Food Bioscience 41 (2021) 100934

Contents lists available at ScienceDirect

Food Bioscience

journal homepage: www.elsevier.com/locate/fbio

Ginger: From serving table to salient therapy

Varsha Menon [a], Mennaallah Elgharib [b], Raafat El-awady [a,c], Ekram Saleh [d,*]

[a] Sharjah Institute of Medical Research, University of Sharjah, Sharjah, United Arab Emirates
[b] College of Engineering, American University of Sharjah, Sharjah, United Arab Emirates
[c] College of Pharmacy, University of Sharjah, Sharjah, United Arab Emirates
[d] Clinical Biochemistry and Molecular Biology Unit, Cancer Biology Department, National Cancer Institute, Cairo University, Egypt

ARTICLE INFO

Keywords:
Ginger
6-Gingerol
6-Shogaol
Anti-inflammatory
Antioxidant
Immunomodulator
Cancer
Adjuvant therapy
Chemotherapeutic
Nano-therapeutic

ABSTRACT

Natural products have for long been receiving wide attention for the prevention and treatment of various diseases. Attention is being given to natural products because they are cost-effective, safe and well tolerated. Ginger (*Zingiber officinale* Roscoe), one of the widely used natural products, has been reported to promote digestion and metabolism in the Ayurvedic and Chinese Medicine. Additionally, it was reported to be effective in acting as a remedy for cough, cold, nausea, vomiting, food poisoning and arthritic pain. The medicinal and nutritional value of ginger has led scientific researchers to explore its anti-microbial, anti-oxidant and anti-cancer properties. The anti-cancer properties of ginger have been attributed mainly to the most active components in ginger, which are 6-gingerol and 6-shogaol. Understanding the mechanisms by which these pungent components control cancer cell proliferation might put ginger in the frontline for cancer treatment. The aim of this review is to cover all the medicinal applications of ginger extract and/or the non-volatile bioactive constituents of ginger (6-gingerol and 6-shogaol) with a focus on both the chemotherapeutic role of ginger and the role it plays as adjuvant therapy in several diseases.

1. Introduction

Ginger (*Zingiber officinale* Roscoe) belongs to the Zingiberaceae family of flowering plants, which includes other plants like turmeric, cardamom and galangal. On a worldwide scale, the most common use of ginger is as a dietary condiment in food and beverages. From a medical point of view, ginger has been used in medicines for the management of various medical diseases (Ujang et al., 2015). Ginger is rich in various chemical constituents. Some of these chemical constituents are phenolic compounds, terpenes, polysaccharides, lipids, organic acids, and raw fibers. The health benefits of ginger are mainly attributed to its bioactive phenolic compounds, such as gingerols and shogaols (Mao et al., 2019). It has been demonstrated that ginger and its bioactive constituents have potential in serving as anti-inflammatory, antioxidant and immunomodulatory agents (Jafarzadeh & Nemati, 2018; Nikkhah Bodagh et al., 2018). Furthermore, Wang et al., (2017) proved that ginger has beneficial effects on obesity and metabolic syndromes such as diabetes mellitus, dyslipidemia, Irritable Bowel Syndrome (IBS) and cardiovascular diseases.

When considering the effects of ginger on cancer, the plant showed dual protective effects against chemotherapy induced nausea and vomiting (Chang & Peng, 2019), and organ toxicity (Attyah & Ismail, 2012; Sheriff et al., 2017). On top of that, ginger derivatives, in the form of extracts or isolated compounds, are able to exhibit relevant anti-proliferative, anti-tumor, anti-invasive, and anti-metastatic activities (De Lima et al., 2018).

This review manuscript covers all the medicinal applications of ginger and its mechanism(s) of action. The manuscript places a focus on the role of ginger and its bioactive constituents as a protective treatment from the side effects produced by cancer treatment. Additionally, the paper discusses how ginger can act as a chemotherapeutic and nano-therapeutic agent against cancer. Finally, the manuscript outlines the molecular mechanisms induced by ginger or its bioactive components in tumor suppression, cell signaling, cell cycle arrest, cell death, invasion and metastasis.

2. Origin and historical background of ginger

Ginger (*Zingiber officinale* Roscoe), a rhizomatous perennial plant that originated in Maritime Southeast Asia, was first cultivated by the Austronesian people and transported to other regions through the indo-pacific oceans 5000-years ago (Ravindran & Babu, 2016; Singh, 2012).

* Corresponding author.
E-mail addresses: ekram.saleh@cu.edu.eg, ekram.saleh@cu.edu.eg (E. Saleh).

https://doi.org/10.1016/j.fbio.2021.100934
Received 12 January 2021; Received in revised form 21 February 2021; Accepted 22 February 2021
Available online 27 February 2021

Ginger had religious significance among the Austronesians. It was used in rituals for healing and seeking protection from the spirits as well as in the blessing of Austronesian ships. Ginger was introduced to India during the Austronesian expansion. From India, ginger was carried by traders to the Middle East and the Mediterranean area around the 1st century (Blust & Trussel, 2013; Ujang et al., 2015). The plant was used by the ancient Greeks and Romans and is considered one of the first spices that were exported from Asia to Europe (Christenhusz & Byng, 2016).

3. Chemistry of ginger

The constituents of ginger may vary from one plant to another, this variation is dependent on two factors. The first factor is how fresh or dry the rhizomes are and the second one is the place of origin of the plant (Sang et al., 2020). There are two distinct groups of chemicals present in ginger that contribute to its sensory perception namely; volatile oils and non-volatile pungent compounds. The first group is the volatile oils group. Volatile oils contribute to the distinct aroma and taste of ginger. Sesquiterpene hydrocarbons, predominantly zingiberene, curcumene and farnesene form the main components of the volatile oils, along with smaller amounts of b-sesquiphel-landren and bisabolene. The second group is the non-volatile pungent compounds group. Non-volatile constituents in ginger are responsible for its hot sensation in the mouth. Among the non-volatile pungent compounds, gingerols, shogaols, paradols and zingerone are considered the main constituents (Fig. 1). In addition to above mentioned pungent components fats, waxes, carbohydrates, vitamins and minerals are other constituents of ginger rhizome (Vedashree et al., 2020; Yi et al., 2019).

3.1. Bioactive components of ginger

The most active component of fresh rhizome is gingerols. Gingerols are a series of chemical homologs differentiated by the length of their unbranched alkyl chains. Upon thermal processing, the OH group at the C-5 position in gingerols is eliminated, resulting in formation of a double bond between the C-4 and C-5 positions in shogaols. This transformation increases the pungency characteristic of ginger (Sang et al., 2020). When rhizomes are dried at a temperature lower than 70°C, the yield of ginger oil is increased without any effect on the 6-gingerol to 6-shogaol transformation. For temperatures higher than 70°C, the transformation of 6-gingerol to 6-shogaol will be enabled (Huang et al., 2012). The yield of 6-shogaol could be maximized by adjusting the pH of the extraction solvent using a strong acid, and by increasing the drying and extracting temperatures. Parameters such as place of origin, cultivar, pH and temperature affect the stability of gingerols (Ok & Jeong, 2012).

Paradols are phenolic ketones with a structural similarity to gingerols and shogaols (Setoguchi et al., 2016). The yielding of paradols happens through the hydrogenation of shogaols (Sapkota et al., 2019). Zingerone, a paradol analogue, also known as 0-paradol, is another pungent component of ginger and part of the paradols family. With the exception of zingerone, 6-paradol is the only naturally occurring member to be isolated from natural sources (Setoguchi et al., 2016).

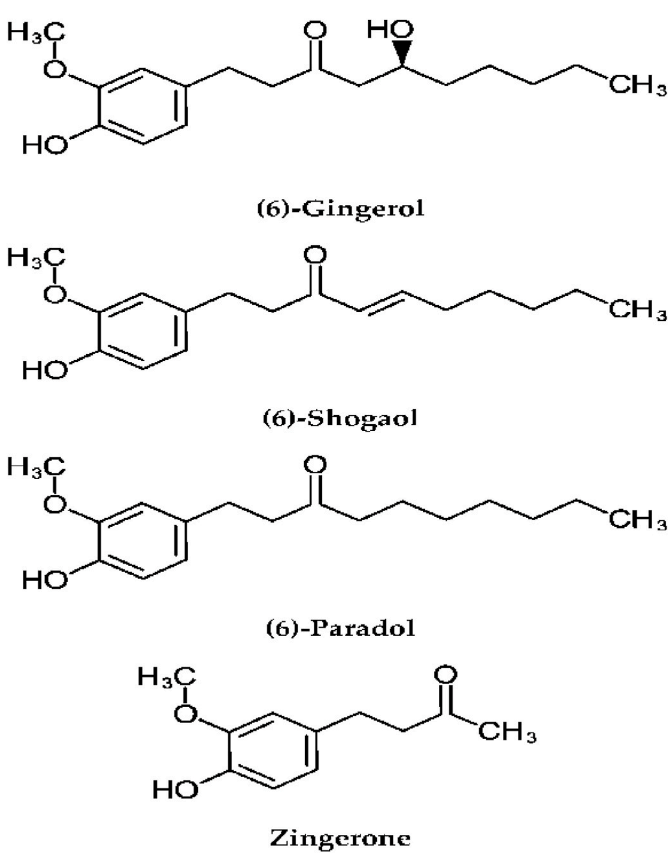

Fig. 1. Non-volatile pungent components of ginger.

4. Current medicinal applications of ginger

There are several medicinal applications of ginger. These medicinal applications are mainly attributed to its anti-inflammatory and antioxidant activity. Additionally, ginger is used as adjuvant therapy in several diseases, enhance immunity and act as a chemoprotective and/or therapeutic for cancer (Fig. 2).

4.1. Ginger and inflammation

The anti-inflammatory and antioxidant characteristics of ginger allow it to possess several medicinal applications. There are several pieces of evidence supporting the anti-inflammatory property of ginger. A study by Kim and Kim (2018b) showed that, the treatment of colitis mice induced by 5% Dextran Sulfate Sodium (DSS) with ginger, resulted in an increase in the body weight, an inhibition of colon shortening, and a reduction in the activity of myeloperoxidase and pro-inflammatory cytokines namely; interleukin (IL)-1β, IL-6, and tumor necrosis factor

Fig. 2. General medicinal properties of ginger.

(TNF)-α. These results demonstrated the protective effect of ginger against DSS-induced colitis. Yang et al. (2014) studied the effect of ginger extract on fructose-fed rats and identified the protective effect of ginger on metabolic syndrome-associated with kidney injury via suppressing the renal-induced overexpression of proinflammatory cytokines in rats. High-hydrostatic pressure extract of ginger induced lowering of the mRNA levels of pro-inflammatory cytokines, downregulated the microRNA-miR 21 and miR 132 expression and enhanced the activity of metabolism regulator, adenosine monophosphate-activated protein kinase (AMPK) in mice fed with 45% high fat diet (Kim, Lee, et al., 2018). An in-vivo study in murine house dust mite model demonstrated that 6-Shogaol, one of the bioactive compounds of ginger, mitigated inflammation in lung and airway hyper-responsiveness thereby combating asthma. Furthermore, 6-shogaol increased the concentrations of cAMP in CD4 cells, inhibited induction of NF-κB signaling, altered pro-inflammatory cytokine release and augmented Treg polarization in-vitro (Yocum et al., 2019). A similar in-vivo study was previously reported on ginger where gingerol, another active constituent of ginger, reduced airway eosinophilia, Th2 cytokines, and allergen-specific antibodies thereby inhibiting allergen-induced lung inflammation (Ahui et al., 2008).

In sepsis, 6-gingerol has been displayed to possess anti-inflammatory properties in vivo and in vitro. In mice established models of sepsis, 6-gingerol reduced the level of pro-inflammatory cytokines IL-18 in serum and colon tissues. In BMDMs and RAW264.7 cell lines, 6-gingerol alleviated the release of caspase-1p20, HMGB1 and IL-18 in response to adenosine 5′-triphosphate (ATP) and lipopolysaccharide (LPS) treatment and relieved the macrophages pyroptosis via inhibition of MAPK signaling pathways (Zhang et al., 2020). Another study by Hong et al. (2020) used cecal ligation and puncture (CLP) to induce polymicrobial sepsis and liver injury in mice. 6-Gingerol administration ameliorated sepsis by inhibiting the expression of pyroptosis-related proteins, including NOD-like receptor protein 3 (NLRP3), IL-1β, and caspase-1. In addition, 6-Gingerol administration improved sepsis by another mechanism, which is the activation of the Nrf2 pathway.

4.2. Ginger as antioxidant

The ability to function as an antioxidant is another important property of ginger. Masuda et al. (2004) evaluated structure-activity relationship of gingerol related compounds by substituting with an alkyl group bearing 10-, 12- or 14-carbon chain length. The study reported that the substituents on the alkyl chain might contribute to the inhibitory effect of autoxidation of oils and the radical scavenging effect thereby suggesting their antioxidant activity. Similarly, studying Ginger extract and its constituent components (6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol) identified that their hydroxyl groups and the suitable solubilizing side chains are responsible for the antioxidant property. The study showed that 6-Shogaol and 10-gingerol exhibited higher activity than 6-gingerol and 8-gingerol at 60 °C. At high temperatures (120/180 °C) low antioxidant activity was detected (Si et al., 2018).

Ginger inhibited the oxidative stress and the inflammation by enhancing antioxidant enzymes and decreasing inflammatory TNF-α level (Morakinyo et al., 2011). A study on rats, compared the antioxidant activity of ginger against ascorbic acid, a natural antioxidant. The results exhibited that ginger maintained the activities of the antioxidant enzymes, superoxide dismutase, catalase and glutathione peroxidase. Moreover, in tuberculosis patients, supplementation of ginger along with antitubercular therapy significantly lowered the concentrations of malondialdehyde, ferritin and TNF-α. The study concluded that ginger has antioxidant activity and it possesses strong free radical scavenging property (Kulkarni & Deshpande, 2016). The presence of polyphenol compounds is reported to be responsible for the antioxidant activity in ginger extract. The total phenolic content of the ginger alcohol extract is 870.1 mg/g dry extract. The 2,2-Diphenyl-1-picril hydrazyl radical (DPPH) scavenging activity of the extract was estimated to be 90.1% with the IC50 concentration of 0.64 μg/ml (Stoilova et al., 2007).

Investigating two different extracts of steamed ginger: ethanolic (SGE) and water extract (SGW), identified that the ethanolic extract has higher contents of flavonoids, polyphenols, DPPH and ABTS+, free radical scavenging activities compared to water extract, which supports its antioxidant activity (Kim, Kim, et al., 2018). Moreover, an in vivo study by Fahmi et al. (2019) reported that diethylnitrosamine (DEN) induced rats treated with ginger essential oil showed a significant increase in serum catalase and GSH-Px compared to the positive control DEN induced rats. A recent study reported that ginger-based fruit drink in the ratio Ginger 50: Pineapple 10: Apple 40 showed a highest phenolic distribution, highest 2, 2-diphenyl-1-picrylhydrazyl (DPPH), 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS+) scavenging abilities as well as ferric reducing antioxidant property (FRAP) (Ademosun et al., 2020).

4.3. Ginger and immunity

Ginger is used as dietary supplement to boost immunity by enhancing the levels of interferon gamma (INF-α) and interleukin 2 (IL-2). Zidan et al. (2016) studied the effect of ginger on one-day old broiler chicks and identified that adding ginger to their diet significantly enhanced the serum levels of INF-αand IL-2. Interferon gamma (INF-γ) is crucial for immune response and its aberrant expression causes many autoimmune and autoinflammatory diseases (Schoenborn & Wilson, 2007).

Adding 0.1% ginger extract to basal diet of laying hens increased lysozyme (LZM) activity, maintained the contents of serum total protein (TP), albumin (ALB) and globulin (GLB) unaltered. Enhancing LZM activity reflected the cellular immunity and the anti-infection ability of the body (An et al., 2019). Similarly, in zebra fish, the mRNA expression level of lysozyme was upregulated by feeding them with 3% ginger. Moreover, alkaline phosphatase, a representative of anti-bacterial activity was also significantly increased in fish fed with ginger (Ahmadifar et al., 2019).

Adding gingerols to activated T-lymphocytes augmented the intracellular Ca^{2+} concentrations and increased cytokine IFN-γ secretion. The results of the study pointed to an interaction of gingerols with TRPV1 in activated T lymphocytes leading to an augmentation of IFN-γ secretion (Schoenknecht et al., 2016).

A recent study examined mice infected with strains of *Mycobacterium tuberculosis* and it found that 6-gingerol one of the active components of ginger, confirmed its immunomodulatory action by enhancing Th1/Th17 responses. Moreover, CD4± and CD8+T cells which constitute the main components of adaptive immunity and CD11b± and CD11c ± cells which are required to activate the acquired immunity were increased (Bhaskar et al., 2020).

The conditions of thermal drying could also differentially impact the immunomodulatory function of ginger. Lee et al. (2019) reported that ginger dehydrated at specific conditions (50 °C) exhibited immune-stimulatory effects which were attributed to their ability in inducing ERK, JNK, and p38 pathways in RAW264.7 murine macrophage cells.

The medicinal value of ginger has also been investigated in improving the Rheumatoid Arthritis (RA). The study which was performed by Aryaeian et al. (2019) on patients with rheumatoid arthritis reported that ginger decreases the disease manifestations by increasing the expression of forkhead box P3 (Fox P3) genes and decreasing the expression of RORγt and T-bet genes. An increase in Fox P3, which is the transcription factor in T regulatory (Treg) cells, causes an increase in Tregs functionality, down modulate immune system and prevent autoimmune diseases (Nazari et al., 2013).

4.4. Ginger and the blood

On the blood level, ginger was reported to have an antithrombotic and cholesterol-lowering activity. A meta-analysis conducted by Pourmasoumi et al. (2018) identified that ginger at a low dose (≤2 g/day) could cause a favorable effect on triacylglycerol (TAG) and low density lipoprotein cholesterol (LDL-C). Moreover, Zingerone, a phenolic alkanone found in ginger, was reported to act as an antithrombotic compound with both factor Xa (FXa) inhibitory and anti-platelet aggregation activities (Lee et al., 2017).

4.5. Ginger as adjuvant therapy

4.5.1. Ginger for nausea and vomiting

4.5.1.1. In pregnancy. Apart from the above-mentioned protective roles, ginger is effective in ameliorating nausea and vomiting. Nausea and vomiting during pregnancy (NVP), which is otherwise known as morning sickness, affects about 80% of pregnant women (Quinla & Hill, 2003). Nausea and vomiting during early pregnancy are considered to be independently related to the human chorionic gonadotropin (hCG) hormone and some psychological factors (Dekkers et al., 2019). A triple blind clinical trial conducted by Sharifzadeh et al. (2018) on pregnant women suffering from mild to moderate NVP identified that, the effect caused by a 1000 mg dose of ginger taken to reduce NVP is comparable to that caused by an 80 mg vitamin B6 dose taken daily. Similarly, a meta-analysis carried out by Hu et al. (2020) reported that, ginger could significantly relieve general NVP symptoms compared to placebo, with no significant difference between ginger and vitamin B6.

Acupressure at Neiguan point (P6) is another remedy to reduce nausea and vomiting (Werntoft & Dykes, 2001). On comparing the effect of acupressure to ginger, it was found that ginger is more powerful in relieving mild to moderate nausea and vomiting in less than 16 weeks of gestational age (Saberi et al., 2013). Moreover, a study by Kustriyanti and Putri (2019) reported that ginger aromatherapy could be used to minimize the severity of NVP.

In order to test the safety and efficacy of ginger during the pregnancy period, Stanisiere et al. (2018) monitored a total of fifteen different studies and three preclinical trials. It was concluded that at a dose of 1 g of fresh ginger root per day, ginger caused no obvious risk to the mother or future baby. However, medical supervision is mandatory and the quality of ginger should be taken into consideration.

4.5.1.2. For chemotherapy-induced nausea and vomiting (CINV). When considering the efficiency of ginger as a remedy for chemotherapy-induced nausea, the results obtained were contradictory. Ginger is expected to enhance antiemetic effects and counteract oxidative damage to tissues by binding to 5-HT3 receptors and increasing detoxification enzymes (Geiger, 2005). A study by Ryan et al. (2012) speculated that administering ginger prior to chemotherapy could prepare the gut for an anti-nausea response through 5-HT3 receptor binding and induction of detoxification enzymes.

Sanaati et al. (2016) conducted a randomized, double-blind, clinical trial study, which demonstrated that ginger significantly reduced nausea and vomiting in patients treated with chemotherapy for breast cancer. Furthermore, on conducting a meta-analysis to identify the effect of ginger on CINV, it was concluded that ginger administration resulted in reduced acute CINV (Chang & Peng, 2019). Similarly, it was reported that adjuvant ginger supplementation is associated with significantly less chemotherapy-induced nausea and cancer related fatigue (Marx et al., 2017).

On the contrary, Thamlikitkul et al. (2017) reported that, administering 500 mg ginger twice a day to breast cancer patients receiving adriamycin and cyclophosphamide (AC) regimens, along with ondansetron and dexamethasone, did not result in the reduction of nausea. Likewise, Li et al. (2018) conducted a randomized, double-blind, placebo-controlled clinical trial and exhibited that ginger has no evident effect in ameliorating CINV in lung cancer patients receiving cisplatin-based regimens.

Recently, an integrative review performed using Ganong's reference by Borges et al. (2020) reported that there was no statistical confirmation for using ginger as a complementary therapy to reduce CINV.

4.5.2. Ginger for diabetes mellitus

Ginger has been reported to possess antidiabetic activity. Venkateswaran et al. (2021) studied the antidiabetic activity of microwave-assisted polyphenolic extracts of Indian ginger cultivars from Tamil Nadu (MPT) and Odisha (MPO). The research study identified MPT to be a promising candidate to function as an adjuvant therapy for treating diabetes. The results of the study indicated that MPT showed an insulin stimulated glucose uptake of 1.74 ± 0.25 fold at 6.25 μg/ml concentration compared to the control in C2C12 cells. It also possessed anti-glycation and α–amylase, α–glucosidase inhibitory properties with a DPPH radical scavenging activity of 7.69 ± 0.001%. In addition, the results displayed an increased GLUT4 expression even at a lower dose of 6.25 μg/ml.

In a recent in vivo study on a streptozotocin (STZ)-induced mice model of painful diabetic neuropathy (PDN), it was reported that the ginger extract of 400 mg/kg BW and 6-shogaol 15 mg/kg BW significantly attenuated hyperalgesia and allodynia, compared to the diabetic control group. The attenuation in hyperalgesia and allodynia happened by decreasing the expression of nociceptive receptor transient receptor potential vanilloid-1 (TRPV1) and *N*-methyl-D-aspartate receptors (NMDAR2B) in the spinal cord, with very limited effect on the function of pancreatic islet (Fajrin et al., 2020).

4.5.3. Ginger for asthma

Ginger plays a significant role in ameliorating asthmatic conditions. A study by Li et al. (2019) on ovalbumin-sensitized asthma in rats identified that, 6-gingerol lessens immunoglobulin E (IgE) and interleukin IL-4, IL-5 and IL-13. Additionally, 6-gingerol increases the level of interferon-gamma (IFN- γ) like theophylline. Moreover, the glycoprotein accumulation and alveolar epithelium thickness in asthmatic rats were restored to normal conditions by supplementing the rats with 6-gingerol. This restoration to normal conditions represents the protective effect of 6-gingerol on lungs. An earlier study investigated the effect of the bioactive components of ginger, namely 6-gingerol, 8-gingerol and 6-shogaol to potentiate ß-agonist-induced relaxation of the airway smooth muscle (ASM). The results showed that the bioactive components inhibited the degradation of 3′–5′-cyclic adenosine monophosphate (cAMP) in the airway smooth muscle. In addition, they prevented the formation of phosphodiesterase 4D (PDE4D) and phosphatidylinositol-specific phospholipase C (PIPLC). Enzymes that degrade cAMP, the molecule that activates protein kinase A (PKA) and leads to airway relaxation, were prevented from forming as well. Inhibition of both PDE4D and PIPLC in primary human ASM cells regulated the contractile machinery by lowering the level of contractile proteins. They concluded that the bioactive components of ginger act as adjuvant therapy in combination with the traditional therapy to relieve the symptoms of asthma (Townsend et al., 2014).

4.5.4. Ginger for kidney transplantation

Cyclosporine (CYA), which is commonly used in organ transplantation as an immuno-suppressant drug, has been reported to have nephrotoxic effects (Fioretto et al., 2011). A study by Adekunle et al. (2018) on a Wistar rat model identified that, ginger polyphenols attenuate some indices of experimental cyclosporine-induced kidney injury, through antioxidants and membrane stabilizing effects along with transport protein modulation, marking its space in renal and other transplant therapy as an adjuvant treatment.

4.6. Ginger and cancer

Cancer is a major health problem globally (Fidler et al., 2018). There are many treatment strategies such as chemotherapy, radiotherapy, hormonal therapy, targeted therapy and immune therapy to treat cancer. The side effects associated with these treatment modalities reduce the success rate of cancer therapy, therefore there is an urgent need to introduce natural compounds that can not only play a role as an adjuvant therapy but also ameliorate the side effects caused by the current therapies. (Di Bona et al., 2020; Pujade-Lauraine et al., 2010; Wibowo et al., 2016).

4.6.1. Protective role of ginger against chemotherapy-induced organ toxicity

One of the major obstacles that counteract the treatment of cancer patients with chemotherapeutic drugs is the cytotoxicity of different organs. For instance, Doxorubicin which is used to treat multiple types of cancer causes hepatotoxicity (Sakr et al., 2011) and nephrotoxicity (Ajith et al., 2008). Likewise, cisplatin causes hepatotoxicity, cardiotoxicity and testicular toxicity (Attyah & Ismail, 2012; Elshiekh et al., 2019). The following table (Table 1) shows previous studies regarding the protective role of ginger against various toxicities caused by chemotherapeutic drugs.

4.6.2. Therapeutic potential of ginger against cancer

Among the different constituents of ginger, gingerols and shogaols are the main active constituents that contribute to the anti-cancer properties of ginger. 6-Gingerol (1-[4′-hydroxy-3′-methoxyphenyl]-5-hydroxy-3-decanone) and 6-shogaol [(E)-1-(4-hydroxy-3-methoxyphenyl)-dec-4-en-3-one] have been widely studied for their effects against different types of cancer (Bawadood et al., 2020; De Lima Silva et al., 2020; Woźniak et al., 2020; Xu et al., 2020). Below are the main anticancer effects of ginger.

4.6.2.1. Cytotoxicity and tumor suppression. 6-gingerol and 6-shogaol play a vital role in suppressing cancer cell growth. It is known that Leukotriene A4 hydrolase (LTA4H), is overexpressed in several human cancer cell lines, including colorectal cancer. 6-Gingerol was shown to have a capacity to block the activity of LTA4H and to be cytotoxic to HCT116 colon cancer cells (El-Naggar et al., 2017). Furthermore, Fan et al. (2015) showed that 6-gingerol significantly decreased the viability of osteosarcoma cells in a dose dependent manner. Moreover, in a recent study on Sarcoma 180 cells, 6-gingerol showed a notable cytotoxic effect by reducing the cell division rates and cell viability via apoptotic induction (De Lima Silva et al., 2020).

In parallel, 6-shogaol has exhibited cytotoxic effect towards cancer cells. Ray et al. (2015) investigated the effect of 6-shogaol against breast cancer monolayer cells as well as cancer stem cell like spheroid culture

Table 1
Chemoprotective effects of ginger against toxicities after treatment of the experimental animals (mice/rats) with different types of chemotherapeutic agents.

Chemotherapeutic drug	Animal Model	Overall Effect	Molecular Effect		References
			Increase	Decreased	
Doxorubicin	Female Spraque-Dawley rats	Cardio-protective effect	Nil	Serum glutamate oxaloacetate Transaminase Serum lactate dehydrogenase activity Malondialdehyde	Ajith et al. (2016)
	Male Albino rats	Hepato-protective effect	Superoxide dismutase (antioxidant enzyme)	Alanine aminotransferase Aspartate aminotransferase Malondialdehyde (lipid peroxidation marker)	Sakr et al. (2011)
	Female Spraque-Dawley rats	Nephro-protective effect	Superoxide dismutase Catalase Glutathione peroxidase Level of reduced glutathione Glutathione-*S*-transferase	Serum urea creatinine levels Malondialdehyde	Ajith et al. (2008)
Paclitaxel	Male Swiss albino mice	Geno-protective effect	Nil	Number of the chromosomal aberrations Number of micronuclei	Al-Sharif (2011)
Cisplatin	Male Wistar strain albino rats	Testicular protective effect	Epididymal sperm count Sperm motility Superoxide dismutase Reduced glutathione Catalase	Sperm abnormality malondialdehyde	Amin et al. (2006)
	Male and female white albino rats	Hepato-protective effect Cardio-protective effect	Nil	Aspartate aminotransferase Alanine aminotransferase Total serum bilirubin Lactate dehydrogenase Creatine kinase	Attyah et al. (2012)
	Male albino rats	Nephro-protective effect	Nil	Serum creatinine Blood urea nitrogen Over-expressed Bax	Ali et al. (2013)
	Male albino rats	Nephro-protective effect	Nil	Blood urea Creatinine Nitric oxide Malondialdehyde Caspase 3	Sheriff et al. (2017)
	Male albino rats	Testicular protective effect	Catalase Reduced Glutathione Testosterone level Sperm count Sperm motility	Malondialdehyde Chromosomal abberations Tail abnormality Divided sperm head	Elshiekh et al. (2019)
Etoposide	Male albino rats	Cyto- protective effect Geno- protective effect	Mitotic index Superoxide dismutase Catalase Glutathione	Malondialdehyde Nitric oxide Chromosomal aberrations	El Nabi et al. (2017)

and the researchers identified that the CD44 + CD24-/low cells and the secondary sphere content were drastically reduced after treatment of the cells with 6-shogaol, thereby confirming the action of 6-shogaol against cancer stem cells. Moreover, a study on an allograft model mouse HMVP2 prostate cancer cells showed that 6-shogaol significantly inhibited the tumor growth (Saha et al., 2014). Qi et al. (2015) also conducted a similar study on xenograft mouse model and reported that 6-shogaol effectively suppressed the colorectal tumor growth.

4.6.2.2. Cell signaling, cell cycle arrest and cell death. 6-gingerol and 6-shogaol have been reported to target different cell signaling pathways and to sensitize and arrest cancer cells at different phases of the cell cycle (Fig. 3). A study by Luo et al. (2018) reported that 6-gingerol enhanced sensitivity of gastric cancer HGC-27 cells to ionization radiation (IR) through inducing G2/M phase arrest and apoptotic cell death. In a later study, the same author used a combined treatment of 6-gingerol and cisplatin (CDDP) to treat HGC-27 gastric cancer cells. The combination therapy enhanced G1 phase arrest as well as suppressed migration and invasion via inhibiting PI3K/AKT signaling pathway (Luo et al., 2019).

Recent study reported that 6-gingerol suppressed AKT–CDK4–cyclin D1 pathway in renal cell carcinoma. The results demonstrated concentration-dependent accumulation of cells at the G1 phase in vitro, significant decrease in *p*-AKT Ser 473, CDK4, and cyclin D1 protein amounts. In addition, significant increase in glycogen synthase kinase (GSK 3β) protein amounts in vitro and in vivo (Xu et al., 2020). On the other hand, 6-gingerol when chemically modified using acetone-2, 4-dinitrophenylhydrazone, the resulting compound (semi-synthetic analogue SSi6) arrested triple negative breast cancer cells (MDA MB 231) at the G1-phase, mainly by decreasing Cdk4/6-Rb axis levels (Luna-Dulcey et al., 2020).

Parallel to 6-gingerol, 6-shogaol also exhibited effects on different signaling pathways to sensitize different types of cancer. 6-shogaol suppressed the survival signaling of the AKT/mTOR signaling pathway in human non-small cell lung cancer A549 cells via blocking the activity of AKT, mTOR, forkhead transcription factors (FKHR) and glycogen synthase kinase-3β (GSK-3β) (Hung et al., 2009). In a similar study on A549 cells, 6-shogaol and its Synthetic metabolite, cysteine conjugated 6-shogaol utilized p53 pathway for induction of apoptosis via generating oxidative stress and released mitochondria-associated apoptotic molecules such as cytochrome C, cleaved caspases 3 and 9 (Warin et al., 2014). Another survival signaling pathway was blocked by 6-shogaol, in MDA-MB-231 breast cancer cells 6-shogaol strongly inhibited STAT3 and MAPKs signaling cascade and induced ROS-mediated JNK, p38 MAPK, and ERK activation. 6-shogaol down-modulated gene products such as Bcl-2, Bcl-xL, and Survivin that mediate tumor cell survival, proliferation, invasion, and metastasis thus inducing substantial apoptosis (Kim et al., 2015). In another study, 6-shogaol arrested HCT116 colon cancer cells at G2/M by up-regulating p53, CDK inhibitor p21waf1/cip1 and GADD45α, and down-regulating cdc2 and cdc25A (Qi et al., 2015). A similar study was reported that 6-shogaol induced irreversible G2/M arrest partly through down-regulation of cdk1, cyclin B and cdc25C cell cycle checkpoint proteins, as well as mad2, cdc20 and surviving spindle assembly checkpoint proteins (Gan et al., 2011).

4.6.2.3. Invasion and metastasis. 6-gingerol and 6-shogaol have also been studied for their anti-invasive and anti-metastatic activity. Lee et al. (2008) reported that the treatment of triple negative breast cancer cells (MDA MB 231) with 6-gingerol led to a decrease in cell migration and motility in a dose dependent manner. Moreover, the activity of matrix metalloproteinases (MMPs), MMP2 or MMP9, which are the mediators of invasion and metastasis was also decreased. Similarly, a study on rat ascites hepatoma cells (AH109A) showed that 6-gingerol commenced the suppression of AH109A invasion at 50 μM concentration. Furthermore, the ROS potentiated invasive activity of the cells pre-cultured with either hypoxanthine (HX) and xanthine oxidase (XO) or with hydrogen peroxide was inhibited by 6-gingerol at 20 μM concentration (Yagihashi et al., 2008).

Parallel to the previous study both 6-shogaol and 6-gingerol exerted anti-invasive activity against phorbol 12-myristate 13-acetate (PMA)-treated HepG2 and PMA-untreated Hep3B cells via decreasing the activity of matrix metalloproteinase (MMP)-9 and increasing the expression of tissue inhibitor metalloproteinase protein (TIMP)-1. Additionally, 6-shogaol decreased the activity of urokinase-type plasminogen activator (uPA) in Hep3B cells (Weng et al., 2010).

Weng et al. (2012) further explored the underlying molecular

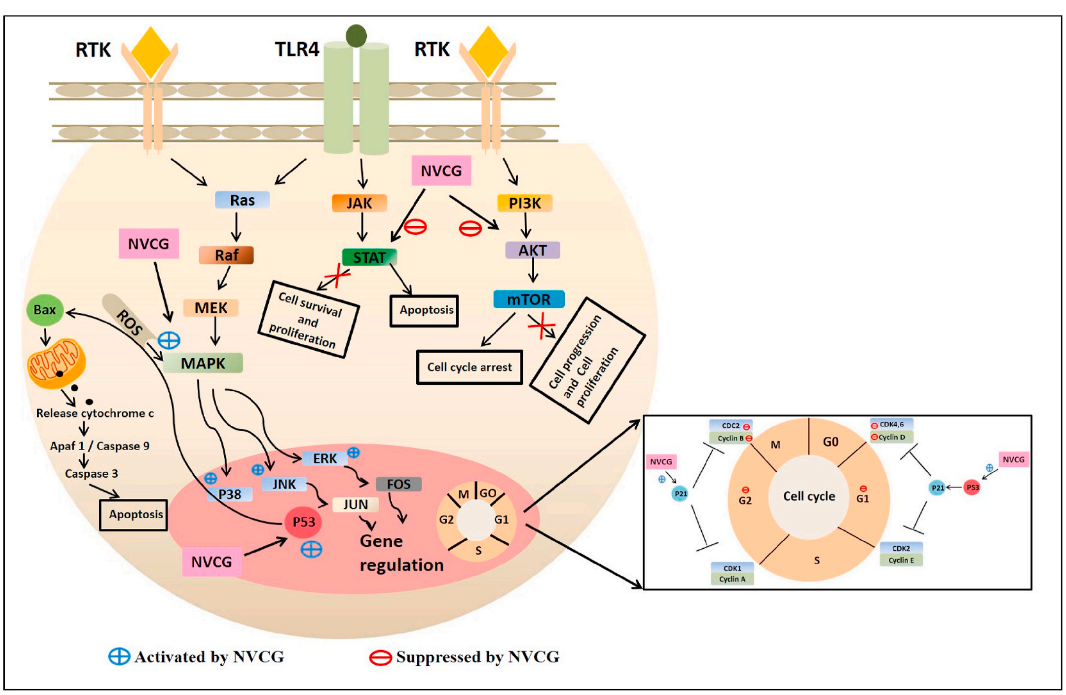

Fig. 3. Signaling pathways targeted by Nonvolatile constituents of ginger (NVCG) 6- gingerol and/or 6-shogaol.

mechanism involved in the inhibition of invasion and metastasis by 6-gingerol and 6-shogaol on Hepatocellular carcinoma (HCC) cells. The study reported that the inhibition of MAPK, PI3k/Akt pathways and the reduction of NF-κB and STAT3 activity resulted in decreased transcription of MMP-2/-9 and the expression of uPA.

Another study examined the effect of 6-gingerol on tight junction (TJ) molecules and signal transduction pathways in human pancreatic duct cell-derived cancer cell line (PANC-1). TJ protein levels increased which correlated with a decrease in paracellular flux and matrix metalloproteinase (MMP) activity in 6-gingerol-treated cells. Moreover 6-gingerol suppressed invasion and metastasis through inhibition of NF-κB/Snail via ERK pathway inhibition (Kim & Kim, 2013).

5. Nano-therapeutic applications of ginger

In order to enhance the drug bioavailability within the cells, tissues or both; a non-toxic and efficient carrier system for battered delivery is required. Nanoparticles are one such carriers where the drugs or natural compounds can be efficiently encapsulated (Khalil et al., 2016). Abdu et al. (2017) explored the previous concept and they found that Ginger encapsulated in poly-lactic-*co*-glycolic acid (GNPs) suppressed the initiation of colon cancer induced by 2,3,7,8-Tetracholorodibenzo-p--dioxin (TCDD) in albino male rats via enhancing the level of the anti-oxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione-*S*-transferase (GST). In addition, GNPs decreased the expression of cancer related genes such as Bcl2, Bax and p53 and lowered the necrotic/apoptotic rate in TCDD treated rats.

Zhang, Viennois, et al. (2016) conducted a study for treating the inflammatory bowel disease (IBD) including crohn's disease and ulcerative colitis using specific population of nanoparticles derived from edible ginger (GDNPs 2). Oral administration of GDNPs 2 to mouse colitis models led to reduction of acute colitis, enhancement of intestinal repair, prevention of chronic colitis and colitis-associated cancer. This is measured by increasing the survival and proliferation of intestinal epithelial cells, reducing the pro-inflammatory cytokines (TNF-α, IL-6 and IL-1β), and increasing the anti-inflammatory cytokines (IL-10 and IL-22) in mouse colitis models.

Metals such as zinc, silver, copper and iron could also be used as nanoparticles. El-Refai et al. (2018) synthesized these metal -ginger nanoparticles and evaluated their anti-cancer effect against Caco (colorectal adenocarcinoma), HepG2 (liver cancer) and T47D (breast cancer) cell lines. The results suggested that among the metal-ginger combination, ginger-copper nanoparticle was found to be the most effective anticancer agent.

Another recent study explored the cytotoxic and antioxidant effect of ginger extract-gold nanoparticles (AuNPs) on human follicular thyroid carcinoma, lymph node metastasis (FTC-133) cells. The results demonstrated that the antioxidant properties of the synthesized nanoparticles were effective. The High-content screening (HCS) assay showed that the nano ethanol extract had a toxic effect on FTC-133 cells at a dose-dependent manner. An increase in nuclear intensity, membrane permeability and cytochrome *c* were also observed in addition to decrease in cell viability and change in mitochondrial membrane potential (Ascar et al., 2019).

Another effective method is to formulate nanoparticles of ginger or its bioactive constituents along with chemotherapeutic drugs to increase the cytotoxic effect on cancer cells. Manatunga et al. (2018) combined 6-gingerol with doxorubicin using magnetically attractive hydroxyapatite (m-HAP) based alginate polymer bound nanocarrier (6-Gin--Dox-m-HAP). Using the cell proliferation assays, fluorescence imaging and flow cytometric analysis for MCF7 and HepG2 cells showed that the drug loaded nanoparticles have more antiproliferative effect than their free counterparts. Moreover, the drug loaded nanoparticles when tested against non-targeted non-cancerous cells showed significantly reduced toxic effect.

Ginger could also be used as a nanovector to load chemotherapeutic drugs. An earlier study explored the efficacy of ginger to be used as a nano-vector (GDNV) that is loaded with doxorubicin. The study demonstrated that targeting the delivery of Dox using GDNV conjugated with the targeting ligand folic acid (DOX-FA-GDNV) to Colon-26 tumors in vivo resulted in enhanced chemotherapeutic inhibition of tumor growth compared to free DOX thereby stipulating the role of ginger to act as nanovectors (Zhang, Xiao, et al., 2016).

Micelles are another group of nanocarriers used for encapsulation of ginger. 6-Shogaol rich Ginger oleoresin (6-SRGO) was incorporated into mixed micelles using phospholipid (Soya Lecithin S80) and sodium cholate hydrated (SCH) to prepare 6-SRGO loaded mixed micelles (6-SRGO-LMM). When 6-SRGO-LMM tested in vitro against MCF7, the results revealed that 6-SRGO-LMM had a better growth inhibition in comparison to 6-SRGO alone. Treatment of mice carrying dalton's ascitic lymphoma (DAL) cells with 6-SRGO-LMM exhibited a better life span in comparison to free 6-SRGO (Kiran et al., 2018). A similar finding was reported when micelles of a Poly ethylene glycol derivative of linoleic acid (mPEG2k-LA) were prepared to load 6-shogaol. 6-shogoal loaded micelles (SM) were found to be more cytotoxic for HePG2 cells than free 6-shogaol in vitro. Intriguingly, SM also showed a better hepatoprotective effect against carbon tetrachloride (CCl4)-induced hepatic injury than free 6-shogaol in vivo (Zhang et al., 2019). These studies show that using nanocarriers to load ginger constituents or using ginger coupled nanoparticles act as an efficient strategy for drug delivery.

6. Safety and risky factors of ginger

Ginger as per U.S. Food and Drug Administration (FDA) is generally considered to be a safe food additive. However, there are few articles that have reported some problems associated with ginger or with its constituents. A study showed that the mutagenesis ability of 2(2-furyl)-3 (5-nitro-2-fury) acryl amide (AF2) or *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (NTG) was increased when rhizome juice of ginger was added. The same study also identified that 6-gingerol was the active component that caused this mutagenic effect (Nakamura & Yamamoto, 1982) while 6-shogaol was found to be less mutagenic in comparison to 6-gingerol (Nakamura & Yamamoto, 1983). However, there has not been any recent report or studies suggesting the mutagenic characteristics of ginger.

A standardized ethanol extract of dry rhizomes of ginger at a dose of 100 mg/kg was given to Normal male Wistar rats and the results suggested that there is no effect on blood glucose, blood coagulation (native as well as warfarin prolonged), systolic blood pressure or heart rate in rats (Weidner & Sigwart, 2000).

An observational study in humans examined pregnant women who took ginger in their first trimester and compared them to women exposed to nonteratogenic drugs that were not antiemetic drugs. The results suggested that the ginger group did not increase the rate of major malformations above the baseline rate of 1%–3% (Portnoi et al., 2003). A case study by Stanisiere et al. (2018) on ginger consumption in early pregnancy to reduce nausea and vomiting mentioned that factors such as the quality of ginger, the transformation process (powder, extract, oils, etc.) and the relative standardization should be taken in to consideration before attributing the safe tag for ginger.

Moreover, in an earlier study to evaluate the toxicity of ginger, 35-day toxicity study was conducted on male and female Sprague–Dawley rats where they were treated with ginger powder at a dosage of 500, 1000 and 2000 mg/kg body weight for 35 days by oral gavage method. The results demonstrated no association of mortality and abnormality in general conditions, behavior, growth, and food-water consumption. Except for a decrease in serum lactate dehydrogenase activity in males in a dose-dependent manner and slightly reduced absolute and relative weights of testes at high dose (2000 mg/kg), no overt organ abnormality was reported. The hematological and blood biochemical parameters were also reported to be similar to that of the control groups (Rong et al., 2009). A supportive evidence was provided in recent reports mentioning that at normal doses (up to 2 gm of ginger daily) there is no interference with blood clotting or individual coagulation parameters (Supu et al., 2019). Overall, these reports suggest that consumption of ginger appears to be safe with minimal side effects.

7. Conclusion

Ginger has been in the field of research from time immemorial. The multidimensional medicinal properties of ginger have made it a versatile natural compound to treat several diseases. This review exhibited the medicinal applications of ginger and its bioactive components, 6 gingerol and 6-shogaol, as therapeutic agents or adjuvant therapy. In Cancer, the bioactive constituents of ginger exert their therapeutic function by regulating different cancer cell signaling pathways, which leads to programmed cell death. In addition, the bioactive components participated in the nanotechnology field as a natural, nontoxic delivery system, to either treat irritable bowel diseases (IBD) and colitis associated cancer, or to load the chemotherpeutic drugs to increase the cytotoxic effect on cancer cells. Most of the research conducted so far is either in-vitro or in-vivo using experimental animals. Hence, there is a need for well controlled human studies to authenticate its efficacy.

Declaration of competing interest

All authors declare that they have no conflict of interest.

References

Abdu, S., Abdu, F., & Khalil, W. (2017). Ginger nanoparticles modulate the apoptotic activity in male rats exposed to dioxin-induced cancer initiation. *International Journal of Pharmacology, 13*, 946–957.

Adekunle, I. A., Imafidon, C. E., Oladele, A. A., & Ayoka, A. O. (2018). Ginger polyphenols attenuate cyclosporine-induced disturbances in kidney function: Potential application in adjuvant transplant therapy. *Pathophysiology, 25*(2), 101–115.

Ademosun, M. T., Omoba, O. S., & Olagunju, A. I. (2020). Antioxidant properties, glycemic indices, and carbohydrate hydrolyzing enzymes activities of formulated ginger-based fruit drinks. *Journal of Food Biochemistry*, 13324.

Ahmadifar, E., Sheikhzadeh, N., Roshanaei, K., Dargahi, N., & Faggio, C. (2019). Can dietary ginger (*Zingiber officinale*) alter biochemical and immunological parameters and gene expression related to growth, immunity and antioxidant system in zebrafish (Danio rerio)? *Aquaculture, 507*, 341–348.

Ahui, M. L. B., Champy, P., Ramadan, A., Pham Van, L., Araujo, L., Brou André, K., Diem, S., Damotte, D., Kati-Coulibaly, S., Offoumou, M. A., Dy, M., Thieblemont, N., & Herbelin, A. (2008). Ginger prevents Th2-mediated immune responses in a mouse model of airway inflammation. *International Immunopharmacology, 8*(12), 1626–1632.

Ajith, T. A., Aswathy, M. S., & Hema, U. (2008). Protective effect of *Zingiber officinale* Roscoe against anticancer drug doxorubicin-induced acute nephrotoxicity. *Food and Chemical Toxicology, 46*(9), 3178–3181.

Ajith, T. A., Hema, U., & Aswathi, S. (2016). *Zingiber officinale* Roscoe ameliorates anticancer antibiotic doxorubicin-induced acute cardiotoxicity in rat. *Journal of Experimental Therapeutics and Oncology, 11*(3), 171–175.

Al-Sharif, M. M. Z. (2011). Effect of therapeutic ginger on genotoxic of taxol drug (Anti-Cancer) in bone marrow cell of male mice. *Journal of Life Sciences, 5*, 897–905.

Ali, D. A., Abdeen, A. M., Ismail, M. F., & Mostafa, M. A. (2013). Histological, ultrastructural and immunohistochemical studies on the protective effect of ginger extract against cisplatin-induced nephrotoxicity in male rats. *Toxicology and Industrial Health, 31*(10), 869–880.

Amin, A., & Hamza, A. A. (2006). Effects of Roselle and Ginger on cisplatin-induced reproductive toxicity in rats. *Asian Journal of Andrology, 8*(5), 607–612.

An, S., Liu, G., Guo, X., An, Y., & Wang, R. (2019). Ginger extract enhances antioxidant ability and immunity of layers. *Animal Nutrition, 5*(4), 407–409.

Aryaeian, N., Shahram, F., Mahmoudi, M., Tavakoli, H., Yousefi, B., Arablou, T., & Jafari Karegar, S. (2019). The effect of ginger supplementation on some immunity and inflammation intermediate genes expression in patients with active Rheumatoid Arthritis. *Gene, 698*, 179–185.

Ascar, I. F., Al-a'araji, S. B., & Alshanon, A. F. (2019). Cytotoxicity and antioxidant effect of ginger gold nanoparticles on thyroid carcinoma cells. *Journal of Pharmaceutical Sciences and Research, 11*(3), 1044–1051.

Attyah, A. M., & Ismail, S. H. (2012). Protective effect of ginger extract against cisplatin-induced hepatotoxicity and cardiotoxicity in rats. *Iraqi Journal of Pharmaceutical Sciences, 21*, 27–33.

Bawadood, A. S., Al-Abbasi, F. A., Anwar, F., El-Halawany, A. M., & Al-Abd, A. M. (2020). 6-Shogaol suppresses the growth of breast cancer cells by inducing apoptosis and suppressing autophagy via targeting notch signaling pathway. *Biomedicine & Pharmacotherapy, 128*, 110302.

Bhaskar, A., Kumari, A., Singh, M., Kumar, S., Kumar, S., Dabla, A., Chaturvedi, S., Yadav, V., Chattopadhyay, D., & Prakash Dwivedi, V. (2020). [6]-Gingerol exhibits potent anti-mycobacterial and immunomodulatory activity against tuberculosis. *International Immunopharmacology, 87*, 106809.

Blust, R., & Trussel, S. (2013). The austronesian comparative dictionary: A work in progress. *Oceanic Linguistics, 52*, 493–523.

Borges, D. O., Freitas, K., Minicucci, E. M., & Popim, R. C. (2020). Benefits of ginger in the control of chemotherapy-induced nausea and vomiting. *Revista Brasileira de Enfermagem, 73*(2), Article e20180903.

Chang, W. P., & Peng, Y. X. (2019). Does the oral administration of ginger reduce chemotherapy-induced nausea and vomiting?: A meta-analysis of 10 randomized controlled trials. *Cancer Nursing, 42*(6), E14–E23.

Christenhusz, M., & Byng, J. W. (2016). The number of known plants species in the world and its annual increase. *Phytotaxa, 261*, 201–217.

De Lima Silva, W. C., Conti, R., de Almeida, L. C., Morais, P. A. B., Borges, K. B., Júnior, V. L., Costa-Lotufo, L. V., & de Souza Borges, W. (2020). Novel [6]-gingerol triazole derivatives and their antiproliferative potential against tumor cells. *Current Topics in Medicinal Chemistry, 20*(2), 161–169.

De Lima, R. M. T., Dos Reis, A. C., de Menezes, A. P. M., Santos, J. V. O., Filho, J., Ferreira, J. R. O., de Alencar, M., da Mata, A., Khan, I. N., Islam, A., Uddin, S. J., Ali, E. S., Islam, M. T., Tripathi, S., Mishra, S. K., Mubarak, M. S., & Melo-Cavalcante, A. A. C. (2018). Protective and therapeutic potential of ginger (*Zingiber officinale*) extract and [6]-gingerol in cancer: A comprehensive review. *Phytotherapy Research, 32*(10), 1885–1907.

Dekkers, G. W. F., Broeren, M. A. C., Truijens, S. E. M., Kop, W. J., & Pop, V. J. M. (2019). Hormonal and psychological factors in nausea and vomiting during pregnancy. *Psychological Medicine, 50*(2), 229–236.

Di Bona, D., Magistà, S., Masciopinto, L., Lovecchio, A., Loiodice, R., Bilancia, M., Albanesi, M., Caiaffa, M. F., Nettis, E., & Macchia, L. (2020). Safety and treatment compliance of subcutaneous immunotherapy: A 30-year retrospective study. *Respiratory Medicine, 161*, 105843.

El Nabi, S. E. H., El-Garawani, I. M., Salman, A. M., & Ouda, R. I. (2017). The possible antigenotoxic potential of ginger oil on etoposide–treated albino rats. *Saudi Journal of Medical and Pharmaceutical Sciences, 3*(7A), 693–703.

El-Naggar, M. H., Mira, A., Abdel Bar, F. M., Shimizu, K., Amer, M. M., & Badria, F. A. (2017). Synthesis, docking, cytotoxicity, and LTA4H inhibitory activity of new gingerol derivatives as potential colorectal cancer therapy. *Bioorganic & Medicinal Chemistry, 25*(3), 1277–1285.

El-Refai, A. A., Ghoniem, G., El-Khateeb, A. Y., & Hassaan, M. M. (2018). Cytotoxicity of aqueous garlic and ginger metal nanoparticles extracts against tumor cell lines "in vitro. *Journal of Food and Dairy Sciences, 9*(2), 51–58.

Elshiekh, A. A., Elkolaly, H. R., Tawfeek, N. M., Mohamed, A. A., & Mohamed, A. A. (2019). Possible protective effect of ginger extract and beetroot juice against cisplatin induced testicular and cytogenetic toxicity in adult male albino rats. *The Egyptian Journal of Hospital Medicine, 76*(5), 4046–4054.

Fahmi, A., Hassanen, N., Abdur-Rahman, M., & Shams-Eldin, E. (2019). Phytochemicals, antioxidant activity and hepatoprotective effect of ginger (*Zingiber officinale*) on diethylnitrosamine toxicity in rats. *Biomarkers, 24*(5), 436–447.

Fajrin, F. A., Nugroho, A. E., Nurrochmad, A., & Susilowati, R. (2020). Ginger extract and its compound, 6-shogaol, attenuates painful diabetic neuropathy in mice via reducing TRPV1 and NMDAR2B expressions in the spinal cord. *Journal of Ethnopharmacology, 249*, 112396.

Fan, J., Yang, X., & Bi, Z. (2015). 6-Gingerol inhibits osteosarcoma cell proliferation through apoptosis and AMPK activation. *Tumor Biology, 36*(2), 1135–1141.

Fidler, M. M., Bray, F., & Soerjomataram, I. (2018). The global cancer burden and human development: A review. *Scandinavian Journal of Public Health, 46*(1), 27–36.

Fioretto, P., Najafian, B., Sutherland, D. E. R., & Mauer, M. (2011). Tacrolimus and cyclosporine nephrotoxicity in native kidneys of pancreas transplant recipients. *Clinical Journal of the American Society of Nephrology, 6*(1), 101.

Gan, F.-F., Nagle, A. A., Ang, X., Ho, O. H., Tan, S.-H., Yang, H., Chui, W.-K., & Chew, E.-H. (2011). Shogaols at proapoptotic concentrations induce G2/M arrest and aberrant mitotic cell death associated with tubulin aggregation. *Apoptosis, 16*(8), 856–867.

Geiger, J. L. (2005). The essential oil of ginger, *Zingiber officinale*, and anaesthesia. *International Journal of Aromatherapy, 15*(1), 7–14.

Hong, M. K., Hu, L. L., Zhang, Y. X., Xu, Y. L., Liu, X. Y., He, P. K., & Jia, Y. H. (2020). 6-Gingerol ameliorates sepsis-induced liver injury through the Nrf2 pathway. *International Immunopharmacology, 80*, 106196.

Hu, Y., Amoah, A. N., Zhang, H., Fu, R., Qiu, Y., Cao, Y., Sun, Y., Chen, H., Liu, Y., & Lyu, Q. (2020). Effect of ginger in the treatment of nausea and vomiting compared with vitamin B6 and placebo during pregnancy: A meta-analysis. *Journal of Maternal-Fetal and Neonatal Medicine*, 1712714.

Huang, B., Wang, G., Chu, Z., & Qin, L. (2012). Effect of oven drying, microwave drying, and silica gel drying methods on the volatile components of ginger (*Zingiber officinale* Roscoe) by HS-SPME-GC-MS. *Drying Technology, 30*(3), 248–255.

Hung, J. Y., Hsu, Y. L., Li, C. T., Ko, Y. C., Ni, W. C., Huang, M. S., & Kuo, P. L. (2009). 6-Shogaol, an active constituent of dietary ginger, induces autophagy by inhibiting the AKT/mTOR pathway in human non-small cell lung cancer A549 cells. *Journal of Agricultural and Food Chemistry, 57*(20), 9809–9816.

Jafarzadeh, A., & Nemati, M. (2018). Therapeutic potentials of ginger for treatment of multiple sclerosis: A review with emphasis on its immunomodulatory, anti-inflammatory and anti-oxidative properties. *Journal of Neuroimmunology, 324*, 54–75.

Khalil, W., El-Bassyouni, G., & Booles, H. (2016). Nano-encapsulated form of Citrus medica for osteoporosis treatment in animal model. *International Journal of Pharmaceutical Chemistry Research, 8*, 49–59.
Kim, S. O., & Kim, M. R. (2013). [6]-Gingerol prevents disassembly of cell junctions and activities of MMPs in invasive human pancreas cancer cells through ERK/NF- κ B/ snail signal transduction pathway. *Evidence-based Complementary and Alternative Medicine*, 761852.
Kim, M. S., & Kim, J. Y. (2018b). Ginger attenuates inflammation in a mouse model of dextran sulfate sodium-induced colitis. *Food Science and Biotechnology, 27*(5), 1493–1501.
Kim, S.-M., Kim, C., Bae, H., Lee, J. H., Baek, S. H., Nam, D., Chung, W.-S., Shim, B. S., Lee, S.-G., Kim, S.-H., Sethi, G., & Ahn, K. S. (2015). 6-Shogaol exerts anti-proliferative and pro-apoptotic effects through the modulation of STAT3 and MAPKs signaling pathways. *Molecular Carcinogenesis, 54*(10), 1132–1146.
Kim, H. J., Kim, B., Mun, E. G., Jeong, S. Y., & Cha, Y. S. (2018). The antioxidant activity of steamed ginger and its protective effects on obesity induced by high-fat diet in C57BL/6J mice. *Nutrition Research and Practice, 12*(6), 503–511.
Kim, S., Lee, M.-S., Jung, S., Son, H.-Y., Park, S., Kang, B., Kim, S.-Y., Kim, I.-H., Kim, C.-T., & Kim, Y. (2018). Ginger extract ameliorates obesity and inflammation via regulating MicroRNA-21/132 expression and AMPK activation in white adipose tissue. *Nutrients, 10*(11), 1567.
Kiran, K., Sathiyanarayanan, L., Arulmozhi, S., & Kakasaheb, M. (2018). 6-Shogaol rich ginger oleoresin loaded mixed micelles enhances in vitro cytotoxicity on MCF-7 cells and in vivo anticancer activity against DAL cells. *International Journal of Pharmacy and Pharmaceutical Sciences, 10*(1), 160–168.
Kulkarni, R., & Deshpande, A. (2016). Anti-inflammatory and antioxidant effect of ginger in tuberculosis. *Journal of Complementary and Integrative Medicine, 13*, 201–206.
Kustriyanti, D., & Putri, A. A. (2019). The effect of ginger and lemon aromatherapy on nausea and vomiting among pregnant women. *Jurnal Keperawatan Soedirman, 14*, 15–22.
Lee, J. S., Kim, B., Kim, J. H., Jeong, M., Lim, S., & Byun, S. (2019). Effect of differential thermal drying conditions on the immunomodulatory function of ginger. *Journal of Microbiology and Biotechnology, 29*(7), 1053–1060.
Lee, W., Ku, S. K., Kim, M. A., & Bae, J. S. (2017). Anti-factor Xa activities of zingerone with anti-platelet aggregation activity. *Food and Chemical Toxicology, 105*, 186–193.
Lee, H. S., Seo, E. Y., Kang, N. E., & Kim, W. K. (2008). [6]-Gingerol inhibits metastasis of MDA-MB-231 human breast cancer cells. *The Journal of Nutritional Biochemistry, 19*(5), 313–319.
Li, Z., Liu, Z., Uddandrao, V. V. S., Ponnusamy, P., Balakrishnan, S., Brahmanaidu, P., Vadivukkarasi, S., & Ganapathy, S. (2019). Asthma-alleviating potential of 6-gingerol: Effect on cytokines, related mRNA and c-myc, and NFAT1 expression in ovalbumin-sensitized asthma in rats. *Journal of Environmental Pathology, Toxicology and Oncology, 38*(1), 41–50.
Li, X., Qin, Y., Liu, W., Zhou, X.-Y., Li, Y.-N., & Wang, L.-Y. (2018). Efficacy of ginger in ameliorating acute and delayed chemotherapy-induced nausea and vomiting among patients with lung cancer receiving cisplatin-based regimens: A randomized controlled trial. *Integrative Cancer Therapies, 17*(3), 747–754.
Luna-Dulcey, L., da Silva, J. A., & Cominetti, M. R. (2020). SSi6 promotes cell death by apoptosis through cell cycle arrest and inhibits migration and invasion of MDA-MB-231 human breast cancer cells. *Anti-Cancer Drugs, 31*(1), 35–43.
Luo, Y., Chen, X., Luo, L., Zhang, Q., Gao, C., Zhuang, X., Yuan, S., & Qiao, T. (2018). [6]-Gingerol enhances the radiosensitivity of gastric cancer via G2/M phase arrest and apoptosis induction. *Oncology Reports, 39*(5), 2252–2260.
Luo, Y., Zha, L., Luo, L., Chen, X., Zhang, Q., Gao, C., Zhuang, X., Yuan, S., & Qiao, T. (2019). [6]-Gingerol enhances the cisplatin sensitivity of gastric cancer cells through inhibition of proliferation and invasion via PI3K/AKT signaling pathway. *Phytotherapy Research, 33*(5), 1353–1362.
Manatunga, D. C., de Silva, R. M., de Silva, K. M. N., Wijeratne, D. T., Malavige, G. N., & Williams, G. (2018). Fabrication of 6-gingerol, doxorubicin and alginate hydroxyapatite into a bio-compatible formulation: Enhanced anti-proliferative effect on breast and liver cancer cells. *Chemistry Central Journal, 12*(1), 119.
Mao, Q.-Q., Xu, X.-Y., Cao, S.-Y., Gan, R.-Y., Corke, H., Beta, T., & Li, H.-B. (2019). Bioactive compounds and bioactivities of ginger (*Zingiber officinale* Roscoe). *Foods, 8*(6), 185.
Marx, W., McCarthy, A. L., Ried, K., McKavanagh, D., Vitetta, L., Sali, A., Lohning, A., & Isenring, E. (2017). The effect of a standardized ginger extract on chemotherapy-induced nausea-related quality of life in patients undergoing moderately or highly emetogenic chemotherapy: A double blind, randomized, placebo controlled trial. *Nutrients, 9*(8), 867.
Masuda, Y., Kikuzaki, H., Hisamoto, M., & Nakatani, N. (2004). Antioxidant properties of gingerol related compounds from ginger. *BioFactors, 21*, 293–296.
Morakinyo, F., Akindele, A., & Ahmed, Z. (2011). Modulation of antioxidant enzymes and inflammatory cytokines: Possible mechanism of anti-diabetic effect of ginger extracts. *African Journal of Biomedical Research, 14*(3), 195–202.
Nakamura, H., & Yamamoto, T. (1982). Mutagen and anti-mutagen in ginger, *Zingiber officinale*. *Mutation Research, 103*(2), 119–126.
Nakamura, H., & Yamamoto, T. (1983). The active part of the [6]-gingerol molecule in mutagenesis. *Mutation Research Letters, 122*(2), 87–94.
Nazari, B., Amirzargar, A., Nikbin, B., Nafar, M., Ahmadpour, P., Einollahi, B., Lesan Pezeshki, M., Khatami, S. M., Ansaripour, B., Nikuinejad, H., Mohamadi, F., Mahmoudi, M., Soltani, S., & Nicknam, M. H. (2013). Comparison of the Th1, IFN-γ secreting cells and FoxP3 expression between patients with stable graft function and acute rejection post kidney transplantation. *Iranian Journal of Allergy, Asthma and Immunology, 12*(3), 262–268.
Nikkhah Bodagh, M., Maleki, I., & Hekmatdoost, A. (2018). Ginger in gastrointestinal disorders: A systematic review of clinical trials. *Food science & nutrition, 7*(1), 96–108.
Ok, S., & Jeong, W. S. (2012). Optimization of extraction conditions for the 6-Shogaol-rich extract from ginger (*Zingiber officinale* Roscoe). *Prev Nutr Food Sci, 17*(2), 166–171.
Portnoi, G., Chng, L. A., Karimi-Tabesh, L., Koren, G., Tan, M. P., & Einarson, A. (2003). Prospective comparative study of the safety and effectiveness of ginger for the treatment of nausea and vomiting in pregnancy. *American Journal of Obstetrics and Gynecology, 189*(5), 1374–1377.
Pourmasoumi, M., Hadi, A., Rafie, N., Najafgholizadeh, A., Mohammadi, H., & Rouhani, M. H. (2018). The effect of ginger supplementation on lipid profile: A systematic review and meta-analysis of clinical trials. *Phytomedicine, 43*, 28–36.
Pujade-Lauraine, E., Wagner, U., Aavall-Lundqvist, E., Gebski, V., Heywood, M., Vasey, P. A., Volgger, B., Vergote, I., Pignata, S., Ferrero, A., Sehouli, J., Lortholary, A., Kristensen, G., Jackisch, C., Joly, F., Brown, C., Le Fur, N., & du Bois, A. (2010). Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. *Journal of Clinical Oncology, 28*(20), 3323–3329.
Qi, L.-W., Zhang, Z., Zhang, C.-F., Anderson, S., Liu, Q., Yuan, C.-S., & Wang, C.-Z. (2015). Anti-colon cancer effects of 6-shogaol through G2/M cell cycle arrest by p53/p21-cdc2/cdc25A crosstalk. *The American Journal of Chinese Medicine, 43*(4), 743–756.
Quinla, J. D., & Hill, D. A. (2003). Nausea and vomiting of pregnancy. *American Academy of Family Physicians, 68*(1), 121–128.
Ravindran, P. N., & Babu, K. (2016). *Ginger: The genus zingiber*. Florida: CRC Press, ISBN 9780415324687.
Ray, A., Vasudevan, S., & Sengupta, S. (2015). 6-Shogaol inhibits breast cancer cells and stem cell-like spheroids by modulation of notch signaling pathway and induction of autophagic cell death. *PloS One, 10*(9), Article e0137614.
Rong, X., Peng, G., Suzuki, T., Yang, Q., Yamahara, J., & Li, Y. (2009). A 35-day gavage safety assessment of ginger in rats. *Regulatory Toxicology and Pharmacology, 54*(2), 118–123.
Ryan, J. L., Heckler, C. E., Roscoe, J. A., Dakhil, S. R., Kirshner, J., Flynn, P. J., Hickok, J. T., & Morrow, G. R. (2012). Ginger (*Zingiber officinale*) reduces acute chemotherapy-induced nausea: A URCC CCOP study of 576 patients. *Supportive Care in Cancer, 20*(7), 1479–1489.
Saberi, F., Sadat, Z., Abedzadeh-Kalahroudi, M., & Taebi, M. (2013). Acupressure and ginger to relieve nausea and vomiting in pregnancy: A randomized study. *Iranian Red Crescent Medical Journal, 15*(9), 854–861.
Saha, A., Blando, J., Silver, E., Beltran, L., Sessler, J., & Digiovanni, J. (2014). 6-Shogaol from dried ginger inhibits growth of prostate cancer cells both in vitro and in vivo through inhibition of STAT3 and NF-kappa B signaling. *Cancer Prevention Research, 7*(6), 627–638.
Sakr, S., Mahran, H., & Lamfon, H. (2011). Protective effect of ginger (*Zingiber officinale*) on adriamycin -induced hepatotoxicity in albino rats. *Journal of Medicinal Plants Research, 5*(1), 133–140.
Sanaati, F., Najafi, S., Kashaninia, Z., & Sadeghi, M. (2016). Effect of ginger and chamomile on nausea and vomiting caused by chemotherapy in Iranian women with breast cancer. *Asian Pacific Journal of Cancer Prevention, 17*(8), 4125–4129.
Sang, S., Snook, H. D., Tareq, F. S., & Fasina, Y. (2020). Precision research on ginger: The type of ginger matters. *Journal of Agricultural and Food Chemistry, 68*(32), 8517–8523.
Sapkota, A., Park, S. J., & Choi, J. W. (2019). Neuroprotective effects of 6-shogaol and its metabolite, 6-paradol, in a mouse model of multiple sclerosis. *Biomolecules and Therapeutics, 27*(2), 152–159.
Schoenborn, J. R., & Wilson, C. B. (2007). Regulation of interferon-gamma during innate and adaptive immune responses. *Advances in Immunology, 96*, 41–101.
Schoenknecht, C., Andersen, G., Schmidts, I., & Schieberle, P. (2016). Quantitation of gingerols in human plasma by newly developed stable isotope dilution assays and assessment of their immunomodulatory potential. *Journal of Agricultural and Food Chemistry, 64*(11), 2269–2279.
Setoguchi, S., Daisuke Watase, D., Nagata-Akaho, N., Haratake, A., Matsunaga, K., & Takata, J. (2016). Pharmacokinetics of paradol analogues orally administered to rats. *Journal of Agricultural and Food Chemistry, 64*(9), 1932–1937.
Sharifzadeh, F., Kashanian, M., Koohpayehzadeh, J., Rezaian, F., Sheikhansari, N., & Eshraghi, N. (2018). A comparison between the effects of ginger, pyridoxine (vitamin B6) and placebo for the treatment of the first trimester nausea and vomiting of pregnancy (NVP). *Journal of Maternal-Fetal and Neonatal Medicine, 31*(19), 2509–2514.
Sheriff, M. H., Abas, A.-s. M., & Abd- El- Rahman, B. M. (2017). Protective effect of ginger extract against cisplatin-induced nephrotoxicity in rats. *Biochemistry Letters, 13*(1), 230–247.
Si, W., Chen, Y. P., Zhang, J., Chen, Z.-Y., & Chung, H. Y. (2018). Antioxidant activities of ginger extract and its constituents toward lipids. *Food Chemistry, 239*, 1117–1125.
Singh, R. (2012). *Genetic resources, chromosome engineering, and crop improvement series medicinal plants*. Florida: CRC Press, ISBN 9780367382407.
Stanisiere, J., Mousset, P.-Y., & Lafay, S. (2018). How safe is ginger rhizome for decreasing nausea and vomiting in women during early pregnancy? *Foods, 7*(4), 50.
Stoilova, I., Krastanov, A., Stoyanova, A., Denev, P., & Gargova, S. (2007). Antioxidant activity of a ginger extract (*Zingiber officinale*). *Food Chemistry, 102*(3), 764–770.
Supu, R. D., Diantini, A., & Levita, J. (2019). Red Ginger (*Zingiber Officinale* var. runbrum): Its chemical constituents, pharmacological activities and safety. *Fitofarmaka, 8*, 25–31.
Thamlikitkul, L., Srimuninnimit, V., Akewanlop, C., Ithimakin, S., Techawathanawanna, S., Korphaisarn, K., Chantharasamee, J., Danchaivijitr, P., &

Soparattanapaisarn, N. (2017). Efficacy of ginger for prophylaxis of chemotherapy-induced nausea and vomiting in breast cancer patients receiving adriamycin-cyclophosphamide regimen: A randomized, double-blind, placebo-controlled, crossover study. *Supportive Care in Cancer, 25*(2), 459–464.

Townsend, E. A., Zhang, Y., Xu, C., Wakita, R., & Emala, C. W. (2014). Active components of ginger potentiate β-agonist-induced relaxation of airway smooth muscle by modulating cytoskeletal regulatory proteins. *American Journal of Respiratory Cell and Molecular Biology, 50*(1), 115–124.

Ujang, Z., Nordin, N., & Subramaniam, T. (2015). Ginger species and their traditional uses in modern applications. *Journal of Industrial Technology, 23*, 59–70.

Vedashree, M., Asha, M. R., Roopavati, C., & Naidu, M. M. (2020). Characterization of volatile components from ginger plant at maturity and its value addition to ice cream. *Journal of Food Science & Technology, 57*(9), 3371–3380.

Venkateswaran, M., Jayabal, S., Hemaiswarya, S., Murugesan, S., Enkateswara, S., Doble, M., & Periyasamy, S. (2021). Polyphenol-rich Indian ginger cultivars ameliorate GLUT4 activity in C2C12 cells, inhibit diabetes-related enzymes and LPS-induced inflammation: An in vitro study. *Journal of Food Biochemistry*, Article e13600.

Wang, J., Ke, W., Bao, R., Hu, X., & Chen, F. (2017). Beneficial effects of ginger *Zingiber officinale* Roscoe on obesity and metabolic syndrome: A review. *Annals of the New York Academy of Sciences, 1398*(1), 83–98.

Warin, R. F., Chen, H., Soroka, D. N., Zhu, Y., & Sang, S. (2014). Induction of lung cancer cell apoptosis through a p53 pathway by [6]-Shogaol and its cysteine-conjugated metabolite M2. *Journal of Agricultural and Food Chemistry, 62*(6), 1352–1362.

Weidner, M. S., & Sigwart, K. (2000). The safety of a ginger extract in the rat. *Journal of Ethnopharmacology, 73*(3), 513–520.

Weng, C.-J., Chou, C.-P., Ho, C.-T., & Yen, G.-C. (2012). Molecular mechanism inhibiting human hepatocarcinoma cell invasion by 6-shogaol and 6-gingerol. *Molecular Nutrition & Food Research, 56*(8), 1304–1314.

Weng, C.-J., Wu, C.-F., Huang, H.-W., Ho, C.-T., & Yen, G.-C. (2010). Anti-invasion effects of 6-shogaol and 6-gingerol, two active components in ginger, on human hepatocarcinoma cells. *Molecular Nutrition & Food Research, 54*(11), 1618–1627.

Werntoft, E., & Dykes, A. K. (2001). Effect of acupressure on nausea and vomiting during pregnancy. A randomized, placebo-controlled, pilot study. *Journal of Reproductive Medicine, 46*(9), 835–839.

Wibowo, E., Pollock, P. A., Hollis, N., & Wassersug, R. J. (2016). Tamoxifen in men: A review of adverse events. *Andrology, 4*(5), 776–788.

Woźniak, M., Makuch, S., Winograd, K., Wiśniewski, J., Ziółkowski, P., & Agrawal, S. (2020). 6-Shogaol enhances the anticancer effect of 5-fluorouracil, oxaliplatin, and irinotecan via increase of apoptosis and autophagy in colon cancer cells in hypoxic/aglycemic conditions. *BMC Complementary Medicine and Therapies, 20*(1), 141.

Xu, S., Zhang, H., Liu, T., Yang, W., Lv, W., He, D., Guo, P., & Li, L. (2020). 6-Gingerol induces cell-cycle G1-phase arrest through AKT-GSK 3β-cyclin D1 pathway in renal-cell carcinoma. *Cancer Chemotherapy and Pharmacology, 85*(2), 379–390.

Yagihashi, S., Miura, Y., & Yagasaki, K. (2008). Inhibitory effect of gingerol on the proliferation and invasion of hepatoma cells in culture. *Cytotechnology, 57*(2), 129–136.

Yang, M., Liu, C., Jiang, J., Zuo, G., Lin, X., Yamahara, J., Wang, J., & Li, Y. (2014). Ginger extract diminishes chronic fructose consumption-induced kidney injury through suppression of renal overexpression of proinflammatory cytokines in rats. *BMC Complementary and Alternative Medicine, 14*(1), 174.

Yi, J.-K., Ryoo, Z.-Y., Ha, J.-J., Oh, D.-Y., Kim, M.-O., & Kim, S.-H. (2019). Beneficial effects of 6-shogaol on hyperglycemia, islet morphology and apoptosis in some tissues of streptozotocin-induced diabetic mice. *Diabetology & Metabolic Syndrome, 11*, 15.

Yocum, G. T., Hwang, J. J., Mikami, M., Danielsson, J., Kuforiji, A. S., & Emala, C. W. (2019). Ginger and its bioactive component 6-shogaol mitigate lung inflammation in a murine asthma model. *American Journal of Physiology - Lung Cellular and Molecular Physiology, 318*(2), L296–L303.

Zhang, M., Viennois, E., Prasad, M., Zhang, Y., Wang, L., Zhang, Z., Han, M. K., Xiao, B., Xu, C., Srinivasan, S., & Merlin, D. (2016a). Edible ginger-derived nanoparticles: A novel therapeutic approach for the prevention and treatment of inflammatory bowel disease and colitis-associated cancer. *Biomaterials, 101*, 321–340.

Zhang, H., Wang, Q., Sun, C., Zhu, Y., Yang, Q., Wei, Q., Chen, J., Deng, W., Adu-Frimpong, M., Yu, J., & Xu, X. (2019). Enhanced oral bioavailability, anti-tumor activity and hepatoprotective effect of 6-shogaol loaded in a type of novel micelles of polyethylene glycol and linoleic acid conjugate. *Pharmaceutics, 11*(3), 107.

Zhang, M., Xiao, B., Wang, H., Han, M. K., Zhang, Z., Viennois, E., Xu, C., & Merlin, D. (2016). Edible ginger-derived nano-lipids loaded with doxorubicin as a novel drug-delivery approach for colon cancer therapy. *Molecular Therapy, 24*(10), 1783–1796.

Zhang, F. L., Zhou, B. W., Yan, Z. Z., Zhao, J., Zhao, B. C., Liu, W. F., Li, C., & Liu, K. X. (2020). 6-Gingerol attenuates macrophages pyroptosis via the inhibition of MAPK signaling pathways and predicts a good prognosis in sepsis. *Cytokine, 125*, 154854.

Zidan, D., Kahilo, K., El-Far, A., & Sadek, K. (2016). Ginger (*Zingiber officinale*) and thymol dietary supplementation improve the growth performance, immunity and antioxidant status in broilers. *Global Veterinaria, 16*, 530–538.