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REVIEW

Revisiting the therapeutic potential of gingerols against different pharmacological activities

Samridhi Sharma[1] · Monu Kumar Shukla[1] · Krishan Chander Sharma[2] · Tirath[1] · Lokender Kumar[3] · Jasha Momo H. Anal[4] · Santosh Kumar Upadhyay[5] · Sanjib Bhattacharyya[6] · Deepak Kumar[1]

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Abstract

The rhizomes of ginger have been in use in many forms of traditional and alternative medicines. Besides being employed as condiment and flavoring agent, it is used in the treatment of nausea, osteoarthritis, muscle pain, menstrual pain, chronic indigestion, Alzheimer's disease, and cancer. Ginger rhizome contains volatile oils, phenolic compounds and resins, and characterization studies showed that [6]-gingerol, [6]-shogaol, and [6]-paradol are reported to be the pharmacologically active components. Gingerol is a major chemical constituent found as volatile oil in the rhizomes of ginger. It has several medicinal benefits and used for the treatment of rheumatoid arthritis, nausea, cancer, and diabetes. Many studies have been carried out in various parts of the world to isolate and standardize gingerol for their use as a complementary medicine. The present review summarizes wide range of research studies on gingerol and its pharmacological roles in various metabolic diseases.

Keywords Ginger · Gingerol · *Zingiber officinale* · Volatile oil · Resins · Cancer · Inflammation

Introduction

Ginger (*Zingiber officinale*) has always been used as a remedy for a wide range of diseases (Bode and Dong 2004). The plant was first cultivated in China and other Southeast Asian parts, but it is now extensively grown throughout Asia, including the Western regions of the world (Park and Pezzuto 2011). Ginger is popular as a spice and its therapeutic benefits such as nausea, asthma, arthritis, gastrointestinal disorders, headache, and other diseases. It is also helpful in chemotherapy-related nausea, vomiting, and motion sickness (Bode and Dong 2011; Butt and Sultan 2011).

✉ Deepak Kumar
guptadeepak002@gmail.com

Samridhi Sharma
samridhi.sharma1634@gmail.com

Monu Kumar Shukla
monushukla02@gmail.com

Krishan Chander Sharma
krishan14chander@gmail.com

Tirath
tktirathkumar007@gmail.com

Lokender Kumar
lokenderkumar@shooliniuniversity.com

Jasha Momo H. Anal
hmunshel.jasha@iiim.res.in

Santosh Kumar Upadhyay
skupadhyay@pu.ac.in

Sanjib Bhattacharyya
bhattacharyya.Sanjib2k12@gmail.com

[1] Department of Pharmaceutical Chemistry, School of Pharmaceutical Sciences, Shoolini University, Solan-173229, Himachal Pradesh, India

[2] Department of Entomology, School of Agriculture, Shoolini University, Solan-173229, Himachal Pradesh, India

[3] School of Biotechnology, Faculty of Applied Sciences and Biotechnology, Shoolini University, Solan, Himachal Pradesh-173229, India

[4] Natural Products and Medicinal Chemistry Division, CSIR-Indian Institute of Integrative Medicine, Jammu-180001, India and Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India

[5] Department of Botany, Panjab University, Chandigarh, Punjab, India

[6] Department of Pharmaceutical Sciences and Chinese Traditional Medicine, Southwest University, Beibei, Chongqing 400715, People's Republic of China

For decades, people had quest for curing different types of diseases by the use of drugs derived from different medicinal plants (Jindal et al. 2021; Regassa et al. 2022; Shukla et al. 2022). The records show that the drug preparations from plants were found in Nagpur, India, about 6000 years old. These records comprise of about 12 recipes for different types of drug preparation from 250 plant species (Kelly 2009). Besides this, the *Vedas* also mentioned the treatment of various diseases with plants. Scientific work on plants was started as the knowledge on identification and isolation of various phytoconstituents from the beginning of the nineteenth century (Bhardwaj et al. 2018). Over the last few decades, people started the use of plant-based medicines in their diets as supplements (Cohen et al. 2002).

Ginger is most commonly used medicinal plant in Asia and many other countries for combating various digestive disorders like indigestion, constipation, headache, rheumatism, cold, and cough (Bhargava et al. 2012). Besides these applications, it has also been found to possess anticancer, antioxidant, antidiabetic, hepatoprotective, larvicidal, analgesic, anti-inflammation, and immunomodulatory properties (Kumar et al. 2011; Ghasemzadeh et al. 2010; Ho et al. 2013). Various secondary plant metabolites and compounds have been reported from ginger for their pharmaceutical uses among which flavonoids and phenolics are the important groups (Ho et al. 2013). All the three compounds namely gingerol, shogaol, and paradol possess various types of medicinal properties which include antioxidant, antitumor, and COX inhibitor activities (Mohammad 2016).

To understand the mechanism of action of ginger has piqued researchers in to the ginger related research in recent years. There has been remarkable research and reviews on the therapeutic effects of ginger and its principal components (Bode and Dong 2004, 2011, 2008; Butt and Sultan 2011; Ali et al. 2008; Ding et al. 1991; Habib et al. 2008; Jolad et al. 2005; Poltronieri et al. 2014; Semwal et al. 2015; Shukla and Singh 2007; Surh et al 1998). Keeping in view the importance of gingerols in treating various human diseases, this review discusses the use and the mechanism of action of gingerols against potential human diseases.

Mode of action of gingerol

Several researchers have revealed that [6]-, [8]-, [10]-gingerols, and [6]-shogaol exhibited antiemetic effects. These compounds bind to a modulatory region on the 5-HT3 receptor of ion-channel complex (Abdel-Aziz 2006).

According to Radhakrishnan et al., [6]-gingerol is responsible for inhibition of cell augmentation in human colon cancer SW-480 cells and HCT116 cells, as well as inducing cell death in SW-480 cells. The mode of action is related to caspase-8, caspase-9, caspase-3, and caspase-7 activation, and also breakdown of poly-ADP ribose polymerase (PARP) (Radhakrishnan et al. 2014).

One of the mechanisms by which gingerol affects cancerous cells has been discovered to be protein breakdown. These compounds hinder the transformation of healthy tissue into cancerous cells via inhibition of AP-1 proteins. On the occurrence of cancer, paradol promotes apoptosis because of its cytotoxic effect (Bode et al. 2001; Wei et al. 2005).

[6]-Gingerol has also been reported to exhibit cell cycle arrest, apoptosis, and enzyme-coupled cell signaling receptor degeneration in tumor cells. Besides this, gingerol was found to inhibit proliferative action by blocking the translation of cyclin required for duplication during the G1 and G2 stages of cell division (Mao et al. 2019).

Additionally, gingerol has been shown to weaken A549 cells to TNF-related apoptosis instigating ligand (TRAIL)-induced apoptosis via decreasing autophagy flux (Nazim et al. 2015).

Chemical constituents and properties of gingerols

Chemically, gingerol or [6]-gingerol (Fig. 1) is a relative of piperine and capsaicin, which occurs in black pepper and chili pepper for their respective spiciness (Girhepunje et al. 2017). It is low-melting crystalline solid with pungent smell. On heating, ginger form gingerol, a less pungent and spicy-sweet aromatic compound, namely, zingerone. Also, on drying or heating gingerol turns to shogaols by dehydration reaction which is more pungent than gingerol. This type of conversion is more at higher temperature (Jung et al. 2018). [8]-Gingerol, [10]-gingerol [31], and [12]-gingerol [32] are also found in ginger and these together are called as the deemed gingerols. Various investigations have revealed that gingerols and shogoals are found to be mutagenic in nature (Fig. 2 Mao et al., 2019).

Isolation of gingerols

Countercurrent chromatography was used by Farthing et al. for separating [6]-, [8]-, and [10]-gingerols from the powdered root of ginger. Further, [4]-gingerol was also isolated with some minor modifications of this process. In these techniques, diol-bonded columns were used which separated the gingerols present in crude methanol extracts from the interfering constituents [34]. [6]-, [8]-, and [10]-Gingerols were isolated from fresh ginger rhizomes via fractionation method normal phase HPLC. These compounds were also characterized by mass spectral studies (Hiserodt et al. 1998).

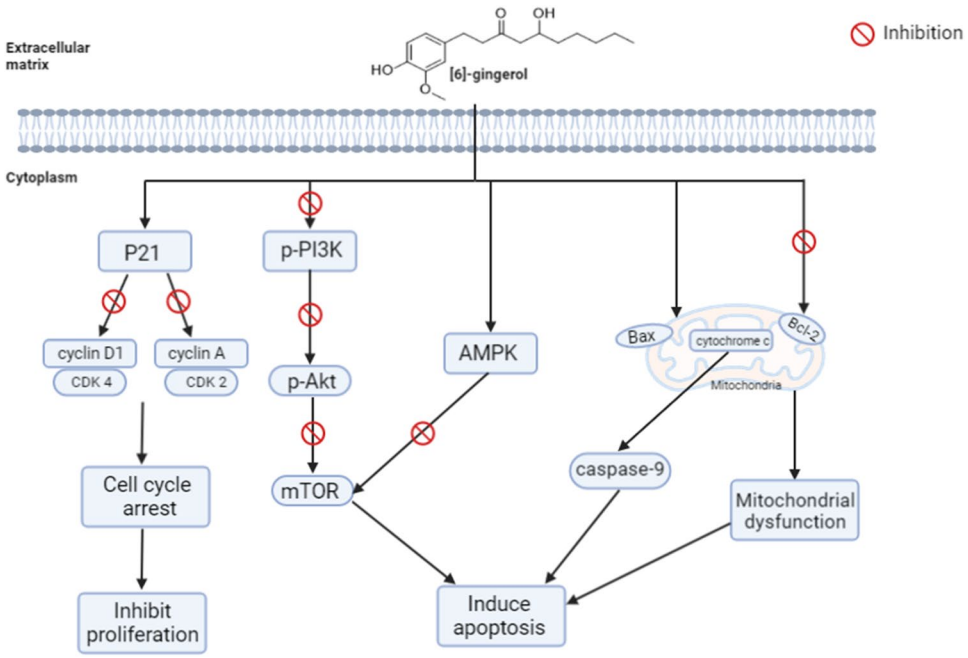

Fig. 1 Signaling pathways involved in anticancer mechanism of [6]-gingerol (Mao et al. 2019)

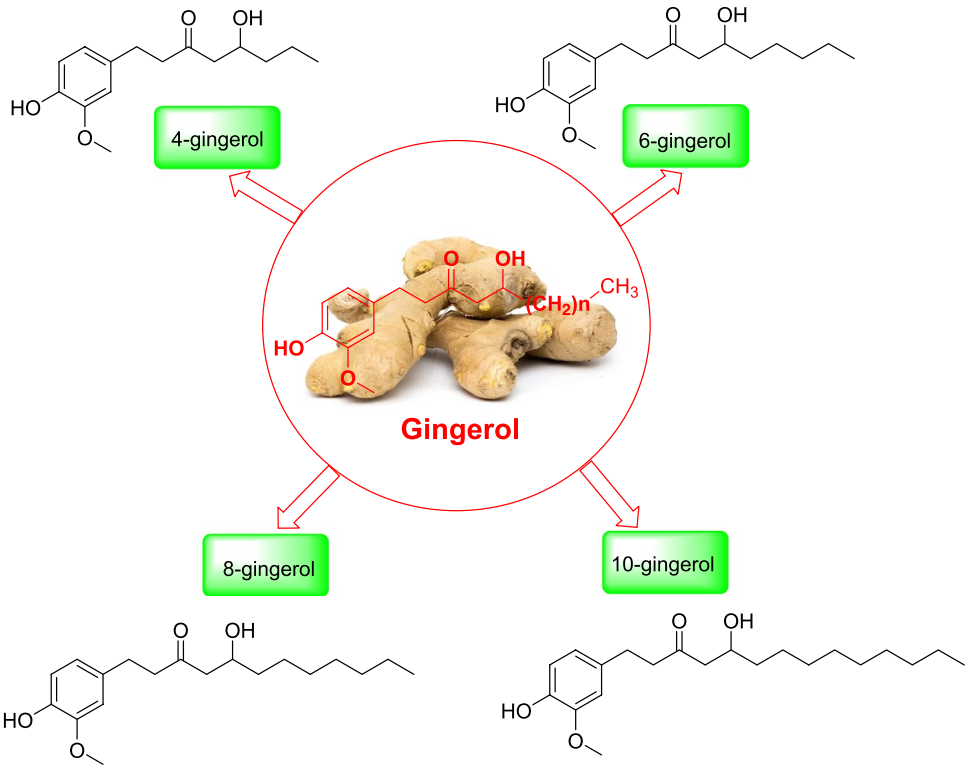

Fig. 2 Different kinds of gingerols with their structures (Girhepunje et al. 2017)

In a study, dichloromethane was used to extract gingerol and related compounds from ginger rhizomes and then substituted with alkyl groups. Then, these compounds using chromatographic techniques were evaluated for the antioxidant activities and were further evaluated (Yuki et al. 2004). In another study, 6-gingerol was isolated from ginger rhizomes and was chemically modified. This modified compound was tested against diabetic mice which improved the insulin signaling (Chakraborty et al. 2012).

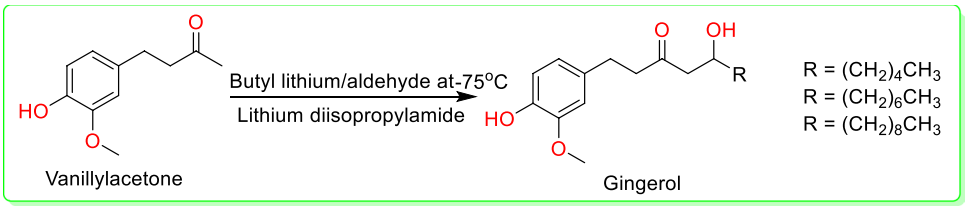

Fig. 3 Synthesis scheme of [6]-, [8]-, and [10]-gingerols (Fleming et al. 1999)

Synthesis of gingerols

In 1999, Flemming and co-workers synthesized [6]-, [8]-, and [10]-gingerols in a single-step synthesis (Fig. 3). Vanillylacetone was treated with butyl lithium (C_4H_9Li) and then lithium diisopropylamide ($C_6H_{14}LiN$) along with an appropriate aldehyde to give gingerol (Fig. 3) (Fleming et al. 1999).

In 1980, Denniff et al. synthesized [6]-gingerol via phenylalanine. This precursor formed p-coumaric acid and later dihydroferulic acid, followed by [6]-gingerdione leading to the resultant compound (Denniff et al. 1980).

Ramirez-Ahumada et al., in 2006 used the same amino acid, phenylalanine, while making use of enzymes such as phenylalanine ammonia lyase, p-coumaroyl quinate transferase, p-coumaroyl shikimate transferase, caffeic acid O-methyltransferase, caffeoyl-CoA-O-methyltransferase, and reductase (Ramirez-Ahumada et al. 2006).

Kumar et al., in 2012 achieved [6]-, [7]-, and [9]-gingerols with the help of eugenol that was converted to the nitro compound and then reacted with terminal alkenes to produce isoxazolines. After catalytic hydrogenation along with Raney nickel, respective gingerols were yielded (Kumar et al. 2012).

In 2009, Ma et al. opted a different approach to synthesize (+)-(S)-[6]-, [8]-, and [10]-gingerols via enantioselective method for desirable production (Ma et al. 2009).

Therapeutic applications of gingerols

Gingerols are one of the important key ingredients that are found in ginger. [6]-Gingerol has various pharmacological properties that are effective in cancer, diabetes, emesis, inflammation, and many more (Fig. 4) (Bode and Dong 2011; Butt and Sultan 2011).

Anticancer

An anticancer activity of ginger was performed on an animal model having carcinoma cells (Katiyar et al. 1996). The study was concluded that the introduction of [6]-gingerol to SENCAR mice with DMBA-induced skin cancer gave them considerable protection and reduced tumor. Nigam et al. revealed that [6]-gingerol reduced the development of epidermoid carcinoma (A431) by producing reactive oxygen species (ROS) (Nigam et al. 2009). Increased ROS caused a change in mitochondrial membrane potential that resulted in the discharge of cytochrome-C and activation of apoptotic

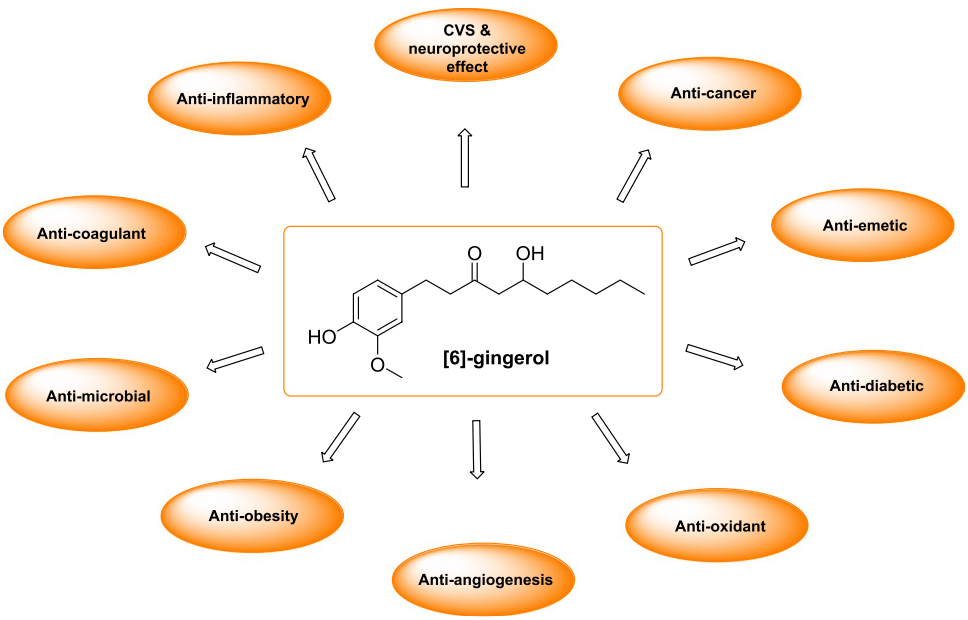

Fig. 4 Therapeutic properties of [6]-gingerol in different types of diseased conditions

protease activating factor-1 (Apaf-1) that further resulted in caspase expression, implying apoptosis. The findings suggested that [6]-gingerol could be successful in the skin cancer treatment. They also concluded in another study that providing [6]-gingerol before and after benzo[a]pyrene therapy for 32 weeks lowered the skin tumors, elevated repressed p53 and Bax concentrations, and reduced the Bcl-2 levels and survivin in benzo[a]pyrene-induced skin cancer (Nigam et al. 2010).

The most fatal, malignant, and dangerous astrocytoma in adults is glioblastoma multiforme (GBM). Lee et al. discovered that [6]-gingerol induces TRAIL-mediated glioblastoma cell death. The bioactive component in ginger increased death receptor 5 (DR5) levels in a p53-dependent pathway, decreased antiapoptotic proteins (survivin, c-FLIP, Bcl-2, and XIAP), and increased pro-apoptotic proteins, Bax, and reduced Bid (ROS). The findings implied that TRAIL and [6]-gingerol could be used together to treat TRAIL-resistant glioblastoma tumors (Lee et al. 2008).

In an in vitro research, [6]-gingerol increased caspase-3 and caspase-7 activation and triggered apoptosis in gastric cancer cells. The stimulation of apoptosis was mediated by [6]-gingerol via blocking TRAIL-induced NF-kB activation and downregulating cellular inhibitor of apoptosis 1 (cIAP)-1 (Ishiguro et al. 2007; Prasad and Tyagi 2015). Mahady et al. studied the impact of [6]-, [8]-, and [10]-gingerols on 19 strains of *Helicobacter pylori* including the most vulnerable type cagA+. Infection with cagA+*Helicobacter pylori* strain significantly increased the probability of gastritis (Mahady et al. 2003).

According to Yagihashi et al., [6]-gingerol suppressed the growth and infiltration of rat ascites hepatoma cells. Cell cycle disruption and apoptosis are responsible for the therapeutic action of [6]-gingerol in these malignant cells (Yagihashi et al. 2008). Yusof et al. showed that ginger oleoresin had a chemoprotective effect against hepatocellular carcinoma in rats (Yusof et al. 2009), whereas Habib et al. discovered that ginger oleoresin reduced inflammation by lowering elevated levels of NF-kB and TNF-α in hepatocellular carcinoma cells (Habib et al. 2008). [6]-Gingerol triggered cell death in human HepG2 hepatoma cells by releasing cathepsin D prior to the production of ROS and the release of cytochrome-C from mitochondria (Yang et al. 2012). In HepG2 cells, [6]-gingerol suppressed the invasive and metastatic capabilities of phorbol 12-myristate 13-acetate (PMA) via blockage of MMP-9 and urokinase-type plasminogen activator (uPA), and also enhanced the production of tissue inhibitor metalloproteinase protein-1 (TIMP-1). Suppression of the MAPK and PI3k/Akt pathways, along with the functions of NF-kB and STAT3, revealed the process of invasion and metastasis (Weng et al. 2010).

Kim and Kim discovered that [6]-gingerol modulates tight junction-related proteins and decreases infiltration and metastasized pancreatic cancer cells via ERK/NF-kB/snail signaling pathway (Kim and Kim 2013). According to Akimoto et al., ginger extract slows down the cell cycle development and, as a result, accelerated cell death in human pancreatic cancer cell lines, notably PANC-1 cells (Akimoto et al. 2015).

Colorectal cancer (CRC) is one of the most prevalent cancers in men followed by lung and prostate cancer and in women after breast cancer (Jemal et al. 2011). A multistage genetic model of cancer development encompassing genetic variations of the APC gene, Kras, PI3k, and Wnt/-catenin, as well as bridge between these mechanisms, had a significant role in cell cycle advancement deregulation, cell death prevention, initiation of genomic instability, and improved intrusiveness and metastasis (Moran et al. 2010; Wu et al. 2013). Reduced apoptosis in the colon epithelium is linked to a higher probability of colorectal cancer. [6]-Gingerol treatment of human colon cancer cell elicited significant G2/M phase arrest having enhanced negative cell cycle regulators p27Kip1 and p21Cip1 while decreasing the amount of cyclin A, cyclin B1, and CDK1 (Lin et al. 2012).

Anti-inflammatory effect

The detailed study of *S*-[6]-gingerol revealed its anti-inflammatory activities. Tumor necrosis factor (TNF-α) and interleukin 1 (IL-1) are regarded as alarmins that trigger inflammatory cell recruitment by promoting the production of pro-inflammatory genes, whereas anti-inflammatory activities have been reported to be mediated by mitogen-activated protein kinase phosphatase-5 (MKP5) (Apte and Voronov 2002). TNF-α and IL-1β have been reported to enhance p38-dependent nuclear factor κB (NFκB) activation. These have also been reported to increase the expression of pro-inflammatory genes cyclooxygenase-2 (COX-2), IL-6, and IL-8 in normal prostatic epithelial cells. 6-Gingerol is also responsible to increase the regulation of MKP5, while decreasing the cytokine-induced p38-dependent pro-inflammatory changes (Nonn et al. 2007). Li et al. reported that nuclear factor κB (NFκB) and cyclooxygenase-2 (COX-2) are important inflammatory mediators of interleukins (Li et al. 2013).

Antioxidant effect

6-Gingerol possesses antioxidant properties by donating electrons and also behaves as free radical scavenger (Croft 1999; Ma et al. 2004). Many studies have revealed that 6-gingerol possessed significant genotoxic activity (Nonn et al. 2007; Yang et al. 2011; Wang et al. 2014). Moreover, it decreases elevated glucose amount and oxidative stress by raising superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), and decreased glutathione concentration

(GSH). Gingerols, shogaols, and paradols have also been reported to prevent angiogenesis and metastasis, apoptosis activation and suppression of cell cycle development (Chakraborty et al. 2012).

Cardiovascular effect

At low doses, gingerols and shogaols have been reported to induce depressant activity while at higher doses possessed cardiotonic properties (Wang et al. 2003). Liu et al. investigated that [6]-gingerol blocked the angiotensin-II type 1 receptor activation indicating thereby that ginger regulates the blood pressure and strengthens the cardiovascular system (Liu et al. 2013). The phenolic constituents 6-, 8-, and 10-gingerol were also reported for atropine-resistant and l-NAME-sensitive vasodilator activity (Ghayur et al. 2005). 6-Gingerol was reported to have some beneficial effects on cardiovascular disease due to decrease in intracellular Ca^{2+} (Han et al. 2019).

Antimicrobial activity

Gingerol and its related compounds possessed antimicrobial activities. Studies on [10]-gingerol have been found to suppress the development of bacteria *Mycobacterium avium* and *Mycobacterium tuberculosis* in an in vitro culture, while [6]-gingerol and [12]-gingerol reported to inhibit periodontal bacteria (Miri et al. 2008). In another study, [10]-gingerol and [12]-gingerol are found to inhibit three bacterial growth; *Porphyromonas gingivalis*, *Porphyromonas endodontalis*, and *Prevotella intermedia* (Park et al. 2008).

Anticoagulant effect

Gingerols and other related analogues are also essential for the inhibition of arachidonic acid-induced human platelet serotonin generation and coagulation. They provided a strong base for some more active synthesized gingerol derivatives with aspirin like potencies (Koo et al. 2001). Nurtjahja-Tjendraputra also reported the antiplatelet activities of gingerol, 8-shogaol, and 8-paradol (Nurtjahja-Tjendraputra et al. 2003).

Antiobesity activity

In in vitro studies, gingerols have been found to improve the expression of specific genes and insulin-dependent glucose uptake in mouse 3T3-L1 pre-adipocytes(Sekiya et al. 2004). Also, in a mice model, [6]-gingerol was found to have a potential role in lowering the lipid in treating type 2 diabetes (Singh et al. 2009). It also possesses anti-obesity effect which helps to reduce the accumulation of lipid in mice when fed on high-fat diet (Okamoto et al. 2011). Investigations on 6-gingerol were revealed to depict anti-adipogenic effects as compared to 6-shogaol (Tzeng and Liu 2013; Tzeng et al. 2014). Activities of gingerol also reported in rat models which revealed the low levels of glucose, body weight, leptin, insulin, amylase, lipase plasma, and tissue lipids (Saravanan et al. 2014). [6]-Gingerol was also found to inhibit adipogenic differentiation and lipid deposition by activating the Wnt/β-catenin signaling mechanism. The β-catenin is important in adipogenic differentiation (Li and Zhou 2015). In another study, gingerenone A, [6]-shogaol, and [6]-gingerol had been found to show antiobesity property by reducing adipogenesis and enhanced the fatty acid catabolism (Mao et al. 2019).

Antiemetic effect

In the ileum of guinea pig, [6]-gingerol, [6]-shogaol, and galanolactone displayed anti 5-hydroxytryptamine (5-HT) effect (Yamahara et al. 1989; Huang et al. 1991) and the antiemetic effect is related to [6]-, [8]-, and [10]-gingerols and shogaols (Kawai et al. 1994). In another study, gingerols, shogaols, galanolactone, and di-terpenoid have been found to exhibit an important role in nausea and vomiting (Huang et al. 1991; Bhattarai et al. 2001), whereas in minks, gingerol possessed antiemetic activity. Although most of the studies in human beings have been supportive of the pre-clinical observations, yet some of these studies are found to be contradictory. It has also been found that [6]-gingerol, [8]-gingerol, [10]-gingerol, and 6-shogaol played important role as a 5-hydroxytryptamine 3 (5-HT3) antagonist, neurokinin-1 (NK-1) antagonist, antihistaminic, and possessed prokinetic activities (Haniadka et al. 2012). Many researchers have indicated that gingerols exhibited antiemetic activity but there are contradictory findings to prevent chemotherapy-induced nausea and vomiting (CINV) (Palatty et al. 2013). Extracts of gingerols and shogoals were found to increase gastric emptying effect and stimulated gastric antral contractions by their activity on cholinergic M receptors and serotonergic 5-HT and 5-HT receptors (Giacosa et al. 2015). The antiemetic efficacy of gingerol was demonstrated by using two vomiting models which revealed the reduction of cisplatin-induced consumption of kaolin in rats and emesis in minks. The pathway of gingerol has been associated to the modulation of 5-HT, SP, and DA mechanism (Li et al. 2020).

Antidiabetic activity

Antidiabetic properties of gingerols have been studied in a clinical trial with patients having diabetes and hypercholesterolemia. In this trial, a dose of 3 g/day (for a period of 30 days) had been given which reduced the blood glucose, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and very low-density

lipoprotein-cholesterol (VLDL-C) levels (Andallu et al. 2003). In another study, gingerols are reported for the delayed of diabetic complications (Saraswat et al. 2010). The major pungent components of ginger (gingerols) were found to improve diabetes. It also inhibited the enzymes relevant to type 2 diabetes which revealed a high ability to inhibit α-glucosidase and α-amylase in the management of type 2 diabetes (Rani et al. 2011). The ginger extract in ethyl acetate extract (5 µg/mL) had been found to improve glucose absorption in cells and expressed glucose transporter type 4 (GLUT4) on the outer membrane of the cells. These findings revealed that the antidiabetic activity of ginger (Rani et al. 2012). In type 2 diabetic patients, the ginger supplement significantly decreased the glucose concentrations and raised the insulin-sensitivity check index (Mahluji et al. 2013). Gingerols exhibited six types of mechanisms which revealed the antidiabetic effects such as the following: (1) elevated glucose absorption, (2) induction of 5′ adenosine monophosphate-activated protein kinase phosphorylation, (3) advancement of glucose transporter 4 (GLUT-4) translocation to cytoplasm, (4) suppression of glycation end product induced upsurge of ROS levels in pancreatic β-cells, (5) decline in fasting blood glucose amount and enhanced glucose intolerance, (6) optimization of hepato genetic expression of enzymes associated to glucose metabolism towards the reduction of gluconeogenesis and glycogenolysis whilst enhancing glycogenesis, resulting in lower blood glucose levels (Samad et al. 2017). The studies showed that by activation of GLP-1, 6-gingerol enhanced glucose-stimulated insulin production and increased glucose uptake in skeletal muscle (Son et al. 2015). In another study, [10]-gingerol was reported to exhibit potent antidiabetic effects due to decrease in serum glucose concentration (Yadav and Garg 2019).

Antiangiogenesis

Angiogenesis is a critical phase in cancer in which new blood vessels develop, allowing metastasized cancers to survive and expand. Matrix metalloproteinases (MMPs) are proteolytic enzymes which are abundant in a variety of malignant tumors. They are vital in tumor growth and metastasis. MMPs suppression may be a useful technique for preventing the invasion and metastasis of carcinoma cells (Rundhaug 2005).

The antiangiogenic effect of [6]-gingerol has been displayed in numerous investigations. [6]-Gingerol suppressed VEGF-induced multiplication of human endothelial cells by triggering G1 cell cycle arrest, according to Kim and coworkers. It also prevented endothelial cells from forming capillary-like tubes in response to VEGF, as well as endothelial cell sprouting in the rat aorta and the development of a VEGF-induced new blood channel in the mouse cornea (Kim et al. 2005). Weng et al. found that [6]-gingerol inhibited the release of VEGF and IL-8 in Hep3B hepatoma cells. They also revealed that [6]-gingerol can inhibit capillary tube development and shorten its length using HUVEC cells in a tube formation experiment, implying that it has antiangiogenic and anti-invasive properties (Weng et al. 2010, 2012). They also reported that [6]-gingerol might have anti-invasive effect against hepatoma cells (HepG2 and Hep3B) by regulating MMP-9 and TIMP-1 (tissue inhibitor metalloproteinase 1 (Weng et al. 2012). Furthermore, Kim et al. reported that [6]-gingerol had anti-angiogenic characteristics, inhibiting VEGF and fibroblast growth factor-induced multiplication and capillary-like tube development in endothelial and ovarian cancer cells (Kim et al. 2005). In a separate research, it was discovered that [6]-gingerol suppressed MMP-2 and MMP-9 in MDA-MB-231 (human breast cancer cells) and PANC-1 (pancreatic duct-like carcinoma) cells, respectively (Lee et al. 2008; Kim and Kim 2013).

Neuroprotective activity

In neuroblastoma cells, the neuroprotective potential of [6]-gingerol had been investigated in Ab(25–35)-induced oxidative stress. [6]-Gingerol inhibited intracellular ROS accumulation as well as stabilized Ab(25–35)-depleted endogenous antioxidant glutathione quantity, and also stimulated the mRNA and protein expression levels of antioxidant enzymes like c-glutamylcysteine ligase (GCL) and heme oxygenase-1 (HO-1) via induction of NF factor 2 (NFf2) (Lee et al. 2011).

Clinical studies

Recently, the clinical studies of ginger are gaining importance due to its beneficial effects in various types of diseases like cancer, nausea and vomiting, gynecological problems, etc. Various types of studies on ginger have been carried out in different parts of the world. The literature on clinical trials has been revealed with encouraging evidence regarding its efficacy on human health and safety (Marx et al. 2017; Danwilai et al. 2017).

In cancer patients, the multiple randomized clinical trials (RCTs) have revealed the potency of ginger in reducing CINV and also in dysmenorrheal, while in another study, ginger has been shown to improve lipid levels and improved glucose regulation, insulin susceptibility, and glycosylated hemoglobin of type-2 diabetes mellitus. The ginger treatment was reported to enhance the health and quality of life in patients of the CINV and also helped in reducing and delaying the CINV in children and adults (Pillai et al. 2011; Konmun et al. 2017).

Table 1 Clinical trials performed on ginger and its chemical constituents

S. no	Ginger	Clinical trials	Phase	Ref
1	Ginger oil	Reduction in knee pain rating	Double-blind, placebo-controlled experimental study	(Yip and Tam 2008)
2	[4]-, [6]-, [8]-, [10]-gingerol	No hypo-analgesic impact on quadriceps pain level in contrast to placebo	Double-blind, crossover design	(Black and O'Connor 2008)
3	Ginger	Equal to ibuprofen and mefenamic acid	Double-blind comparative study	(Ozgoli et al. 2009)
4	Ginger versus salicylate	This plant mixture is therapeutically useful for individuals with knee AO in reducing pain, muscle tightness, and restricted movement; its impact is equivalent to salicylate ointment	Block randomization method	(Zahmatkash and Vafaeenasab 2011)
5	Sublingual formulation of fever few/ginger	Reliable and efficacious as first-line therapy for abortion with patients suffering from migraine	Randomized 3:1	(Cady et al. 2011)
6	Plygersic gel (*Zingiber officinale; Zingiber cassumunar)*	Improves knee joint pain following 6 weeks of treatment	Double-blind, randomized, controlled trial	(Niempoog et al. 2012)
7	Ginger	If provided at the start and 3 days prior, it is an efficient and acceptable medication to alleviate pain in females with primary dysmenorrhea	Randomized, controlled trial	(Rahnama et al. 2012; Jenabi 2013; Kashefi et al. 2014)
8	Ginger combination (340 mg EV.EXT 35 *Zingiber officinalis* extract) + glucosamine	Upper SODA pain severity was reduced little but dramatically	Randomized controlled study	(Drozdov et al. 2012)
9	Ginger supplement in combination with other botanicals	Effective to lessen pain in the knee	Randomized, double-blind, parallel-efficacy, four-arm multicentre equivalence drug trial	(Drozdov et al. 2012; Chopra et al. 2013; Nieman et al. 2013)
10	Ginger supplement	Accelerates muscular strength recovery after rigorous training	Randomized groups	(Matsumura et al. 2015)
11	Ginger powder supplementation	Decrease inflammation markers in knee AO population	Double-blind randomized placebo-controlled clinical trial	(Naderi et al. 2016)

Table 2 Reported ginger extract based nanoformulations for the treatment of various types of diseased conditions

S. no	Nanoformulations	Properties	Experimental results	Ref
1	Ginger rhizome water extract	Antimicrobial activity	Bacterial growth suppression; *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Streptococcus pyogenes*, *Staphylococcus aureus, Bacillus subtilis*, *Rhizopus* sp., *Aspergillus niger*, *Candida albicans* thus may be employed as anti-bacterial medication industries	(Norhidayah et al. 2015)
2	Ginger extract	Protection against alcohol induced liver damage	Oral therapy of GNPs helped in protection of the liver against harmful effects of alcohol mainly due to presence of Shogaols in ginger	(Zhuang et al. 2015)
3	Ginger extract	Drug bioavailability	GNPs may help in improving in delivery of the nanoparticles to various parts of the body without inducing adverse effects and further improving the bioavailability in the target cells	(Khalil et al. 2016)
4	Ginger-derived nanoparticles	Molecular targeting and gene regulation	GNPs serve a part in molecular targeting and the regulation of genomic expression	(Zhang et al. 2016a, b)
5	Ginger-derived lipid nano-vectors	Prevention against IBD (Inflammatory bowel disease) and CAC (Coronary artery calcification)	The GDNP system is simple to develop and might even offer a viable treatment approach for the prevention and treatment of IBD and CAC	(Zhang et al. 2016a, b)
6	Ginger-derived nanoparticles	Anti-colitis	Useful in treating colitis without any side effect	(Zhang et al. 2016a)
7	Ginger-derived nanoparticles	Prevention of intestinal inflammation	Could prevent intestinal inflammation in mice suffering from acute colitis and chronic colitis	(Zhang et al. 2016a, b)
8	Ginger nanoparticles	Apoptosis	Responsible for inducing apoptotic activity against chemical-induced cancer in male rats. GNPs enhanced the amountof enzymatic antioxidants and reduced necrotic/apoptotic rate	(Abdu et al. 2017)
9	Ginger-derived nanoparticles	Drug delivery	GNPs may be beneficial in drug delivery to colon	(Zhang et al. 2016a, b)
10	Hydrogel system encapsulating shogaol	Anti-colitis	Reported to weaken symptoms and improve colitis wound repair in mice	(Zhang et al. 2018)
11	mRNAs of ginger exosome like nanoparticles (GELN)	Anti-colitis	GELN ameliorate mouse colitis	(Teng et al. 2018)
12	Ginger-derived nanoparticles	Body weight, hematological parameters and histological analysis	GNPs showed no symptoms of cytotoxicity and offer a safe route of medication administration	(Zhang et al. 2018)
13	Ginger-derived nanoparticles	Prevention against IBD	It has the ability to improve the therapy and management of IBD	(Mao et al. 2019)
14	Ginger extract	Antihepatotoxicity and nephrotoxicity	Helpfulin improving liver and kidney biochemical markers, oxidative stress and histopathological structure in rats	(Bakr et al. 2020)
15	Ginger-derived exosome-like nanoparticles	NLRP3 inflammasome assembling, IL-1β, and IL-18 production, pyroptosis	Impede the organization of the NLRP3 inflammasome, production of IL-1 and IL-18, along with pyroptosis in mice macrophages	(Chen et al. 2019)

Table 2 (continued)

S. no	Nanoformulations	Properties	Experimental results	Ref
16	Ginger-derived nanoparticles	Drug delivery	GNPs were combined with chitosan to provide a drug delivery method for the controlled release of 5-ASA favours at the gastric pH, that is advantageous towards IBD	(Markam and Bajpai 2020)
17	Silver nanoparticles of ginger	Protection against SARS-CoV-2	Ginger silver nanoparticles exhibit an inhibitory potential against SARS-CoV-2	(Mohammad et al. 2021)

Besides this, gingerols have been reported to prevent vomiting induced by an antiretroviral regimen (Dabaghzadeh et al. 2014). On the other hand, its treatment in postoperative nausea and vomiting (PONV) had no significant effect (Anh et al. 2020). The cinical trials on giner and its chemical constituents are given in (Table 1).

Also, nanoformulation of gingerols has been reported for treating the various types of activities (Table 2).

Discussion

Ginger has been reported for various types of diseases like gastrointestinal disorders, inflammatory bowel disease, peptic ulcer, motion sickness, etc. Lately, different gingerols have been found to show strong anticoagulant effects, anti-inflammatory effects, antiemetic effects, antinociceptive effects, antioxidant effects, cardiovascular effects, antitussive effects, immunomodulatory effects, lipid effects, weight loss effects, antimicrobial activities, and chemopreventive activities. Various studies also revealed that gingerol and its derivativesare responsible to inhibit tumor promotion in mouse skin. However, not much is understoodabout the processesthrough which ginger and its derivatives accomplish these properties. Recently, many studies have demonstrated the different types of mechanisms with animalmodels. Moreover, more research is needed to determine the properties and mechanisms of gingerol and its compounds in human intervention trials and gene expression.

Conclusion and future prospects

Ginger and its phytoconstituents are considered as a safe option to treat different diseases due to no significant adverse effects. Among several chemical constituents like gingerols, shogaols, paradols, dihydroparadols, diarylheptanoids, zingiberene, phellandrene, etc., gingerols are found to be accountable for different therapeutic and pharmacological actions. Many studies have revealed its therapeutic applications in the therapy of cancer, its effect as antioxidant, antibiotic, antiemetic, antidiabetic, antiangiogenesis etc., [6]-, [8]-, [10]-gingerols and [6]-shogaol act on the 5-HT3 receptor ion-channel complex, by binding to a modulatory site (Abdel-Aziz 2006). Various studies have thus confirmed that these can be exploited for future phyto-medicine. However, more studies are required for the control of the disease development via modulation of antioxidant, metabolic and genetic activities. Therefore, more systematic research with detailed methodologies and numerous clinical trials are required to address the functional characteristics of ginger.

Current treatments for various types of human diseases are based upon the use of synthetic drugs which give good results. However, these also show adverse side effects. Various constituents of gingerol have been found to be quite effective against many human diseases such as cardiovascular diseases, cancer, diabetes, obesity and many more. Besides, these constituents are safe and competitively inexpensive. Therefore, gingerol and its constituents have created optimism towards the unique and novel therapeutic strategies against these diseases. More research is needed to investigate the molecular pathway for the mechanism of action of gingerol which will open a newvista for its use in large scale.

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Data Availability No datasets were generated or analyzed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval Since no slaughtering of animal was done so there is no need for ethical approval for publishing this manuscript.

Conflict of interest The authors declare no competing interests.

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