with the formation of HDL (Oh *et al.,* 2017). The hypercholesterolemic properties of ginger attribute to its cardioprotective function. In Wistar mice, ginger extract prevented isoproterenol-induced myocardial infarction (Amran *et al.,* 2015).

Pretreatment with ginger extract at a dose of 400 mg/kg for 4 weeks significantly reduced cardiac markers, including enzyme activities of creatine kinase-MB isoenzyme, infarction–troponin, alanine transaminase, aspartate transaminase and lactate dehydrogenase. In addition, significant increase was found in cardiac antioxidant enzymes and improvement in cell membrane integrity in ginger-pretreated mice (Srinivasan, 2017).

Aqueous ginger extract at a low dose (50 mg/kg) administered orally or intraperitoneally did not cause significant reduction in platelet thromboxane-B2 (TBX2) level. However, significant changes were observed in serum prostaglandin-E2 (PGE2) levels when ginger extract was given orally. These results provided an insight regarding the anti-thrombotic potential of ginger (Thomson *et al.,* 2002). In anesthetized mice, crude extract of ginger (0.3–3 mg/kg) induced a dose-dependent decrease in arterial blood pressure. Crude extract depicted a cardiodepressant activity on the force and rate of spontaneous contractions in guinea pig paired atria. In addition, crude extract of ginger at a dose 10 times higher than required against K-induced contraction resulted in the relaxation of phenylephrine-induced vascular contraction in rabbits. These results demonstrated that ginger lowered blood pressure through the blockage of voltage-dependent calcium channels (Ghayur and Gilani, 2005). Another study reported that aqueous ginger extract mediated blood pressure lowering effect by inhibition of both Ca^{2+} channels and muscarinic receptors (Ghayur *et al.,* 2005). It has been observed that cardiovascular protective effects of ginger are attributed to its potential to alleviate hypertension and dyslipidemia.

Anti-cancer activity

Recently, increasing number of studies have focused on the anticancer effects of ginger and its bioactive compounds in different cancer cell lines, including cervical, breast, leukemia, colorectal, lung, liver, nasopharyngeal, prostate, retinoblastoma and ovarian cell lines. In the breast cancer cell line MDA-MB-231, 86.7-µg/mL and 57.5-µg/mL methanolic solution of ginger given for 24 h and 48 h, respectively, exhibited cytotoxic effect in a time-dependent manner (Ansari *et al.,* 2016). In MCF-7 cell line, Z-6-oxo-6-shogaol and Z-6-oxo-8-shogaol treatment with half-maximum inhibition concentration (IC_{50}) values of 6.27-µM and 47.22-µM for 48 h demonstrated significant cytotoxic action (Li *et al.,* 2018). In addition, 6-shogaol inhibited growth of both breast and

colon cancer cells through up-regulation of peroxisome proliferator-activated receptor gamma (PPARγ) (Tan *et al.,* 2013), and 10-gingerol inhibited orthotopic tumor growth by inducing apoptosis through caspase-3 in breast cancer and suppressed metastasis to lung, brain and bone cancers (Martin *et al.,* 2017). Researchers demonstrated that ginger and its bioactive compounds were found effective against prostate cancer cell lines such as LNCaP, DU145, C4-2, PC-3 and C4-2B. 10-gingerol with IC_{50} value of 59.7-μM was more effective than 6-shogaol with IC_{50} value of 100.0 μM against PC-3 cells (Peng *et al.,* 2012).

In LNCaP human prostate cancer cell lines, 6-gingerol induced apoptosis via caspase-3 in time- and dose-dependent manner and degraded poly(ADP-ribose) polymerase (PARP) (Kim *et al.,* 2011). In H-1299 lung cancer cells, 6-gingerol demonstrated cytotoxic effect with IC_{50} value of 136.73-μM for 24 h (Lv *et al.,* 2012), and initiated autophagy by inhibiting the AKT/mTOR pathway (Hung *et al.,* 2009). In liver cancer, ginger extract suppressed NF-κB and TNF-α in mice (Habib *et al.,* 2008). Additionally, Z-6-oxo-8-shogaol, Z-6-oxo-6-shogaol and E-4-isoshogaol revealed cytotoxic effect against HepG2 cell lines (van Breemen *et al.,* 2011). In HL-60 and K562 leukemic cell lines, 6-shogaol (with IC_{50} values of 24.2 μM and 7.9 μM) proved more effective than 10-gingerol (Mahomoodally *et al.,* 2021). In another study, 6-shogaol induced apoptosis and transformed cellular leukemia through eIF2α dephosphorylation (Liu *et al.,* 2013). It has been noted that 6-gingerol induced apoptosis in colorectal cancer cells by up-regulating G1 and NAG-1 cell cycle arrest through down-regulation of cyclin D1 (Lee *et al.,* 2008). Another study confirmed that p53/p21 contributed to cell cycle arrest by G2/M check point induced by 6-shogaol (Radhakrishnan *et al.,* 2014). Besides, 6-shogaol induced apoptosis primarily through mitochondrial pathway and Bcl-2 family proteins (Qi *et al.,* 2015). However, additional studies are required to elucidate the complete molecular mechanisms associated with the anticancer effects of ginger.

Other beneficial effects

In addition to the above-mentioned bioactivities, ginger and its bioactive compounds have several other multiple health benefits. Recently, a study has reported that ginger demonstrated several positive effects on neuroinflammatory disorders and memory function (Huh *et al.,* 2018). 10-gingerol inhibited neuroinflammation through the suppression of NF-κB, NO, IL-1β, TNF-α and IL-6 in LPS-stimulated BV2 microglia culture model (Ho *et al.,* 2013). Ginger extract alleviated scopolamine-induced memory deficits in mice. In addition, ginger extract promoted the formation of synapses in C6 glioma cells and hippocampi in mice by the activation of cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) and nerve growth factor (NGF) (Lim *et al.,* 2014). Moreover, ginger alleviated narcotics-induced neurotoxicity and memory deficits in the hippocampus through modulation of cholinergic activity and memory retrieval ability (Gomar *et al.,* 2014). A previous study demonstrated that ginger extract effectively alleviated epilepsy-like symptoms. For example, pentylenetetrazole (PTZ)-induced incidence of seizures and its duration was reduced by ginger therapy (Hosseini and Mirazi, 2014). Overall, ginger and its compounds alleviated epileptic symptoms, including involuntary movement and recurrent seizures; these findings provided evidence for the application of ginger against epileptic patients.

Ginger also demonstrated antiallergic, nephroprotective and hepatoprotective effects. A study conducted by Rodrigues *et al.* (2014) demonstrated that gingerol alleviated gentamicin-induced kidney damage by reducing stress and lipid peroxidation and increased superoxide dismutase (SOD) activity and levels of *glutathione* (GSH) in a dose-dependent manner. Similarly, ginger extract attenuated biochemical and histological alterations through anti-inflammatory and antioxidant activities in a radiation-induced kidney model of mice (Saberi *et al.,* 2017). The above-mentioned discussion established that ginger and its bioactive compounds played a crucial role in treating various diseases and, therefore, must be evaluated additionally for their nutraceutical properties.

Absorption and Tissue Distribution of Ginger Compounds

Information about the pharmacokinetics and bioavailability profile of an active substance is very important for understanding its nutraceutical properties. A previous study investigated the distribution profile of 6-gingerol in the blood and other tissues of mice. It was observed that this component was absorbed quickly if given orally at a dose of 240 mg/kg (ginger extract having 53% 6-gingerol). The maximum concentration found in the plasma was 4.24 mg/mL after 10 min that declined in a biexponential pattern with time. 6-gingerol is distributed to the heart, brain, spleen, lung, kidney, liver, small intestine and stomach. The highest concentration was found in the GIT, and the elimination half-life was 1.77 h (Jiang *et al.,* 2008).

A clinical trial studied the pharmacokinetics of the following ginger constituents: 6-shogaol, 6-gingerol, 8-gingerol and 10-gingerol. In human volunteers, ginger was given orally at a dose of 100–2.0 g. The ginger constituents were absorbed and detected as sulfate and glucuronide conjugates in blood samples after 15 min to

72 h. Importantly, no free 6-shogaol, 6-, 8-, or 10-gingerol was detected and the calculated half-lives of these compounds was less than 2 h (Zick *et al.,* 2008). Another clinical trial reported the pharmacokinetics of 6-shogaol, 6-, 8-, and 10-gingerols in colon tissues and plasma. Free forms of 6-shogaol and 10-gingerol were observed in plasma after oral intake, with a maximum level reaching in 1 h. However, no free forms of 6-gingerol and 8-gingerol were detected in plasma. The half-lives of these ginger constituents in plasma ranged from 1 to 3 h. Traces of 10-gingerol sulfate and glucuronide conjugate were detected in colon tissue, while traces of free forms of 6-shogaol and 10-gingerol, as well as glucuronide metabolites of 6-shogaol and 6-, 8-, and 10-gingerol, were detected with a more sensitive technique 1 h after oral intake (Yu *et al.,* 2011). In experimental mice, free 6-shogaol, 8-, and 10-gingerols were discovered in the plasma after single oral dose of ginger oleoresin (300 mg/kg) whereas 6-gingerol administered orally at a rate of 50 mg/kg was excreted in bile as glucuronide conjugate over 60 h (Wang *et al.,* 2009). In addition, 6-shogaol (78.5%) was excreted in bile over 48 h after oral intake (Asami *et al.,* 2010).

Nano-formulations

Recently, owing to certain beneficial effects in treating diseases, nano-formulations in nanomedicine have received increasing interest from researchers (Kumar *et al.,* 2017). Nanomedicine has certain benefits in drug delivery system, for the drug is delivered at correct sites, thereby making drug absorption more successful (Aneja *et al.,* 2014). Significant research is in progress in the area to study its pharmacokinetics, mechanisms and delivery along with exploring of new nanocomposites, such as hybrid polymer-metal composites or grapheme, for drug delivery (Rahman *et al.,* 2015).

Rahman *et al.* (2017) reviewed the therapeutic applications and benefits of nano-formulations in the context of liposomal-based drug delivery. The study demonstrated that PEGylated nanoliposomal formulation of gingerol allowed a slower release of drug and enhanced its cytotoxic effect in breast cancer MCF-7 cells compared to standard gingerol and liposomal gingerol. PEGylation has the advantage of controlled drug release and ensures longer blood circulation to reach the target site by protecting liposomes against lipase enzymes and immune system (Khalili *et al.,* 2013).

Another research established that PEGylated nanoliposomal gingerol proved more effective than the standard drug. The release of gingerol from nanoparticles enclosed in PEGylated nanoliposomal formulation (76% gingerol) was fast and instant at the start and then became slower (Behroozeh *et al.,* 2018). Similarly, 6-shogaol-made liposomes in a 1,2-dimyristoyl-sn-glycero-3-phosphoglycerol-sodium (DMPG-Na) carrier exhibited anticancer action both *in vitro* and *in vivo*. It was observed that 6-shogaol was released slower from liposomes compared to ginger oleoresin (Ahmad *et al.,* 2015). In a recent *in vitro* study, drug delivery system was designed with ginger nanoparticles and chitosan for controlled release of 5-amino salicylic acid (5-ASA) to treat inflammatory bowel disease. It was concluded that design system for the controlled release of 5-ASA was appropriate and favorable at gastrointestinal pH and beneficial in treating inflammatory bowel disease (Markam and Bajpai, 2020). However, additional studies are required to investigate and develop ginger as an effective candidate of nanomedicines for treating different cancers and neurodegenerative diseases.

Conclusion and future trends

This review demonstrated the biological activities of ginger and its bioactive constituents in a number of diseases, with particular interest for having digestive stimulation and antioxidant potential, and anti-inflammatory, antiobesity, antidiabetic, cardiovascular and blood protective, and anticancer activities. The underlying mechanisms of ginger and its bioactive compounds were discussed from the context of modulating various cellular enzymes, including cytochrome p450, cyclooxygenases, lipoxygenases, Nrf2, NF-κB and several other pathways considering apoptotic and cell cycle check points. In addition, available information about the absorption and tissue distribution of ginger and its bioactive compounds was highlighted. The use of ginger and its bioactive compounds in nanomedicine, especially nano-formulations, was viewed in the light of available literature.

The future studies should provide a complete understanding of the interactions of ginger and its bioactive compounds. However, lack of knowledge makes it difficult to use ginger in human clinical cases. Although nanotechnology provides effective delivery system for ginger and its constituents, more pharmacokinetic and pharmacodynamics trials could provide in-depth information regarding the bioavailability and molecular pathways associated with these nano-formulations.

Omic studies such as proteomics, transcriptomics and metabolomics are recommended to dig out the possible adverse reactions and molecular targets of ginger and its compounds. There is still a challenge for researchers to evaluate ginger and its constituents as nutraceuticals because of the complex systems that involve multiple signaling pathways, choice of route administration, dose optimization, intensity, and treatment duration. Notably, the efficacy of ginger and its active constituents against

diseases requires more well-designed human clinical trials. Gas chromatography and high-performance liquid chromatography fingerprinting could provide valuable insights into the nutraceutical uses, and more bioactive compounds of ginger could be identified and isolated. Nevertheless, we established in this review the potential uses of ginger as a safe herbal medicine and food ingredient for managing various diseases; still this spice deserves to be considered for additional investigations to enhance its bioavailability and controlled release via advance technologies, including nano-formulations.

Declaration of competing interest

None.

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Author contributions

Muhammad Ishfaq was involved in the conceptualization of project, writing of original draft, review, and editing. Wanying Hu was involved in writing-review and editing. Ruihong Zhang did the visualization of project. Yurong Guan was involved in project administration and software. Zhihua Hu was involved in project administration and data curation.

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