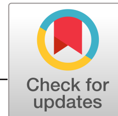
Received: 2 February 2018 | Revised: 31 May 2018 | Accepted: 5 June 2018
DOI: 10.1002/ptr.6134



REVIEW

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Protective and therapeutic potential of ginger (*Zingiber officinale*) extract and [6]-gingerol in cancer: A comprehensive review

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Natural dietary agents have attracted considerable attention due to their role in promoting health and reducing the risk of diseases including cancer. Ginger, one of the most ancient known spices, contains bioactive compounds with several health benefits. [6]-Gingerol constitutes the most pharmacologically active among such compounds. The aim of the present work was to review the literature pertaining to the use of ginger extract and [6]-gingerol against tumorigenic and oxidative and inflammatory processes associated with cancer, along with the underlying mechanisms of action involved in signaling pathways. This will shed some light on the protective or therapeutic role of ginger derivatives in oxidative and inflammatory regulations during metabolic disturbance and on the antiproliferative and anticancer properties. Data collected from experimental (in vitro or in vivo) and clinical studies discussed in this review indicate that ginger extract and [6]-gingerol exert their action through important mediators and pathways of cell signaling, including Bax/Bcl2, p38/MAPK, Nrf2, p65/NF-κB, TNF-α, ERK1/2, SAPK/JNK, ROS/NF-κB/COX-2, caspases-3, -9, and p53. This suggests that

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ginger derivatives, in the form of an extract or isolated compounds, exhibit relevant antiproliferative, antitumor, invasive, and anti-inflammatory activities.

KEYWORDS

[6]-gingerol, anticancer activity, ginger extract, mechanism of action

1 | INTRODUCTION

Cancer continues to be a global burden, despite the advent of various technological and pharmaceutical improvements over the past two decades (Seyed, Jantan, Bukhari, & Vijayaraghavan, 2016). According to statistics released by the Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA), it is estimated that 600,000 new cases of cancer will be reported in Brasil between 2016 and 2017 (INCA, 2016). Excluding cases of nonmelanoma skin cancer, the most frequent types in men are prostate (28.6%), lung (8.1%), intestine (7.8%), stomach (6.0%), and oral cavity (5.2%), whereas in women, mammary carcinoma (28.1%), intestine (8.6%), cervix (7.9%), lung (5.3%), and stomach (3.7%; INCA, 2016). Cancer is a set of heterogeneous genetic instabilities linked by common alterations in multiple cell signaling pathways (Luo, Solimini, Elledge, & Stephen, 2009). In this regard, numerous markers have been identified as important mediators in cancer cells, with apoptotic evasion reported as one of the major changes that determine tumor growth (Hanahan & Weinberg, 2011). In addition, other features may be included, such as self-sufficiency in growth signaling, cellular energy mismatch, sustained angiogenesis, evasion of immune detection, and metastasis (Hanahan & Weinberg, 2000; Luo et al., 2009). Cancer treatment methods include surgery, radiotherapy, and anticancer drugs (chemotherapy), in addition to other specialized techniques. Published reports indicated that approximately 90%–95% of all cancers are due to lifestyle, such as alcohol consumption, obesity, pollution, alcohol consumption, and food additives and the remaining 5%–10% to defective genes (Rauf et al., 2018).

The optimal effect of treatment involves improving quality of life, prolonging survival time, and lessening side effects. Thus, the concept of “survival with cancer” has emerged (Qi et al., 2015). For years, humans have used herbs as complementary therapy or dietary agents to treat different types of cancer and to influence cellular signaling (Martin, 2006). In this regard, natural compounds or natural dietary agents, in particular spices and herbs, have attracted the attention of scientists owing to their various properties in promoting health and have been employed as alternative drugs in the treatment of cancer (Kaefer & Milner, 2008). In this context, numerous reports have indicated that compounds found in ginger can be effective in attenuating the symptoms of chronic inflammatory disorders, as well as antitumor, antioxidant, bactericidal, and antiviral agents (Manasa, Srinivas, & Sowbhagya, 2013). Thus, they can provide a wide range of preventive and therapeutic options against different types of cancer. In addition, infusions prepared from ginger are popular folk remedies in several countries for a wide range of diseases (Khaki & Fathiazad, 2012).

Alternative and complementary medicine, involving the use medicinal plants as a source of therapeutic agents, has been used for ages. In addition, phytochemicals extracted from medicinal plants have been extensively studied in several countries and have been used to treat various disorders including inflammation, hypertension, kidney problems, immune deficiency, and cancer (Cragg & Newman, 2013). The major phytochemical constituents that have shown promising activities are secondary metabolites. They are widely distributed in the plant kingdom and have been a great source in preventive and therapeutic medicine, including anticancer drug molecules. In this context, recent trends in cancer prevention revealed that ginger, its extract, and single compounds, have promising biomedical impacts. Ginger (*Zingiber officinale*), a spice widely utilized in food, is recognized for its healing properties in traditional medicine. Ginger rhizome is widely cultivated as a spice for its aromatic and pungent components, including essential oil and oleoresins (Kaur, Deol, Kondepudi, & Bishnoi, 2016). It was used in traditional medicine in the treatment of various gastrointestinal diseases such as nausea, vomiting, abdominal discomforts, and diarrhea and for the treatment of arthritis, rheumatism, pain, muscle discomfort, cardiovascular, and metabolic diseases. In addition to these documented properties, studies have revealed that ginger exhibits anticancer properties in a wide variety of experimental models (Tuntiwechapikul et al., 2010). Over a hundred of compounds have been reported from ginger. These compounds have been used in several food products such as soft beverages and also in many types of pharmaceutical formulations. Among these, [6]-gingerol, the major component in ginger rhizomes, has shown several interesting pharmacological and physiological activities. It exhibited anti-inflammatory, analgesic, and cardiotonic effects (Kubra & Rao, 2012). The biologically active constituents of ginger include gingerol, shogaol, paradol, and zingerone. Gingerol, or best known as [6]-gingerol (Figure 1) is identified as the main active constituent of fresh ginger and is available in significant quantities in the fresh rhizome. It is responsible for most of the pharmacological activities of ginger described earlier (Chang & Kuo, 2015; Young & Chen, 2002). On the other hand, shogaol can be derived from gingerols by elimination of the C-5 hydroxyl and with consequent formation of a C-4 and C-5 double bond (Benzie & Wachtel-Galor, 2011; Jiang, 2005; Shukla & Singh, 2007). Ju and coworkers have found that administration of [6]-gingerol inhibits tumor growth in several types of murine tumors, such as B16F1 melanomas, Renca renal cell carcinomas, and CT26 colon carcinomas, in mice (Ju et al., 2012). A mixture of aqueous

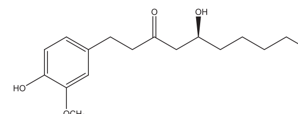

FIGURE 1 Structure of [6]-gingerol

extracts from turmeric, ginger, and garlic showed free radical scavenging potential and anticancer properties against human breast cancer cell lines (MCF-7, ZR-75, and MDA-MB 231) (Vemuri et al., 2017). The extract additionally induced apoptosis in all the breast cancer cell lines by altering the expression of apoptotic markers (p53 and caspase 9). Moreover, this extract showed a synergistically enhanced proapoptotic effect when used in combination with tamoxifen as compared with the extract alone (Vemuri et al., 2017). Components of ginger when used in formulations of novel products may serve for the purpose of pharmacological prevention of diseases.

On the other hand, deregulation of cell signaling pathways, caused by increased or decreased expression of its protein constituents, can lead to uncontrol of physiological events and trigger various types of diseases, including cancer. Signal transduction occurs through signaling pathways, which are usually composed of proteins involved in the regulation of cellular events, such as cell proliferation, migration, and differentiation (Souza, Araujo, Junior, & Morgado, 2014). Based on the above discussion and owing to the wide range of preventive and therapeutic options of ginger against various types of cancer, this review focusses on the current knowledge of the chemo-preventive and therapeutic ability of ginger extracts (EGs) and [6]-gingerol against different types of cancer, along with mechanisms of action. In addition, the current review evaluates the possible antioxidant and anti-inflammatory effects associated with tumor development.

2 | METHODS

2.1 | Search strategy

Recent relevant references pertaining to EGs and [6]-gingerol have been obtained from different databases, such as Science Direct, PubMed, Web of Knowledge, Medline, and Scopus for the period from January to October 2017, using search descriptors, which include "cancer," "antioxidant," and "inflammation" combined with "gingerol." Publications that have the terms described above in their titles or keywords were included.

2.2 | Selection of studies for inclusion in the systematic review

The following types of studies and investigations were included in this review: (a) experimental in vitro/in vivo, (b) clinical, (c) studies that include the use of EG and/or [6]-gingerol, (d) studies that indicate the concentrations or doses employed and the form of administration, and (e) studies that point out to the mechanisms of action associated with the extract treatment and isolated ginger derivatives.

2.3 | Data extraction

Data of each publication that meet the inclusion criteria were extracted according to surname of first author, year of publication, type and method of study, isolated compound and/or EG, concentrations tested, molecular mechanism involved, and main results obtained.

3 | RESULTS AND DISCUSSION

The search strategy identified 5,082 publications from PubMed (1,606), Science Direct (2,099), Web of Knowledge (595), Medline (204), and Scopus (578) databases. Three thousand eight hundred and seventy nine (3,879) items were excluded because they did not conform to the descriptors combination, whereas 667 were excluded due to duplication.

In the systematic review (qualitative synthesis), 131 publications were read in full, 96 of them were not adequate because they did not present mechanisms of action associated with the treatment of extract and ginger and [6]-gingerol, whereas 35 articles were used in the present review. Studies evaluated were published between 2000 and 2017, and those that met the criteria established cover the time period from 2005 to 2017; these are listed in an ascending order according to year of publication.

Common extraction procedures for ginger involve hydrodistillation, steam distillation, and solvent extraction. Solvent extraction with acetone resulted in a high ginger oleoresin content, which contains the essential oils as well as the pungent principles and other nonvolatile compounds present in ginger (McLaughlin, 2005). Additionally, ginger rhizhome extraction in acetone or ethanol resulted in isolation of gingerols (about 33%); however, extraction of ginger with ethyl ether, acetone, and hexane solvents has been established and is the preferred method. On the other hand, ethyl acetate extracted ginger was shown to have potent antioxidant activity. Similarly, microwave-assisted extraction of gingerol is also an efficient process, which results in increased total polyphenol content. Microwave-dried extract showed the highest quantity (1.5 fold) in TPP, [6]-gingerol content, and antioxidant activity when compared with the cross-flow dried extract (Kubra & Rao, 2012a). Moreover, a study focusing on extraction procedures for gingerol demonstrated that extraction temperature (50–80 °C) and extraction time (2–4 hr) are also important aspects (Ghasemzadeh, Jaafar, & Rahmat, 2015).

3.1 | Role of ROS in the body and oxidative stress

Reactive oxygen species (ROS) play an intriguing role in cells of normal and diseased phenotype through a number of mechanisms. Under normal physiological conditions, limited ROS generation assists in maintaining cellular homeostasis with the help of insulin, cytokines, and many growth factors (Sundaresan, Yu, Ferrans, Irani, & Finkel, 1995), leading to regulation of classical signaling cascades such as extracellular ERK, JNK, and mitogen-activated protein kinase (MAPK), including PI3-K/Akt, PLC-γ1, and JAK/STAT pathways (Droge, 2002). These pathways, in turn, exert their phenotypic effects, largely, by modulating the activities of central transcription factors, including NF-κB, AP1, Nrf2, FoxOs, HIF-1α, and p53 (Hamanaka & Chandel, 2010; Trachootham, Lu, Ogasawara, Valle, & Huang, 2008). Furthermore, activities of enzymes such as catalase, glutathione peroxidase, and peroxiredoxins regulated by kinases and phosphatases are susceptible to oxidative modification, thus creating a regulatory network (Flohe, 2010; Yu, 1994). At high levels, ROS can promote damage to several molecules, including DNA, that may trigger carcinogenic developments (Liou & Storz, 2010; Sundaresan et al., 1995; Waris & Ahsan, 2006).

In cancer patients, oxidative stress alters the expression of genes that inhibit cell cycle progression (called tumor suppressor genes) and thus increases proliferation of cancer cells (Afanas, 2014). Additionally, ROS promote expression of proteins involved in the control of inflammation, cell transformation, tumor cell survival, proliferation, invasion, angiogenesis, and metastasis. They also play an important role in the transformation of normal cells into carcinogens. In this respect, higher levels of ROS were identified in tumor cells than in normal cells. Collectively, reactive oxygen species play a dual role, they can kill cancer cells or promote tumor survival (Gupta et al., 2012; Krystona, Georgieva, Pissis, & Georgakilas, 2011). High amounts of ROS are detected in almost all types of cancer, where they promote many aspects related to the development of the tumor (Liou & Storz, 2010). Although ROS are protumorigenic, their high concentration may be toxic to even cancer cells. However, cancer cells also maintain elevated levels of antioxidant proteins expression that detoxify excess ROS. This indicates a necessary balance of intracellular ROS generation and quenching processes (Nogueira & Hay, 2013).

3.2 | Antioxidant effect of [6]-gingerol and EG

Antioxidants are substances, present in low concentrations when compared with the oxidizable substrate, which delay or inhibit its oxidation. These antioxidants protect the body from damage caused by the action of free radicals (Dias, Moura, & D'Angeliz, 2011; Machado, Nagem, Peters, Fonseca, & Oliveira, 2010). Antioxidants exert their action through different mechanisms of action, which include preventing the formation of free radicals (prevention systems), preventing the action of these reactive species (sweep systems), or even repair and reconstitute structures of biological damage (repair systems; Clarkson & Thompson, 2000; Koury & Donangelo, 2003). Free radicals generated from antioxidants are not reactive to the point of propagating the chain reaction. They react with other radicals and form stable products or can be recycled by other antioxidants (Barreiros, David, & David, 2006; Omoni & Aluko, 2005).

According to their mode of action, antioxidants can still be classified into primary and secondary. Primary antioxidants act by interrupting the chain of reaction by donating electrons or hydrogen atoms to free radicals, thus converting them into thermodynamically stable products and/or reacting with free radicals to form the antioxidant lipid complex that can react with other free radicals. On the other hand, secondary antioxidants act by delaying the initiation stages of autoxidation by different mechanisms, which include metal complexation, oxygen sequestration, decomposition of hydroperoxides to form nonradical species, absorption of ultraviolet radiation, and deactivation of singlet oxygen (Sousa et al., 2007). In the enzymatic antioxidant defense system, the enzymes superoxide dismutase, glutathione peroxidase, and catalases are present. These substances can remove oxygen or highly reactive compounds, react with oxidizing compounds, and protect cells and tissues from oxidative stress (Giustarini, Dalle-Donne, Tsikas, & Rossi, 2009). Nonenzymatic components of the antioxidant defense involves (a) minerals such as copper, manganese, zinc, selenium, and iron; (b) vitamins such as ascorbic acid, vitamin E, and vitamin A; (c) carotenoids such as beta-carotene, lycopene, and lutein; (d) bioflavonoids such as genistein and quercetin; and (e) tannins such as catechins (Papas, 1999).

Natural products contain a large number of phytochemicals and phenolic compounds that are associated with low occurrence of cancer in humans. Numerous studies indicated that consumption of foods rich in antioxidants provide protection against oxidative processes (Yildrin, Mavi, & Kara, 2001). The use of crude and phytochemical extracts isolated from medicinal plants is gaining popularity and is becoming more acceptable and preferable, possibly due to the cost of production, availability, and accessibility, as well as lower toxicity in most cases (Yehya et al., 2017). A large number of natural antioxidants have been isolated from different types of plant materials, such as oil seeds, cereals, vegetables, fruits, leaves, roots, spices, aromatic herbs, among others (Jayakumar, Thomas, & Geraldine, 2009). In this context, [6]-gingerol, a naturally occurring phenol obtained from edible ginger (*Z. officinale*), exhibits antioxidant, anti-inflammatory, free radical scavenging, antitumor, and antiendocrine activity. In addition, it acts as an immunomodulator, antiosteoarthritis, and antimicrobial agent (Oyagbemi, Saba, & Azeez, 2010; Prasad & Tyagi, 2015a; Srinivasan, 2014).

Based on the antioxidant mechanisms, Table 1 shows the protective effects of EG and/or [6]-gingerol in experimental (in vivo and in vitro) and clinical studies as antioxidants. Lee, Park, Kim, and Jang (2011) evaluated the effect of [6]-gingerol on human neuroblast lineage (SHSY5Y) exposed to β-amyloid peptide (Aβ 25–35), which is involved in the formation of senile plaques, and is a typical neuropathological marker for Alzheimer's disease. These researchers showed that pretreatment with [6]-gingerol (10 μM) significantly reduced Aβ 25–35-induced cytotoxicity; reduced the levels of malondialdehyde (MDA), ROS, and peroxynitrite (ONOO-); and increased the level of intracellular glutathione (GSH), thus suppressing oxidative and/or nitrosative damage induced by excess Aβ 25–35. It was additionally found that pretreatment with [6]-gingerol effectively suppresses the increase of Bax/Bcl2 ratio and reduces caspase-3 activation, increases phosphorylation, nuclear translocation, and subsequent transcriptional activation of nuclear erythroid 2 related to factor 2 (Nrf2; Lee et al., 2011). These results suggest that [6]-gingerol displays preventive and therapeutic potential that can be employed for the management of Alzheimer's disease through its antioxidant activity.

Under basal conditions, Nrf2 is mainly regulated by the Kelch-like ECH-associated protein 1 (Keap1), an adaptor subunit of Culina (Cul3)-Rbx 1 E3 ubiquitin ligase that mediates proteasomal degradation of Nrf2. Oxidative stress leads to conformational changes in the Nrf2-Keap1-Cul3 complex that activates Nrf2. Activated Nrf2 translocates to the nucleus and binds to the antioxidant response element (ARE) in the promoter region of Nrf2 target genes. Binding of Nrf2 to ARE results in synchronized activation of a battery of detoxification enzymes and antioxidants. Phytochemicals present in foods react specifically with the cysteine residues of Keap1, leading to a conformational change, which results in a decreased Nrf2 labeling for proteolysis (Duan et al., 2016; Niture & Jaiswal, 2012). In this context, the expression of Nrf2 and its downstream genes is dramatically enhanced by treatment with ginger phenols (gingerol/shogaol; Bak, Ok, Jun, & Jeong, 2012).

TABLE 1 Antioxidant effect of [6]-gingerol and ginger extract (EG)

Form of use	Method of study Dose or concentration	Mechanism of action EG and/or [6]-gingerol	Reference
EG	In vivo—Male Wistar rats (N = 50) ginger effect in the initiation and postinitiation stages of colon carcinogenesis induced by 1,2-dimethylhydrazine (DMH)—15 weeks—intraperitoneal route Administration of EG (50 mg/kg/day)—28 days—oral—gastric tube	Decreases lipid peroxidation Increases GSx, GST, GR, SOD, and CAT	(Manju & Nalini, 2005)
[6]-G	In vitro—Exposure of SHSY5Y to Aβ 25-35, (2.5, 7.5, 20 μM) and treatment with [6]-G (10 μM)	Decreases cytotoxicity induced by Aβ 25–35 Decreases MDA, ROS, $ONOO^-$, Bax/Bcl2 ratio, caspase-3 Increases GSH; Nrf2/ARE	(Lee, Park, Kim, & Jang, 2011)
EG	In vivo—Male Wistar (N = 8) albino rats with hepatic fibrosis induced by carbon tetrachloride (CCl4). Induction: CCl4 (0.5 ml/kg) intraperitoneally, six consecutive weeks, two times a week Group EG: 200 mg/kg—oral	Increases GSH, SOD, SDH, LDH, G6Pase, AP, and 5′NT Decreases MDA, AST, ALT, ALP, GGT, and total bilirubin	(Motawi, Hamed, Shabana, Hashem, & Naser, 2011)
EG	In vitro—Treatment of the cardiomyocyte (H9c2) line with EG (6–200 μg/ml) + DOX (5 μg/ml)	Decreases MDA and ROS Decreases DOX-induced apoptosis	(Hosseini, Shafiee-Nick, & Mousavi, 2014)
EG	In vitro—Treatment of HaCaT and BJ lines using EG (40 μg/ml)	Increases Nrf2 Increases GSTP1 cell line BJ	(Schadich et al., 2016)
EG	In vivo—Male Wistar rats (N = 10) Exposure to aflatoxin B1 (AFB 1) 200 μg/kg—28 alternate days—intraperitoneal Treatment of EG (100 and 250 mg/kg/day)—28 days—oral—gastric tube	Increases Nrf2 and HO-1 Increase antioxidant enzymes (SOD, CAT, and GST) Decreases MDA	(Vipin, Raksha Rao, Kurrey, Anu Appaiah, & Venkateswaran, 2017)
EG	In vitro—Effect of EG on aflatoxin B1 (AFB1) in HepG2 human hepatoma line. HepG2 pretreatment with EG (0–200 μg/ml) Exposure HepG2 to AFB1 (0–50 μM)	Decreases ROS	(Vipin et al., 2017)
[6]-G	In vivo—Sprague–Dawley (N = 8) rats with ischemic intestinal reperfusion injury (I/R) Pretreatment with [6]-G 25 mg/kg—three consecutive days prior to reperfusion—oral	Inhibition of the MAPK p38 pathway Increases SOD, GSH, and GSHP Decreases MDA	(Li et al., 2017)
[6]-G	In vitro—[6]-gingerol effects on Caco-2 and IEC-6 lines under conditions of hypoxia/reoxygenation (H/R) Pretreatment Caco-2 and IEC-6 with [6]-gingerol (5, 10, 20, 40, 80, and 160 μM)	Decreases ROS Inhibition of phosphorylation of p38 MAPK, p65 NF-κB, and MLCK.	(Li et al., 2017)
EG/[6]-G standardized	Clinical—43 patients newly diagnosed with cancer (19 ginger group and 24 placebo) Administration of two capsules 2 g/day—3 days—oral before the first cycle and during chemotherapy until the fourth cycle.	Increases antioxidant enzymes (SOD, CAT, and GSH/GSSG) Decreases MDA Decreases NO2/NO3	(Danwilai, Konmun, Sripanidkulchai, & Subongkot, 2017)

Note. Aβ 25–35: β-amyloid; GSH: Glutathione; GSx: glutathione peroxidase; GST: Glutathione S-transferase; GR: glutathione reductase; SOD: superoxide dismutase; MDA: malondialdehyde; ONOO-: peroxynitrite; Nrf2: Factor 2 erythroid-related Factor 2, LDH: lactate dehydrogenases; G6Pase: glucose-6-phosphatase; AP: acid phosphatase, 5′NT: 5′nucleotidase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GPx-1: phosphatase glutathione peroxidase-1; MLCK: myosinase kinase; GSTP1: glutathione S-transferase P1; CAT: catalase; ROS: reactive oxygen species; ARE: antioxidant response element; SDH: sorbitol dehydrogenase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; DOX: doxorubicin; GSSG: glutathione disulfide.

Schadich and colleagues evaluated the effects of the phenols present in EG on the activation of the Nrf2-ARE pathway and on the expression of phase II detoxification enzyme glutathione-S-transferase P1 (GSTP1) in immortalized keratinocyte cells (HaCaT) and foreskin fibroblasts. These researchers found a significant increase in the level of Nrf2 activity and that the increased level of Nrf2 in treated HaCaT cells was not associated with an increased GSTP1 enzyme level (Schadich et al., 2016). In HaCaT cells, regulation of Nrf2 independent of GSTP1 expression may have evolved selectively with high proliferation capacity during immortalization (an ability to proliferate an unlimited number of times). As immortalization is a first step in carcinogenesis, a variety of human cancer cells, including breast, colon, kidney, lung, and ovary cancer cells, share genomic instability, loss of senescence genes, p53 mutation, and high expression of GSTP1 (Howells et al., 2004; Tidefelt et al., 1992; Yamamoto et al., 2013). Additionally, the role of GSTP1 in HaCaT cells may be distinct from normal cells (Schadich et al., 2016). Although ginger has many bioactive compounds with pharmacological activities, only few of these

have been tested for their activity in chemoresistant cells. The protein expression of multidrug resistance associated protein 1 (MRP1) and glutathione-S-transferase (GSTπ) is higher in chemoresistant prostate cancer cell PC3R than in PC3. Liu, Kao, Tseng, Lo, and Chen (2017) isolated [6]-gingerol, [10]-gingerol, [4]-shogaol, [6]-shogaol, [10]-shogaol, and [6]-dehydrogingerdione from ginger and tested their anticancer properties in docetaxel-resistant (PC3R) and sensitive (PC3) human prostate cancer cells. These compounds significantly inhibited the proliferation of cells through downregulation of MRP1 and GSTπ (Liu et al., 2017).

Although cytoprotection provided by activation of Nrf2 is important for chemoprevention of cancer in normal and premalignant tissues in completely malignant cells, Nrf2 activity provides growth advantage by increasing cancer chemoresistance and by increasing tumor cell growth. The constitutively abundant Nrf2 protein causes increased expression of genes involved in drug metabolism, thus increasing resistance to chemotherapeutic drugs and radiotherapy. In addition, high levels of Nrf2 protein affect cell proliferation by targeting glucose and glutamine, increasing purine synthesis, and influencing the pentose phosphate pathway to promote cell proliferation (Mitsuishi et al., 2012).

On the other hand, the metabolic balance of oxygen in the intracellular environment is maintained by antioxidant enzymes, also known as phase II detoxification enzymes, such as heme oxygenase 1 (HO-1). Production of these enzymes occurs through activation of Nrf2/ARE antioxidant signaling pathway, by means of several substances investigated with antioxidant potential (Lee et al., 2015; Xia, Liu, Xie, Wu, & Li, 2015). Vipin, Raksha Rao, Kurrey, Anu Appaiah, and Venkateswaran (2017) have demonstrated that pretreatment with EG protects HepG2 cells against aflatoxin B1-induced cytotoxicity through inhibition of ROS generation, DNA damage, and cell death. Similarly, mouse model experiments revealed the protective effects of EG against AFB1-induced hepatotoxicity by improving antioxidant enzyme levels and by upregulation of the Nrf2/HO-1 pathway. The hepatoprotective properties of EG may be due to synergistic effects of different phenolic compounds present therein. According to Wang et al. (2016), antioxidant substances act by inhibiting the excess production of ROS.

Induction of Nrf2 signaling is associated with prevention of hepatotoxicity both in vivo and in vitro. Nrf2 is mainly expressed in metabolically active organs such as the liver. Therefore, Nrf2 is considered as a key therapeutic target for prevention and treatment of liver diseases (Eggler, Gay, & Mesecar, 2008; Lee & Surh, 2005; Zhu et al., 2016). In addition, Nrf2 is important in chronic diseases involving oxidative stress such as inflammatory, neurodegenerative, and cancer diseases (Kaspar, Niture, & Jaiswal, 2009; Kensler, Wakabayashi, & Biswal, 2007).

Furthermore, oxidative stress plays a key role in intestinal H/R injury (Wen et al., 2013). ROS are generated in damaged tissues and cells and trigger activation of a variety of signaling pathways, promoting inflammatory reaction, and damaging the intestinal mucosal barrier function in the H/R process (Bhattacharyya, Chattopadhyay, Mitra, & Crowe, 2014). The signaling pathway of mitogen-activated p38 protein kinase (p38 MAPK) mediates inflammatory, apoptotic response, and differentiation under stress conditions, including H/R lesions (Coulthard, White, Jones, Mcdermott, & Burchill, 2009; Yong, Koh, & Moon, 2009; Zhang, Shen, & Lin, 2007). Under stress conditions, intracellular p38 can be transferred to the nucleus, and expression of genes involved in the regulation of transcription factors is regulated by phosphorylation (Wehner et al., 2009; Yang et al., 2015). In a similar fashion, myosin light chain kinase (MLCK) is a protein kinase closely related to the barrier function. The MLCK-mediated myosin light chain phosphorylation is associated with cytoskeletal contraction and leakage junction (tight junction [TJ]) dysfunction, which may impair the intestinal mucosal barrier function (Al-Sadi et al., 2013; Cunningham & Turner, 2012; Su et al., 2013). Similarly, the p38 MAPK pathway is involved in the MLCK-mediated modulation in the barrier function (Al-Sadi et al., 2013; Araki et al., 2005; Zou et al., 2015).

In Caco2 (human colon adenocarcinoma) and IEC6 (murine normal intestinal epithelium) cells under H/R conditions, expression of NF-κB, MAPK, and MLCK proteins was significantly increased. However, pretreatment with [6]-gingerol exerted inhibitory effects depending on the concentration. Additionally, [6]-gingerol suppressed phosphorylation of p65 which is a critical subunit in the modulation of NF-κB nuclear translocation, and decreased MLCK protein expression and phosphorylation of p38 MAPK in a concentration-dependent manner, highlighting the important role in suppression of [6]-gingerol-induced p38 MAPK in H/R model. Moreover, research findings indicated that drugs that improve oxidative stress, relieve inflammation, and pain, inhibit bacterial growth, and modulate barrier dysfunction are beneficial for the improvement of intestinal lesion (Li et al., 2017).

Li and coworkers investigated the effect of [6]-gingerol on rat intestinal ischemic–reperfusion (I/R) injury. These workers found that treatment of rats with this compound alleviated intestinal injury in I/R injured rats. This was achieved by significantly increasing levels of superoxide dismutase (SOD), GSH, and glutathione peroxidase and by substantially decreasing the level of MDA. These results suggest that [6]-gingerol provides protective effects against I/R-induced intestinal mucosa injury by impeding generation of ROS and p38 MAPK activation, providing insights into the mechanisms of this therapeutic candidate for the treatment of intestinal injury (Li et al., 2017). On the other hand, carbon tetrachloride (CCl_4) is a known hepatotoxin widely used in the induction of toxic liver injury in laboratory animals (Lee et al., 2007; Pereira-Filho et al., 2008). The initial phase involves metabolism of CCl_4 by cytochrome P-450 to trichloromethyl radical ($CCl_3^{\bullet}$). Some of these trichloromethyl radicals generate trichloromethyl peroxyl radical ($OOCCl_3^{\bullet}$), which leads to lipid peroxidation. In this regard, Motawi, Hamed, Shabana, Hashem, and Naser (2011) reported that treatment of rats with hepatic fibrosis induced by carbon tetrachloride, with EG showed a significant increase in GSH, SOD, SDH, LDH, G6Pase, AP, and 5'NT. However, MDA, AST, ALT ALP, GGT, and total bilirubin were significantly decreased. Similarly, ginger supplementation at the initiation and postinitiation stages of colon carcinogenesis induced by 1,2-dimethylhydrazine significantly increased nonenzymatic and enzymatic antioxidant concentrations compared with the nonginger supplemented group (Manju & Nalini, 2005).

In a recently published clinical investigation, the antioxidant activity of EG oral supplement in newly diagnosed cancer patients receiving adjuvant chemotherapy compared with placebo was examined. Results revealed that antioxidant activity parameters including SOD,

CAT, GPx, and GSH/GSSG were significantly increased at Day 64 with patients who received two EG capsules standardized with 5 mg of [6]-gingerol (1.4% w/w EG) 3 days prior to the first cycle of chemotherapy, and continued on this supplement to the fourth cycle, compared with the placebo group. On the other hand, MDA and NO_2^- /NO_3^- levels were significantly lower than the treated group (Danwilai, Konmun, Sripanidkulchai, & Subongkot, 2017).

Similarly, doxorubicin (DOX) is an important component in the multimodal therapy of various combined antineoplastic protocols in chemotherapy. However, despite its high efficacy, DOX's main side effect of cardiotoxicity drastically prevents its clinical use for extended periods. There is much evidence that the protective effects of natural compounds against cardiotoxicity is related to oxidative damage. These compounds lessen some side effects of chemotherapeutic agents in normal cells and thus reduce their genotoxicity (Bryant et al., 2007; Wu et al., 2002). Research findings demonstrated that EG exerts a protective role against DOX-induced toxicity in cardiomyocytes (H9c2), as shown by reduction in the level of lipid peroxidation, ROS, and suppression of apoptosis induced by doxorubicin in H9c2 (Hosseini, Shafiee-Nick, & Mousavi, 2014).

3.3 | Inflammation and cancer

Inflammation is a protective immune response of a vascular organism that assists in the removal of internal and/or external harmful stimuli and operates to maintain tissue homeostasis (Serhan, 2014). The inflammatory reaction basically comprises two defense mechanisms: a nonspecific response (innate response) and a specific immune response (acquired response; Coutinho, Muzitano, & Costa, 2009). At the beginning of an inflammatory response due to tissue aggression, invasive inflammatory cells produce several proinflammatory mediators that increase the degree of local and systemic inflammation (Melo, Yugar-Todelo, Coca, & Júnior, 2007), depending on the type of infection: bacterial, viral, or parasitic (Medzhitov, 2010).

An infection in any tissue rapidly attracts white blood cells to the affected region as part of the inflammatory response, which helps to fight infection and in wound healing (Alberts et al., 2010). However, the initial inflammatory response is not always sufficient, and the process may progress to a state of chronic inflammation (Coutinho et al., 2009). If the agent that causes infection is not completely cleared by the acute inflammatory response, or it persists for some reason, a chronic inflammation may result. This condition can be caused by chronic infections, persistent allergens, and foreign particles or endogenous crystals (Medzhitov, 2010). Moreover, when the inflammatory response is uncontrolled, it becomes harmful to the body. Although symptoms and signs of chronic inflammation are not as severe as those of acute inflammation, chronic inflammation is typically more risky as it can cause additional damage like fibrosis, and can cause chronic and systemic diseases such as rheumatoid arthritis, asthma, diabetes, inflammatory bowel diseases, cardiovascular diseases, neurological disorders (Alzheimer's), age-related muscular degeneration, and cancer (Mantovani, Allavena, Sica, & Balkwill, 2008; Serhan & Petasis, 2011).

Chronic inflammation is linked to several stages of tumorigenesis such as cell proliferation, transformation, evasion of apoptosis, survival, invasion, angiogenesis, and metastasis (Aggarwal, Shishodia, Sandur, Pandey, & Sethi, 2006; Demaria et al., 2010). Inflammation is additionally known to contribute to carcinogenesis by generation of ROS and reactive nitrogen species that can damage DNA at the tumor site (Ohnishi et al., 2013). Furthermore, the inflammatory medium promotes a cellular microenvironment that favors expansion of genomic aberrations and initiation of carcinogenesis (Mantovani, 2009). Studies suggest that approximately 25% of cancers are etiologic in inflammation and/or chronic infection (Kundu & Surh, 2012). In the tumor microenvironment, inflammatory cells are induced to accelerate cancer progression, metastasis, and immune responses against radiation therapy, chemotherapy, and immunotherapy (Gajewski, Schreiber, & Fu, 2013). Therefore, the direction of the inflammatory microenvironment is a reasonable direction for cancer treatment (Q. Zhang, Zhu, & Li, 2017).

3.4 | Mediators of the inflammatory process in the tumor microenvironment

Acute inflammation triggers cellular repair response for damaged tissues leading to tissue homeostasis. Under normal conditions, immune cells including macrophages, granulocytes, mast cells, dendritic cells, innate lymphocytes, and natural killer cells serve as a front line defense against pathogens (Coussens, Zitvogel, & Palucka, 2013; Serhan, 2014). However, in tumor microenvironment, chronic inflammation of “damaged” (tumor) tissue may result. Thus, while acute inflammation normally supports and balances two opposing needs for the repair of damaged tissues (apoptosis and wound healing), chronic inflammation represents a loss of this balance (Khatami, 2009).

Several mechanisms exist by which inflammation contributes to carcinogenesis, including altered biochemical processes such as a high expression, overproduction, or abnormal activation of several inflammatory mediators, with cytokines, chemokines, cyclooxygenase-2 (NOS), nitric oxide (NO), and advanced glycosylation products (Kundu & Surh, 2012). Chronic inflammatory cells can induce genomic instability, alterations in epigenetic events and inappropriate gene expression (Colotta, Allavena, Sica, Garlanda, & Mantovani, 2009; Kundu & Surh, 2008). During tumor progression, cytokines and chemokines produced by immune and inflammatory cells facilitate the survival and proliferation of cancer cells and promote angiogenic tumor growth (Mantovani, 2005). Cytokines and chemokines also induce additional recruitment and differentiation of immune cells in the tumor microenvironment (Lin & Karin, 2007). The genetic regulation that leads to secretion of proinflammatory cytokines from a variety of cells is generally dependent on the transcriptional activation of nuclear factor-kappa B (NF-κB; Freire & Van Dyke, 2014). This factor could be considered as a “nucleus” in the tumorigenesis that links cellular senescence, inflammation, and cancer (Aggarwal & Gehlot, 2009). Inflammation is characterized by an overall increase in plasma levels and cellular capacity to produce proinflammatory cytokines such as interleukin (IL) 6, IL-1, tumor necrosis factor (TNF)-α, and a subsequent increase in the main inflammatory markers such as C-reactive protein and serum amyloid A (Franceschi, 2007; Franceschi et al., 2000). TNF, known for its tumor cytotoxicity, is a cytokine involved in systemic inflammation and stimulation of the acute phase reaction (Sedger & Mcdermott, 2014). On the other hand, products derived from COX-

2, mainly prostaglandin (PG) E2 (thought to be the major tumorigenic COX-2 product), are known to act not only on classical pathways of cancer signaling to promote carcinogenesis in tumor cells but also in the tumor microenvironment that contains multiple resident and infiltrating cells (including immune cells), as well as on the growth factors and cytokines released by them (Bonaccio et al., 2014; Hanahan & Weinberg, 2011). Consequently, the relationship between inflammation and cancer that promotes tumors is important to consider. Overall, mechanisms involving abnormal activation of inflammatory mediators that contribute to the development of tumor microenvironment are depicted in Figure 2. In this respect, macrophage migration inhibitory factor, COX-2, NF-κB, TNF-α, inducible nitric oxide synthase (iNOS), and Akt and chemokines are important targets that may be appropriate for a multifaceted therapeutic approach in suppressing inflammation (Block et al., 2015).

Based on reports on anti-inflammatory mechanisms, Table 2 shows the suppressive effects of EG and/or [6]-gingerol on inflammatory responses associated with chronic and systemic diseases, with emphasis on carcinogenesis, and on experimental and clinical studies in the face of factors released during chronic inflammation. In addition, EG significantly reduced the elevated expression of NF-κB and TNF-α in rats with hepatic cancer, suggesting that ginger can act as an anticancer and anti-inflammatory agent; it inactivates the NF-κB by suppression of proinflammatory TNF-α. Although this factor is expressed in an inactive state in most cells, cancer cells express an activated form of NF-κB induced by various inflammatory and carcinogenic stimuli (Lin & Karin, 2003). Furthermore, TNF-α, interleukins, COX-2, and other chemokines can also be regulated by the NF-κB transcription factor (Balkwill, 2002). In this context, numerous studies have associated the NF-κB signaling pathway and its regulation with the inflammatory response (Escarcega, Fuentes-Alexandro, Garcia-Carrasco, Gatica, & Zamora, 2007; Lin & Karin, 2003). NF-κB acts as transcriptional regulator for Bcl-2 family of apoptosis related poteins. In a carcinogenic process, it mediates the altered expression of proapoptotic and antiapoptotic Bcl-2 family proteins. These observations suggest that inhibition of the NF-κB signaling pathway might be a therapeutic strategy in conjunction with the use of chemopreventive agents such as ginger (Kim, Chun, Kundu, & Surh, 2004; Surh, 2003).

Lipopolysaccharide (LPS), the main constituent of the outer cell wall of Gram-negative bacteria, has been widely used to examine inflammation mechanisms that produce typical hepatic necrosis followed by fulminant hepatic failure (Vincent, Sun, & Dubois, 2002). It was found that, under stimulation of LPS, Kupffer cells release proinflammatory cytokines (Bølling, Samuelsen, Morisbak, Ansteinsson, & Becker, 2013). Activation of LPS-induced NF-κB mediates MAPKs, and subsequently regulates COX-2 expression, and inducible expressions of nitric oxide synthase (iNOS; Mestre et al., 2001). In addition, expressions of COX-2 and iNOS contribute to inflammatory diseases (Jacobs & Ignarro, 2001). Therefore, these cytokines represent an ideal target for neutralization of LPS (Wyckoff, Raetz, & Jackman, 1998). Furthermore, prolonged use of anti-inflammatory drugs is associated with side effects such as fever, flushing, and sore muscles. In this case, the use of a natural product to treat inflammatory diseases may be more effective with fewer side effects (Wong et al., 2003).

Elevated levels of prostaglandin E (PGE) in the tissue, produced by COX, is an early event in colorectal cancer (CRC). Jiang et al. (2013) observed no significant difference in COX-1 protein expression between the ginger and placebo groups of participants at normal risk. However, results indicated that, for patients at increased risk of colorectal cancer, COX-1 protein expression in colon biopsies was significantly inhibited by consumption of ginger root extract after 28 days of intervention compared with the placebo group. Healthy and tumor cells share the same origin; thus, it is difficult to develop selective drugs that are based on biochemical differences between cancer and healthy cells. Consequently, researchers and clinicians need a new perspective and, for this reason, signaling pathways are being intensively investigated to gain ground in the fight against cancer. Inhibition

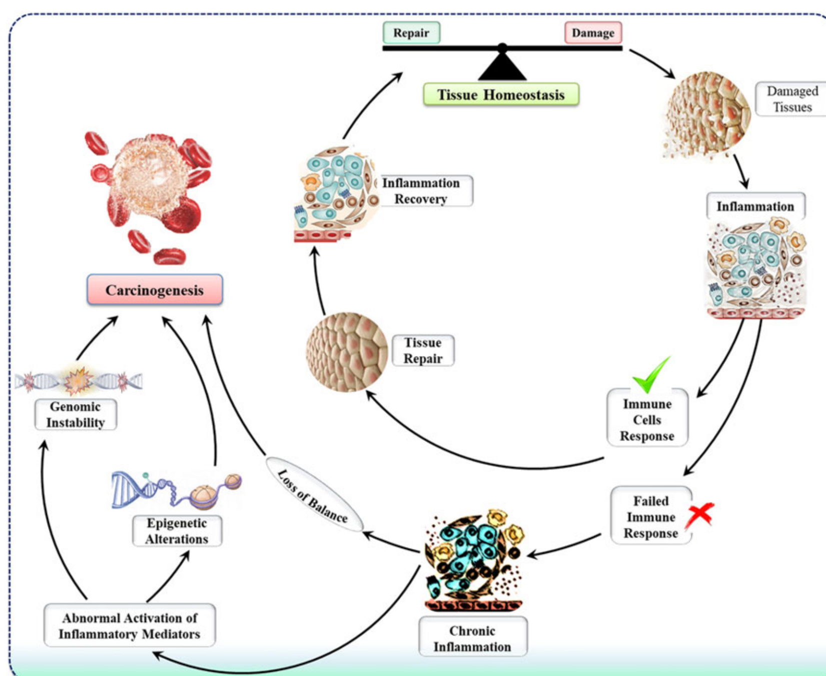

FIGURE 2 Mechanisms involving abnormal activation of inflammatory mediators that contribute to the development of tumor microenvironment [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Anti-inflammatory effect of ginger extract (EG) and/or [6]-gingerol

Form of use	Method of study Dose or concentration	Mechanism of action EG and/or [6]-G	Reference
EG	In vivo—Effect of ginger on ethionine-induced hepatocarcinogenesis, male Wistar rats (*N* = 6) Induction of hepatic cancer with ethionine—15 weeks—intraperitoneal route Food/olive oil controls; EG (100 mg/kg); choline deficient diet (CDE) + 0.1% ethionine; ginger + CDE. 8 weeks—oral	Decreases NF-κB Decreases TNF-α	(Habib et al., 2008)
EG	In vivo—To characterize the possible anti-inflammatory effects of lipopolysaccharide (LPS)-induced EG in female rats (N-5) Pretreatment with EG 100, 1,000 mg/kg—3 days in a row—oral Third day—LPS administration —35 mg/kg—intraperitoneal	Decreases activation IFNγ, IL-6, NF-κB, and I?B-α Decreases expression MAPKs (ERK1/2, SAPK/JNK, and p38) Decreases iNOS and COX-2 expression	(Choi, Kim, Hong, Kim, & Yang, 2013)
EG	Clinical—To verify the efficacy of EG in the regulation of PGE2 in patients with normal and increased risk of CRC Administration of eight capsules 250 mg each for 28 days, followed by biopsy tissue colon Normal group (*N* = 30); increased risk—CRC (*N* = 20)	Decreases COX-1 (group at increased risk CRC)	(Jiang et al., 2013)
[6]-G	In vitro—Effect of [6]-G on human hepatocyte (HuH7) lineage Cell viability [6]-G (50, 100, and 200 μM) HuH7 exposed to cytokine IL-1β (8 ng/ml) and treated with [6]-G (100 μM)	Decreases IL-6, IL-8, SAA1, COX, NF-κB, and ROS Inhibition via ROS/NF-κB/COX-2	(Li et al., 2013)
[6]-G	In vitro—Effects of [6]-G on human MG63 osteoblast-like lineage Exposure of MG63 line (1 × 105) to pretreatment TNF-α (10 ng/ml) and treatment [6]-gingerol (0, 1, 5, 10, and 50 μM)	Increases ALP enzyme	(Fan, Yang, & Bi, 2015)
EG padronizado com 5% [6]-G	In vivo—Albino Wistar rats of both sexes (*N* = 15) Induction diabetes: single dose of STZ 45 mg/kg—intraperitoneal route Treatment: 75 mg/kg/day/24 weeks—oral	Treated group EG/5% [6]-G Decreases TNF-α Decreases NF-κB p65 Decreases VEGF	(Dongare et al., 2016)
[6]-G	In vitro-effect of [6]-gingerol on LTA 4 H in human tumor line (HCT116) and normal cells (TIG1 and HF19) exposed to [6] -G (6.25; 12.5; 25.5 and 100 μM).	Inhibition of activity LTA 4H	(El-Naggar et al., 2017)
[6]-G	In vivo—Characterize the possible protective effects of [6]-G on intestinal reperfusion injury (I/R). Sprague–Dawley rats (*N* = 40) Pretreatment with [6]-G 25 mg/kg—intragastric route—3 days before reperfusion	Inhibition of the p38 MAPK pathway Inhibition of inflammatory cytokines (TNF-α, IL-1β, and IL-6) and mediators (NO/iNOS)	(Li et al., 2017)

Note. LTA 4H: leukotriene A 4 hydrolase; TNF-α: tumor necrosis factor alpha; IL-1β: interleukin 1 beta; IL-6: interleukin 6; iNOS: inducible nitric oxide synthase; NO: nitric oxide; ALP: alkaline phosphatase; COX-1: cyclooxygenase 1; COX-2: cyclooxygenase 2; CRC: colorectal cancer; IFN-γ: interferon-gamma; NF-κB: nuclear factor kappa B; IκBα: inhibitor kappa B; interleukin 8 (IL-8); SAA1: Serum amyloid A; STZ: streptozotocin; VEGF: vascular endothelial growth factor; PGE2: prostaglandin E2; SAPK: stress-activated protein kinase; JNK: Jun N-terminal kinase; ROS: reactive oxygen species; ALP: alkaline phosphatase; MAPK: mitogen-activated protein kinase.

of prostaglandin E2 synthase-1 microsomal (mPGES1) and receptor antagonism of its PGE2 product are considered potential therapeutic targets for cancer cells expressing COX-2 (Reader, Holt, & Fulton, 2011). Eventually, carcinogenesis is promoted by PGE 2 via GSK-3β/β-catenin. Therefore, decreasing the level of PGE2 using mPGES-1 inhibitors may be expected to show anticancer effect, and may have a bright future as therapeutic agents (Ruana & So, 2014).

In a study by Li et al. (2013), human HuH7 hepatocyte cells were stimulated with IL-1β to establish an in vitro hepatic inflammatory model, [6]-gingerol attenuated IL-1β-induced inflammation and oxidative stress in these cells. This was evidenced by the decrease in levels of inflammatory factors IL-6, IL-8, and SAA1, in addition to suppression of ROS generation. Additionally, [6]-gingerol reduced IL-1β-induced positive regulation of COX-2 as well as NF-κB activity. The protective effect of [6]-gingerol with the IL-1β-induced inflammatory response is similar to that of butylated hydroxytoluene, an ROS scavenger. Thus [6]-gingerol could protect HuH7 cells against inflammatory damage induced by IL-1β by inhibiting the ROS/NF-κB/COX-2 pathway (Li et al., 2013).

In a similar fashion, Fan, Yang, and Bi (2015) investigated the effect of [6]-gingerol on the production of IL-6 in osteoblasts. Results revealed that [6]-gingerol lowers the degree of inflammation in TNF-α-treated MG-63 cells. In addition, treatment with [6]-gingerol increased the activity of ALP enzyme in MG-63 cells in a dose-dependent manner, whereas ALP activity was significantly reduced in response to stimulation of TNF-α. [6]-Gingerol was thus reported to be a promising candidate for treating osteoporosis or bone inflammation (Fan et al., 2015). The effect of ginger was even interesting in diabetic conditions where EG standardized with 5% [6]-gingerol attenuated retinal microvascular changes in streptozotocin-induced diabetic Wistar albino rats. Additionally, orally administered [6]-gingerol extract in diabetic rats reduced the levels of the proinflammatory marker TNF-α and expression of NF-κB and vascular endothelial growth factor in the retinal tissue of the (Dongare et al., 2016).

Several types of proinflammatory cytokines and chemokines are produced during carcinogenesis. They influence tumor cell survival, growth, mutation, proliferation, differentiation, and movement. Experimental models of carcinogenesis indicate that these cytokines and chemokines activate the NF-κB transcription factor and TNF-α as well, which are implicated in tumor promotion (Aggarwal, 2003; Philip, Rowley, & Schreiber, 2004). The protective effects of [6]-gingerol on proinflammatory cytokines such as TNF-α, IL-6, and IL-1β and neutrophil infiltration in intestinal tissues with I/R injury was examined. Pretreatment with [6]-gingerol significantly attenuated these cytokines in a dose-dependent manner, inhibited the expression of inflammatory mediators, suppressed p38 phosphorylation, and activated NF-κB by negatively regulating MLCK expression (Li et al., 2017).

Chemoprevention based on dietary plants and/or phytochemicals has emerged as an available and promising strategy for the control and management of cancer with various mechanisms, including the targeting of leukotriene A4 hydrolase (LTA4H; Badria, 1994; Houssen et al., 2010; Surh, 2003). In this regard, [6]-gingerol exhibited a wide range of biochemical and pharmacological activities (Afzal, Al-Hadidi, Menon, Pesek, & Dhami, 2001; Ali, Blunden, Tanira, & Nemmar, 2008; Bode & Dong, 2011). LTA4H is a zinc dependent bifunctional metalloenzyme with the activities of epoxide hydrolase and aminopeptidase. As an epoxide hydrolase, LTA4H catalyzes the last rate-limiting step in the leukotriene B 4 biosynthesis (LTB 4), a potent chemoattractant that induces a vigorous inflammatory response, and is related to the development of cancer (Chen, Wang, Wu, & Yang, 2004; Jeong et al., 2009). LTA4H inhibitory activity of [6]-gingerol derivatives was further reported by El-Naggar et al. (2017). Docking studies indicated that the phenolic –OH groups of [6]-gingerol are essential for inhibiting the activities of LTA4H, due to their chelation with metallic zinc, a factor that may explain the inhibition of aminopeptidase activity of the enzyme (El-Naggar et al., 2017).

3.5 | Medicinal plants

Medicinal plants have been employed as a source for drug discovery since 1805, when morphine became the first pharmacologically active compound to be isolated, in a pure form, from a plant, although its structure was not elucidated until 1923 (Salim, Chin, & Kinghorn, 2008). Natural drugs are used by a large portion of the population in several countries to treat diseases such as inflammation, hypertension, kidney problems, immune deficiency, and cancer (Cragg & Newman, 2013). Additionally, many of the current drugs are derived from plants or their derivatives (Kinghorn, Pan, Fletcher, & Chai, 2011; Newman & Cragg, 2012). Furthermore, polyphenols, secondary metabolites widely diffused in the plant kingdom, are known to provide protection against pathogens and parasites, and reduce the risk of diseases induced by chronic and oxidative damage, including cancer (Aboul-Enein, Berczynski, & Kruk, 2013).

Use of crude and phytochemical extracts isolated from medicinal plants is becoming more acceptable and preferable, possibly due to the cost of production, availability, and accessibility and to lower toxicity in most cases. However, elucidation of molecular pathways and side effects are crucial prior to clinical setting. In this respect, the challenge lies in the fact that phytochemicals are structurally complex, and extraction of pure active compounds is extensively laborious. Therefore, many synthetic drugs are inspired by the structure of active plant molecules, highlighting the enormous potential in the development of plant-based drugs with therapeutic actions against cancer (Yehya et al., 2017). Research findings have identified more than 5,000 individual phytochemicals, and this number is steadily increasing due to the introduction of current and efficient techniques of isolation and characterization. These new agents are widely classified as phenolic compounds, alkaloids, carotenoids, organosulfur, and nitrogen-containing compounds (Asif et al., 2016). Such molecules can act as antioxidants, stimulate enzymatic activity, mimic hormones, interfere with DNA replication, and protect cells from radiation and other abnormal processes during tumorigenesis. In addition, studies have also highlighted the synergistic effects of plant-based medicinal compounds as antiangiogenic agents when used in combination with other antineoplastic drugs (Lachumy et al., 2013).

Cancer is a complex and multifactorial pathology; its etiology presumes genetic mutations that confer unlimited capacity for cell proliferation, loss of response to growth inhibitory factors, evasion of apoptosis, possibilities to invade other body tissues (metastases), and production of new vessels (angiogenesis; Araújo & Galvão, 2010;

Hercos et al., 2014; INCA, 2014). Some phytochemicals have demonstrated relatively low side effects and have even limited the incidence of side effects associated with chemotherapeutic or antiangiogenic agents (Wang et al., 2014). In this context, spices play an important role as aromatic agents in the diet and are used in various regions of the planet. A number of phytochemicals present in spices have been recognized for having health promotion benefits and play a preventive role in chronic diseases (Ferrucci et al., 2010; Kaefer & Milner, 2008). Most of these phytochemicals exhibited promising broad spectrum antiangiogenic activities in in vitro and in vivo models (American Thoracic Society, 2000).

3.6 | *Z. officinalle* Roscoe and cancer

Ginger (*Z. officinale*) is one of the earliest domesticated spices in history. It is commonly used as a food additive (spices) and as a key component in traditional herbal medicine, where its potential has been intensely exploited in health benefits. Furthermore, ginger is considered safe as a herbal supplement by different regulatory authorities (Butt & Sultan, 2011; Shukla & Singh, 2007; Al-Suhaimi, Al-Riziza, & Al-Essa, 2011). The bioactive components of ginger include volatile oils, anthocyanins, tannins, and pungent phenolic compounds known as gingerols, shogaols, and sesquiterpenes (Semwal, Semwal, Combrinck, & Viljoen, 2015). Most of the research on antitumor activities of gingerols has focused on [6]-gingerol, although little attention has been paid to gingerols with longer unbranched alkyl side chains (Semwal et al., 2015). Studies suggest that ginger and its pungent bioactive components, which include gingerols and shogaols, can be used in the prevention and treatment of cancer (Wang et al., 2014).

Experimental (in vitro/in vivo) and clinical trials revealed that EG and [6]-gingerol exhibit antiproliferative, antitumor, and anti-invasive effects via various mechanisms including NF-κB, STAT3, Rb, MAPK, PI3K, Akt, ERK, cIAP1, cyclin A, cyclin-dependent kinase (Cdk), cathepsin D, and caspase-3/7 (Prasad & Tyagi, 2015, 2015). Listed in Table 3 are the molecular mechanisms involved in tumor suppression, as well as the mediators involved in cell signaling pathways in different types of carcinomas and tumor cell lines. Yusof et al. (2009) evaluated the anticancer effect of EG in rats with hepatic carcinoma, induced by a choline deficient diet combined with ethionine. These researchers found that animals treated with ginger showed a significant reduction in the tumor size. In addition, ginger supplementation significantly decreased MDA levels and increased catalase activity.

On the other hand, cancer metastasis consists of a complex cascade of events that ultimately allow the escape of tumor cells and the creation of ectopic environments (Yoon, Kim, & Chung, 2001). However, the effect of [6]-gingerol on metastasis in breast cancer cells was not well understood. In this context, the effect of [6]-gingerol on adhesion, invasion, and motility in MDA-MB-231 human breast cancer cells indicated that there is no effect on cell adhesion at concentrations up to 5 μM but resulted in a 16% reduction when the concentration was increased to 10 μM. Additionally, increasing amounts of [6]-gingerol caused a concentration-dependent decrease in cell migration and motility. Treatment of MDA-MB-231 cells with increasing amounts of [6]-gingerol caused a concentration-dependent decrease in cell migration and motility. Furthermore, the activities of matrix metalloproteinase (MMP) 2 or MMP-9, identified as possible mediators of invasion and metastasis in cancers, in MDA-MB-231 cells decreased in a dose-dependent manner upon treatment with [6]-gingerol (Lee et al., 2008).

Lin and colleagues examined the anticancer effects of [6]-gingerol on human colon cancer cell (LoVo) and observed a significant reduction in cell viability in a dose-dependent manner. Results showed that [6]-gingerol significantly induces cell cycle arrest at the G2/M phase; has little influence on the sub-G1 phase; and decreases the levels of cyclin A, cyclin B1, and CDK1. However, treatment with [6]-gingerol increased levels of negative cell cycle regulators p27Kip1 and p21Cip1 and enhanced ROS levels and phosphorylation of p53. These results highlight the importance of [6]-gingerol in the treatment of colon cancer (Lin et al., 2012). On the other hand, generation of ROS induced by [6]-gingerol is known to cause damage to DNA in cancer cells (Oyagbemi et al., 2010; Lin et al., 2012). To investigate the molecular mechanisms that mediate the apoptotic actions of [6]-gingerol in myeloid leukemia cells, Rastogi et al. (2014) selected chronic myelogenous leukemia (K562) and acute (U937) strains. Results indicated that [6]-gingerol induced generation of ROS in both cells, by inhibiting mitochondrial respiratory complex I, and triggered cell death mediated through an increase in miR-27b expression and DNA damage. These data clearly indicate that treatment with [6]-gingerol alters the cellular oxidant status; induces generation of mitochondrial ROS, leading to G2/M cell cycle disruption; and decreases protein expression (cyclin B1, Cdk1, Cdc25B, and Cdc25C), associated with the phases of the cycle (Rastogi et al., 2014).

Karna and coworkers similarly showed that EG exhibits substantial growth-inhibitory effect and induced death in a panel of prostate cancer cells. Additionally, EG reduced cell cycle progression, decreased the capacity to reproduce, and initiated a caspase-driven, mitochondrially mediated apoptosis (Karna et al., 2012). Recently, the effect of [6]-gingerol on human papilloma virus positive cervical cancer cells (HeLa, CaSki, and SiHa) was evaluated. Results showed that [6]-gingerol induces inhibition of cell viability in lineages tested in dose and time-dependent fashion. At a concentration of 50 μM, [6]-gingerol inhibited the growth and proliferation of HeLa (20%), CaSki (23%), and SiHa (28%) cells after 24 hr of treatment, indicating apoptotic cell death. In nontumor cells HACAT, HEK293, and human peripheral blood monocytes (PBMCs), [6]-gingerol at a dose of 50 μM did not induce cytotoxicity in normal lineages (Rastogi et al., 2015). Research findings indicated that restoration of the p53 function is critical for effective therapeutic targeting and management of cervical cancer (Horner, Defilippis, Manuelidis, & Dimaio, 2004). Rastogi et al., 2015 reported that [6]-gingerol inhibits the proteasome and induced p53 reactivation and apoptotic cell death in cervical cancer cells. [6]-Gingerol additionally potentiated the cytotoxic effects of cisplatin, which is a traditional chemotherapeutic agent. These results suggest that [6]-gingerol may be used as a single agent or in combination with conventional chemotherapeutic drugs and is presented as a promising therapeutic strategy for the management and treatment of cervical cancers (Rastogi et al. (2015).

Transcriptional silencing of human papilloma virus, E6, and E7 oncoproteins is known to inhibit cervical cancer cell proliferation (Tan, De Vries, Van Der Zee, & De Jong, 2012). [6]-Gingerol did not

TABLE 3 Antitumor effect of ginger extract (EG) and/or biologically active phytochemical component [6]-gingerol ([6]-G)

Form of use	Method of study Dose or concentration	Mechanism of action EG and/or [6]-G	Reference
[6]-G	In vitro—to examine the effects of [6]-G on adhesion, invasion, and motility in MDA-MB-231 (human breast cancer) to [6]-G (0, 2.5, 5, and 10 μM)	Decreases activity of MMP-2 and MMP-9	(Lee, Seo, & Kim, 2008)
EG	In vivo—Male Wistar rats (*N* = 6) ginger effect on ethionine-induced hepatocarcinogenesis Induction of hepatic cancer with ethionine—15 weeks—intraperitoneal route Food or olive oil controls; EG (100 mg/kg); choline deficient diet (CDE) + 0.1% ethionine; ginger + CDE. 8 weeks—oral	Group treated with ginger: Decrease tumor incidence Increase CAT Decrease MDA	(Yusof, Ahmad, Sulaiman, & Murad, 2009)
[6]-G	In vitro—To explore the mechanisms of [6]-G in HeLa (human cervical carcinoma) [6]-G (25, 50, 75, 100, 125, 150, and 175 μg/ml)	Induction of apoptosis Upregulation of TNF-α and Bax and citocromo c. Downregulation of NF-κB, AKT, and Bcl2	(Chakraborty et al., 2012)
EG	In vitro—To investigate cytotoxic and apoptotic capacity in human MPC11 (myeloma) and murine WiDr (colorectal cancer) cells. Administration of EG (500–7.81 μg/ml)	Induction of apoptosis Increases p53	(Ekowati et al., 2012)
EG	In vitro—Antiproliferative potential of EG (0.0, 0.025, 0.05, 0.1, 0.15, and 0.2 mg/ml) in breast cancer cell lines (MCF-7 and MDA-MB-231) and lineage epithelial cells (MCF-10A). Assays viability (200×10^3), comet (1 × 106), apoptosis (2×10^4) cells/ml	Increases apoptosis, Bax, caspases-3, PARP, IκBα Decreases NF-κB, Bcl2, BclX, Mcl-1, survivina, cyclin D1, Cdk-4, and hTERT	(Elkady, Abuzinadah, Baeshen, & Rahmy, 2012)
EG	In vitro—Exposure of prostate cancer strains, LNCaP, C4-2, C4-2B, DU145, PC-3, and PrEC (normal) to EG (1; 10; 100; and 1,000 μg/ml) for cell viability Flow cytometry: EG-treated PC-3 line (50; 100; 250; 500; and 1,000 μg/ml) Western blot, immunohistochemistry, Caspase3/7 activity: PC-3 to EG (250 μg/ml)	Cell cycle stop G1 and S Increases sub-G1 population, p21, JC-1, BAX, cytochrome c mitochondrial, PARP cleavage, and caspase-3 Decreases Ki67, cyclin D1, E, Cdk-4, and Bcl2	(Karna et al., 2012)
EG	In vivo—Male nude mouse (*N* = 6) xenograft PC-3. Induction prostate cancer (PC-3/1×10^6)—subcutaneous route Administration of EG (100 mg/kg—8 weeks)—oral	Decreases Ki67, cyclin B, cyclin D1, and cyclin E Increases p21, caspase-3, and PARP	(Karna et al., 2012)
[6]-G	In vitro—Investigating the antitumor effects of [6]-G on LoVo (4×10^4) to [6]-G (0, 5, 10, and 15 μg/ml) human colon cancer cells (LoVo)	Stops cell cycle G2/M phase Decreases cyclin A, B1, and CDK1 Increase $p27^{Kip1}$ and $p21^{Cip1}$	(Lin, Lin, & Tsay, 2012)
[6]-G	In vitro—To examine the effect of [6]-G on metastases of pancreatic cancer and to investigate intracellular signaling pathways involved in PANC1 (1×10^4) to [6]-G (0, 5, 10, 15, or 20 μM)	Increase TER, protein levels TJ, ZO-1, accludin, and E-cadherin Decreases MMP-2, -9, claudin-4, NF-κB/Snail, and ERK	(Kim & Kim, 2013)
EG	In vitro—Exposure of B164A5 melanoma cell line (1×10^3 cells) to EG (0, 20, 60, 80, and 100 μg/ml)	Increases apoptosis	(Danciu et al., 2015)
EG	In vitro—Exposure of U251 cell line (1 × 104) to EG, viability (0, 50, 100, 150, and 200 μg/ml); 0.75 μg/ml	Increases cytochrome c mitochondrial, Bax ratio: Bcl-2, caspases-3, -9, PARP-1 cleavage, p53, and p21	(Elkady, Hussein, & Abu-Zinadah, 2014a)

(Continues)

TABLE 3 (Continued)

Form of use	Method of study Dose or concentration	Mechanism of action EG and/or [6]-G	Reference
		Decreases nuclear NF-κBp65, survivin, XIAP, and cyclin D1	
EG	In vitro—HCT116 human colorectal cancer cell line exposure (5 × 104) to EG, viability (0, 50, 75, 100, and 125 μg/ml); markers (0.75 μg/ml)	Increases cytochrome c mitochondrial, Bax ratio: Bcl-2, caspases-3, −9, PARP-1 cleavage, p53, p21, and p27 Decreases Bcl2, BclX, Mcl-1, survivin, XIAP, cyclin D1, Cdk-4, and c-Myc	(Elkady, Hussein, & Abu-Zinadah, 2014b)
[6]-G	In vitro—Exposure of human glioblastoma U87 line (1×10^5 cells) to [6]-G Viability/apoptosis (10–100 μM) Markers/modulation (0–50 μM)	Increases ROS, DR5, p53, bid cleavage, and BAX Decreases expression survivin, c-FLIP, Bcl2, and XIAP	(Lee, Kimb, Jungc, Leea, & Parkd, 2014)
[6]-G	In vitro—To evaluate the antiproliferative capacity in tumoral lines of acute and chronic myeloid leukemia to [6]-G (0, 10, 25, 50, 100, and 200 μM) To analyze the apoptotic mechanisms of [6]-G in LMC (K562) and AML (U937) to [6]-G (50 μM)	Induction of caspase-3 activity PARP cleavage Generation of mitochondrial ROS G2/M cell cycle disruption Decreases expression of proteins (cyclin B1, Cdk1, Cdc25B, and Cdc25C) Increases expression of miR27b	(Rastogi et al., 2014)
[6]-G	Ex vivo—Investigating the effects of [6]-G on PBMCs cells, obtained from patients with AML (N = 40); LMC (N = 7) and healthy (N = 6) to [6]-gingerol (50 μM)	Induction of apoptosis in AML and CML groups	(Rastogi et al., 2014)
[6]-G	In vivo—Mouse nude (N = 24). K562-induced xenotransplantation tumor model (3×10^6). Administration [6]-G (5 mg/kg)—45 alternate days—intraperitoneal	Decreases PCNA, Bcl2, BclXL, and XIAP Increases Bax, Bak, cleavage of PARP, and activation of caspase-3	(Rastogi et al., 2014)
[6]-G	In vitro—Cytotoxic effects on human tumor cell lines SW-480, HCT 116 (5×10^3), and normal murine colon (5×10^4) to [6]-G (5, 10, 25, 50, 100, 200, and 300 μM) primary cells, evidence possible mechanisms of action in (SW-480)	Activation of caspases-8, -9, -3, -7, and cleavage of PARP Inhibition via ERK1/2, JNK, and AP-1	(Radhakrishnan et al., 2014)
EG	In vitro—Investigating the effects of EG on human pancreatic cancer strains Panc1, AsPC1, BxPC3, CAPAN2, CFPAC1, MIAPaCa2, SW1990, and Panc02 murine pancreatic cancer cell employing EG (SSHE)—25, 50, 100, and 200 μg/ml	Cell cycle arrest at the G0/G1 phase Induction of autose Increases ROS	(Akimoto, Lizuka, Kanematsu, Yoshida, & Takenaga, 2015)
E G	In vivo—C57BL/6 male mice (N = 8). Induction of pancreatic cancer Panc02-Luc-ZsGreen (5×10^5 cells)—intraperitoneal	Decreases tumor incidence	(Akimoto et al., 2015)

(Continues)

TABLE 3 (Continued)

Form of use	Method of study Dose or concentration	Mechanism of action EG and/or [6]-G	Reference
	Administration of EG (SSHE; 80 mg/kg—20 consecutive days immediately after induction)—intraperitoneal		
[6]-G	In vitro—Human HepG2 tumor line	Induces apoptosis	(Impheng et al., 2015)
	Exposure of HepG2 tumor lines to[6]-G (0.01, 0.1, 0.2, 0.3, 0.4, and 0.5 nM)	Cycle stop: Go/G1, S—24 hr; G2/M—48 hr	
		Increases ROS	
		Downregulation of FASN	
EG	In vitro—Exposure of line derived human Burkitt Raji lymphoma (1×10^6 cells) to EG (0.1%, 0.01%, and 0.001%)	Decreases viability	(Parvizzadeh et al., 2014)
[6]-G	In vitro—To explore the mechanism of action of [6]-G (50 μM) in human cervical cancer cells positive for HPV (HeLa, CaSki, and SiHa)	Induction of apoptosis	(Rastogi et al., 2015)
		Reactivation of p53 independent of inhibition of the oncoprotein (E6/E7) in HeLa and CaSki lines.	
		Increases p53, P21, and ROS	
		Induction of G2/M cell cycle arrest	
[6]-G	In vivo—Tumor induction (xenotransplantation) employing HeLa cell (3×10^6) in nude mouse (N = 6)—intraperitoneal route	Induction of apoptosis	(Rastogi et al., 2015)
		Reactivation and increase of p53 levels	
	Administration of [6]-G (2.5 and 5.0 mg/kg)—45 alternate days		
EG	In vitro—Exposure of HT29 colorectal tumor cell line (1×10^6 cells) to EG (2–10 mg/ml)	Induction of apoptosis Downregulation of KRAS, ERK, AKT, Bcl-xL, and p65 NF-κB Upregulation caspase-9	(Tahir et al., 2015)
[6]-G	In vitro—Exposure of the HeLa lines to [6]-G (100 and 200 μM), to evaluate the antitumor potential and its synergy with 5FU drugs (50 μM); Ptx.	Cell cycle stop G0/G1	(F. Zhang et al., 2017)
		Regulation of apoptosis in the PI3K/AKT/MAPK/mTOR pathway	
		Synergy with the 5FU and Ptx antineoplastic drugs led to 83.2% and 52% inhibition	

Note. ROS: reactive oxygen species; MMPs: matrix metalloproteinases; MDA: malondialdehyde; CAT: catalase; TNF-α: tumor necrosis factor alpha; NF-κB: nuclear factor kappa β ; CDKs: cyclin-dependent kinases; JC-1: 5,5′, 6,6′-tetrachloro1,1′, 3,3′-tetraethylbenzimidazolecarbocyanine iodide; PARP: Poly (ADP-ribose) polymerase; TER: transepithelial electrical resistance; TJ: tight junction; ZO-1: zonula occludens; XIAP: X-linked chromosome to apoptosis inhibitor; DR5: death receptor 5; c-FLIP: FLICE inhibitor protein; AML: acute myeloid leukemia; CML: chronic myelogenous leukemia; FASN: fatty acid synthase enzyme; PI3-K: phosphatidylinositol 3-kinases; 5FU: 5-fluorouracil; Ptx: paclitaxel; ERK: extracellular signal-regulated kinase; JNK: Jun N-terminal kinase; HPV: human papilloma virus.

affect the expression of E6 and E7 levels in HeLa and CaSki cells; however, p21 levels were significantly increased in both cells, which might explain the involvement of p53 in the apoptotic process in these cells. In addition, [6]-gingerol increased ROS production in cervical cancer cells. Generation of [6]-gingerol-induced intracellular ROS leads to apoptotic cell death, DNA damage, and p53/p21-mediated G2/M cell cycle arrest (Rastogi et al., 2015). Furthermore, animals treated with [6]-gingerol (2.5 and 5.0 mg/kg body weight) for 6 weeks showed a significant reduction in tumor volume (about 65%). Consistent with the in vitro results, proteasomal inhibition and increased p53 levels were observed in the xenografts of treated mice. Expression of cell cycle regulators and other apoptotic markers were also observed according to in vitro studies. Potent antiproliferative effect of [6]-gingerol in vivo is mediated by proteasomal inhibition and reactivation with p53, leading to inhibition of proliferation and induction of apoptotic cell death (Rastogi et al., 2015). [6]-Gingerol was found to reduce the viability of HeLa (human cervical carcinoma) cells as shown by morphological changes in cells. HeLa cells treated with [6]-gingerol showed altered nuclear and cellular morphology, cell shrinkage, and membrane blebbing, which are characteristics of apoptotic cell death. Additionally, an increase in chromatin condensation and fragmentation of HeLa cells was observed with increased dose of [6]-gingerol during treatment (Chakraborty et al., 2012).

Metastasis is a multistep process involving invasion and migration and is the leading cause of death in cancer patients. In cancer, degradation of extracellular matrix and basement membrane through activation of MMPs and remodeling of tissue via loss, TJ, promotes migration of tumor cells. The effect of [6]-gingerol on transepithelial electrical resistance and paracellular permeability of pancreatic cancer cells was investigated using the PANC-1 cell line. Results indicated that [6]-gingerol restores TJ formation and suppresses paracellular permeability compared with that of untreated cells. In addition, it significantly increased transepithelial electrical resistance and decreased claudin-4 and MMP-9. Furthermore, [6]-gingerol enhanced TJ protein levels, including zonula occludens (ZO-) 1, occludin, and E-cadherin, which is correlated with decreased paracellular flux and MMP-2 and MM-9 activity. Treatment with [6]-gingerol suppressed nuclear translocation of NF-κB/Snail by downregulation of ERK pathway. These results suggest that [6]-gingerol can suppress the invasive activity of PANC-1 cells (Kim & Kim, 2013).

A study by Elkady and colleagues indicated that human breast cancer cell lines MCF-7 and MDA-MB-231 are considerably more sensitive to growth suppression than the normal mammary line MCF-10A when treated with EG. Treatment with EG (0.1 mg/ml) caused a 25- and 20-fold increase in the percentage of labeled apoptotic cells in MCF-7 and MDA-MB-231, respectively. On the other hand, treatment with a 0.2 mg/ml dose of EG triggered a 40- and 30-fold increase in apoptosis in MCF-7 and MDA-MB-231, respectively. The antiproliferative potential of ginger can be attributed to its induction of apoptosis by increasing the Bax/Bcl-2 ratio. Moreover, ginger-dependent growth inhibitory mechanisms may involve, at least in part, the downregulation of major cell molecules, including NF-κB, Bcl-X, Mcl-1, survivin, cyclin D1, CDK-4, proto-oncogene proteins (c-Myc), hTERT, and upregulation of IκBα and p21. As the inhibition of c-Myc and hTERT is a specific target in cancer therapy, EG might be a good candidate as a chemopreventive or therapeutic agent for breast cancer (Elkady et al., 2012).

Similarly, gingerol was found to function as a sensitizing agent to induce tumor necrosis factor-related apoptosis inducing ligand (TRAIL)-mediated apoptosis in glioblastoma cells, which are resistant to TRAIL-induced apoptosis, by TRAIL signaling (Lee et al., 2014). This effect was evidenced by elevated expression level of the death receptor 5, decreased expression of antiapoptotic proteins such as survivin, cFLIP, Bcl2, and X-linked chromosome to apoptosis inhibitor (XIAP), and by increased levels of proapoptotic proteins including Bax and Bid, caused by generation of ROS. These results suggest that gingerol could be used as an antitumor agent that may serve in combination therapies with TRAIL in patients with TRAIL-resistant glioblastoma (Lee et al., 2014).

Treatment of human glioblastoma cells (U251) with EG reduced cell viability, induced apoptosis mediated by cytochrome c-mitochondrial release, increased Bax:Bcl-2 ratio and caspase-3 activity, and caused PARP1 cleavage. In addition, EG decreased the expression levels of nuclear NF-κBp65, survivin, XIAP, and cyclin D1, and increased expression levels of proapoptotic proteins p53 and p21 (Elkady et al., 2014a). On the other hand, treatment of human HCT116 (colorectal) cancer cells with EG caused morphological and biochemical characteristics of apoptotic cell death. Induction of apoptosis was associated with mitochondrial cytochrome c release, increased Bax:Bcl2 ratio, activation of caspase-3 and -9, and PARP cleavage. Furthermore, EG (a) decreased the expression levels of antiapoptotic proteins including Bcl2, BclX, Mcl-1, survivin, and XIAP; (b) elevated expression levels of the oncosuppressive proteins, p53, p21, and p27; (c) reduced the expression of cyclin D1 and cyclin/Cdk-4; and (d) decreased expression of c-Myc (Elkady et al., 2014b).

In a recent publication, Danciu and coworkers showed that EG exhibits antiproliferative and proapoptotic activity in murine melanoma B164A5 cell line (Danciu et al., 2015). On the other hand, research findings indicated a high cytotoxic effect of EG against Raji cells derived from human (non-Hodgkin's) Burkitt's lymphoma (Parvizzadeh et al., 2014). In a similar fashion, Rastogi et al. (2014) studied the effects of [6]-gingerol on myeloid leukemia cells in vitro and in vivo. These researchers found that [6]-gingerol, concentration and time dependently, impedes propagation of myeloid leukemia cell lines and does not affect the normal peripheral blood mononuclear cells. Additionally, and using U937 and K562 cell lines, [6]-gingerol prompted generation of ROS through inhibition of mitochondrial respiratory complex I, which enhanced the expression of oxidative stress response-linked microRNA miR-27b and DNA damage. The increased expression of miR-27b inhibits the peroxisome proliferator-activated receptor γ, which causes inhibition of the inflammatory cytokine gene expression linked with the oncogenic NF-κB pathway. On the other hand, increased DNA damage leads to G2/M cell cycle arrest. In short, the [6]-gingerol-induced death in myeloid leukemia cells triggered by ROS and mediated by an elevation in miR-27b expression and DNA damage (Rastogi et al., 2014).

Research findings indicated that natural compounds can induce inhibition of primary leukemia cells (Sharif et al., 2012). Rastogi et al.

(2014) demonstrated that [6]-gingerol affects the growth of peripheral blood mononuclear cells PBMCs obtained from 40 patients with acute myeloid leukemia (AML), seven patients with chronic myeloid leukemia (CML), and six healthy donors. Each one of these primary cultures of leukemia was exposed to 50 μM of [6]-gingerol for 48 hr, and annexin V (apoptosis marker) binding was measured by means of flow cytometry alone. Results revealed that the optimal effects of [6]-gingerol on induction of apoptosis in AML and CML cells were achieved by 48 hr posttreatment. On the other hand, [6]-gingerol-mediated apoptosis was observed in 30 of the 40 AML samples and six of the seven CML tested samples. In addition, treatment with [6]-gingerol did not markedly affect the viability of normal PBMCs. These results suggest that [6]-gingerol could be effective in inducing apoptosis in both AML and CML cells. It is well known that oxidative stress due to accumulation of ROS causes changes in the expression of miRNA in several cell types (Lin et al., 2009; Simone et al., 2009; Wang et al., 2010); Lee et al., 2009). Rastogi et al. (2014) evaluated the changes in miRNA expression in K562 and U937 myeloid leukemia cell lines after [6]-gingerol-induced accumulation of ROS. Results showed that miR27b expression was increased 4.8 and 4.9-fold in K562 and U937 cells treated with [6]-gingerol, respectively, compared with untreated cells. This indicates that miR27b may be related to proapoptotic effects of [6]-gingerol, suggesting that miR27b expression is critical in mediating its proapoptotic effects in leukemia cells.

To further validate the results obtained in vitro, it was shown that [6]-gingerol could inhibit the development of tumors in a murine xenograft tumor model in vivo. Results revealed that treatment with [6]-gingerol significantly reduced antiapoptotic proteins such as proliferating cell nuclear antigen, Bcl2, BclXL, and XIAP and increased proapoptotic proteins including Bax, Bak, and PARP cleavage and activation of caspase-3. However, [6]-gingerol did not negatively affect hematological parameters or body weights, indicating its chemotherapeutic potential (Rastogi et al., 2014).

[6]-Gingerol exhibited toxicity in both SW-480 and HCT116 tumor cells in a dose-dependent manner, with prominent effect at higher concentrations with IC_{50} values of 205 ± 5 and 283 ± 7 μM, respectively; cell viability in normal cells remained unchanged. These results suggest the specificity of [6]-gingerol in inducing cytotoxicity in cancer cells without being toxic to normal cells, even at higher concentrations. In SW-480 cells treated with [6]-gingerol, significant cleavage of procaspase-8 and -9 to their active fragments p43/41, p35/37, respectively, was observed. Activation of effector caspase-3 and -7 was also induced by [6]-gingerol in a dose-dependent manner, with cleavage of procaspase-3 and -7a to their respective active fragments p17/19 and p20. Similarly, cleavage of the PARP protein, which is a caspase-3 substrate, has also been observed confirming a caspase-mediated apoptosis (Radhakrishnan et al., 2014).

Recently, Akimoto et al. (2015) examined the anticancer activity of EG against pancreatic cancer cells in vitro/in vivo and investigated its potential mechanism. These researchers observed that tumor growth and cell viability in pancreatic cells are mainly mediated through autose by ROS, a way of characterizing cell death. Similarly, treatment of Panc1 cells with EG for 20 hr resulted in a cell cycle arrest at the G0/G1 phase. Normal cells, such as HUVEC and HPAEpiC, were more resistant to EG compared with Panc cells, revealing EG selectivity. In the later stages of cell death of Panc1 cells, focal rupture of the plasma membrane and shrinkage of the nucleus were observed. EG significantly increased the LC3-II/LC3-I ratio, an indicator of autophagosome formation, in a dose- and time-dependent manner. In Panc-1 cells, EG additionally decreased levels of SQSTM1/p62 protein, one of the specific substrates degraded through the autophagic-lysosomal pathway. Moreover, EG activated MAPK, a positive regulator of autophagy and inhibited mTOR, a negative autophagous regulator. Inhibitors of 3-methyladenine and chloroquine autophagy partially prevented cell death. Morphologically, cells treated with EG showed massive vacuolization of the cytoplasm approximately 24 hr after treatment. These cytoplasmic vacuoles were probably autophagosomes because the GFP-LC3 tip appeared after treatment with EG. Changes in the generation of ROS, following the treatment of Panc-1 cells with EG, showed a biphasic pattern. In the initial stages (approximately 10 hr), generation of ROS was inhibited by EG. However, prolonged treatment resulted in a robust increase in the generation of ROS and an increase in mitochondrial superoxide production. These results suggest the generation of ROS as a cause of EG-induced cell death (Akimoto et al., 2015).

Obesity is associated with the metabolic syndrome and the dysregulation of new fatty acid synthesis, leading to numerous consequences, including tumorigenesis and tumor progression (Ameer, Scandiuzzi, Hasnain, Kalbacher, & Zaidi, 2014). Numerous studies have focused on the effect of natural polyphenols in reducing hepatic fat accumulation, overweight, and obesity to reduce the risk of carcinogenesis without disrupting food appetite (Figarola et al., 2013; Huang et al., 2014; Kang et al., 2013). In order to confer rapid proliferation and survival, cancer reorients acetylcoenzyme A into oxidative phosphorylation to develop overexpression of the de novo synthesis pathway of fatty acids (Rodriguez-Enriquez, Marin-Hernandez, Gallardo-Perez, & Moreno-Sanchez, 2009). Enzymes that participate in the synthesis of new fatty acids are regulated or constitutively expressed in most types of cancer cells (Ferreira, 2010; Hopperton, Duncan, Bazinet, & Archer, 2014; Zaidi et al., 2013). In this regard, Impheng et al. (2015) demonstrated that [6]-gingerol reduces fatty acid synthesis, resulting in mitochondrial dysfunction and induction of cell death in HepG2 cells. In addition, [6]-gingerol induced inhibition of fatty acid synthase (FASN) expression, indicating FASN is a major target of [6]-gingerol inducing apoptosis in HepG2 cells mediated by increased generation of ROS. Furthermore, a decrease of fatty acid levels and initiation of apoptosis were restored by inhibition of acetyl-CoA carboxylase activity. This suggests that accumulation of malonyl-CoA level could be the major cause of apoptotic induction of [6]-gingerol in HepG2 cells. The findings of [6]-gingerol as a novel FASN inhibitor provide a potential perspective on anticancer and lipogenesis inhibitor treatments to protect obesity-induced carcinogenesis (Impheng et al., 2015). Findings collectively suggest that that treatment of HeLa cells with [6]-gingerol caused growth inhibition, cell cycle arrest at G0/G1 phase, and apoptosis. In addition, it (a) decreased the expression of cyclin (A, D1, E1); (b) slightly decreased CDK-1, p21 and p27; and (c) increased Bax/Bcl-2 ratio, release of cytochrome c, and cleavage of caspase-3, -8, -9, and phosphoribosyl pyrophosphate (F. Zhang et al., 2017).

4 | CONCLUSIONS

Use of conventional therapies such as natural products, extracted from plants, in the fight against diseases such as cancer has attracted the attention of the scientific and medical communities due to their lesser side effects and cost. In this context, [6]-gingerol, a flavonoid antioxidant and the main active constituent of fresh ginger, has been recognized and employed as an alternative drug in treating different cancers, alone or in combination with other chemotherapeutic drugs. It displays important antioxidant and/or anti-inflammatory effects that could be employed in preventing and treating cancer. Data obtained from experimental (in vitro/in vivo) and clinical studies reveal that EG and/or [6]-gingerol exhibit antiproliferative, antitumor, anti-invasive, and anti-inflammatory effects in chronic diseases and carcinoma. [6]-Gingerol exerts cytotoxic effects on various cancer cell lines at 0.01 nM to 300 μM, whereas in mice, it exhibited anticancer effects at 5, 25, and 45 mg/kg (i.p.).

These natural compounds exert their effect through different mechanisms and cell signaling pathways. In short, the use of crude and phytochemical extracts isolated from medicinal plants is becoming increasingly common and acceptable; however, identification and understanding of molecular pathways and mediators are crucial in elucidating the protective or therapeutic potential, as well as dose response, toxicity, and biological response. In summary, this review reveals that [6]-gingerol can be an important complementary medicine for prevention and treatment of different types of cancers, owing to its natural origin, safety, and low cost relative to synthetic cancer drugs. However, further studies are needed on this natural compound. Additionally, because most of the results and conclusions in this review came from in vitro and in vivo studies, more work that involves different pharmacokinetic parameters are recommended in the future before this substance becomes a prescribed drug. Moreover, development of standardized extract or dosage could also be pursued in clinical trials.

CONFLICT OF INTEREST

The authors do not have any conflict of interest to disclose.

LIST OF ABBREVIATION

5′NT	5′-nucleotidase
5FU	5-fluorouracil
ACC	Acetyl-CoA carboxylase
AFB1	Aflatoxin B1
Akt/PKB	Protein kinase B
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AP	Acid phosphatase
AP-1	Acid phosphatase 1
A-SAA	Serum amyloid A
AST	Aspartate aminotransferase
Aβ	β-amyloid
Bax	(B-cell lymphoma)-associated X
Bcl2	B-cell lymphoma 2
BHT	Butylated hydroxytoluene
BJ	Foreskin fibroblasts
Caco2	Human colon adenocarcinoma
CAT	Catalase
Cdk-4	Cyclin-dependent kinase 4
c-FLIP	FLICE inhibitor protein
CML	Chronic myelogenous leukemia
c-Myc	Proto-oncogene proteins
COX	Cyclooxygenase
COX-1	Cyclooxygenase 1
COX-2	Cyclooxygenase 2
CRC	Colorectal cancer
CRP	C-reactive protein
DMH	1,2-dimethylhydrazine
DOX	Doxorubicin
DR5	Death receptor 5
ECH	Enoyl-CoA hydratase
EG	Ginger extract
ERK	Extracellular signal-regulated kinase
FASN	Fatty acid synthase
FoxOs	Forkhead box protein Os
G6Pase	D-glucose-6-phosphate phosphohydrolase
GFP-LC3	Green fluorescent protein-light chain 3
GGT	Gamma-glutamyl transferase
GPx	Glutathione peroxidase
GPx-1	Phosphatase glutathione peroxidase 1
GR	Glutathione reductase
GSH	Glutathione
GSK3β	Glycogen synthase kinase 3 beta
GSSG	Glutathione disulfide
GST	Glutathione S transferases
GSTP1	Glutathione S-transferase P1
HIF-1α	Hypoxia-inducible factor 1-alpha
HO-1	Heme oxygenase 1
HPV	Human papilloma virus
hTERT	Human telomerase reverse transcriptase
IEC6	Intestinal epithelial cell line 6
IFN-γ	Interferon-gamma
IL-1	Interleukin 1
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
IL-8	Interleukin 8
INCA	Instituto Nacional de Câncer José Alencar Gomes da Silva
iNOS	Inducible nitric oxide synthase
I/R	Ischemic–reperfusion injury
IκBα	Inhibitor kappa B
JAK	Janus associated kinases
JNK	Jun N-terminal kinase
LDH	Lactate dehydrogenase
LPS	Lipopolysaccharide
LTA4H	Leukotriene A4 hydrolase
LTB 4	Leukotriene B 4 biosynthesis
MAPK	Mitogen-activated protein kinase

Mcl-1	Myeloid cell leukemia 1
MDA	Malondialdehyde
MG-63	Human osteoblast-like cells
MLCK	Myosin light-chain kinase
MMP-2	Matrix metalloproteinase 2
MMP-9	Matrix metalloproteinase 9
mPGES	Prostaglandin E2 synthase-1 microsomal
NF-κB	Nuclear factor kappa beta
NO	Nitric oxide
Nrf2	Nuclear erythroid 2 related to factor 2
p38	Protein 38
p53	Protein 53 (tumor)
PARP	Poly (ADP-ribose) polymerase 320
PBMCs	Peripheral blood monocytes
PCNA	Proliferating cell nuclear antigen
PG	Prostaglandin
PGE	Prostaglandin E
PGE2	Prostaglandin E2
PI3-K	Phosphatidylinositol 3-kinase
PLC-γ1	Phospholipase C gamma 1
PPARγ	Peroxisome proliferator-activated receptor γ
PRPP	Phosphoribosyl pyrophosphate
Ptx	Paclitaxel
ROS	Reactive oxygen species
SAPK	Stress-activated protein kinase
SDH	Sorbitol dehydrogenase
SOD	Superoxide dismutase
STAT	Signal transducer and activator of transcription
STZ	Streptozotocin
TER	Transepithelial electrical resistance
TJ	Tight junction
TNF-α	Tumor necrosis factor alpha gene
TRAIL	Tumor necrosis factor-related apoptosis inducing ligand
VEGF	Vascular endothelial growth factor
XIAP	X-linked chromosome to apoptosis inhibitor

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How to cite this article: de Lima RMT, dos Reis AC, de Menezes A-APM, et al. Protective and therapeutic potential of ginger (*Zingiber officinale*) extract and [6]-gingerol in cancer: A comprehensive review. *Phytotherapy Research*. 2018;1–23. https://doi.org/10.1002/ptr.6134