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Ginger and its Health Claims: Molecular Aspects

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Recent research has rejuvenated centuries-old traditional herbs to cure various ailments by using modern tools like diet-based therapy and other regimens. Ginger is one of the classic examples of an herb used for not only culinary preparations but also for unique therapeutic significance owing to its antioxidant, antimicrobial, and anti-inflammatory potential. The pungent fractions of ginger, namely gingerols, shogaols, paradols, and volatile constituents like sesquiterpenes and monoterpenes, are mainly attributed to the health-enhancing perspectives of ginger. This review elucidates the health claims of ginger and the molecular aspects and targets, with special reference to anticancer perspectives, immunonutrition, antioxidant potential, and cardiovascular cure. The molecular targets involved in chemoprevention like the inhibition of NF-κB activation via impairing nuclear translocation, suppresses cIAP1 expression, increases caspase-3/7 activation, arrests cell cycle in G2 + M phases, up-regulates Cytochrome-c, Apaf-1, activates PI3K/Akt/I kappaB kinases IKK, suppresses cell proliferation, and inducts apoptosis and chromatin condensation. Similarly, facts are presented regarding the anti-inflammatory response of ginger components and molecular targets including inhibition of prostaglandin and leukotriene biosynthesis and suppression of 5-lipoxygenase. Furthermore, inhibition of phosphorylation of three mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinases 1 and 2 (ERK1/2), and c-Jun N-terminal kinase (JNK) are also discussed. The role of ginger in reducing the extent of cardiovascular disorders, diabetes mellitus, and digestive problems has also been described in detail. Although, current review articles summarized the literature pertaining to ginger and its components. However, authors are still of the view that further research should be immediately carried out for meticulousness.

Keywords ginger, antioxidants, anticancer, immunonutrition, CVD, diabetes mellitus

INTRODUCTION

The dependence of humans on medicinal plants to cure various ailments has been documented since recorded history. Initially people relied on plants for food, which protected them from physiological threats (Butt et al., 2009). Recently, a number of scientific investigations have led to the recognition of a safe status for such natural products. In the domain of nutrition, great effort has been made to explore the health-promoting potential of many culinary herbs. The knowledge generated from such studies resulted in the development of modern concepts, for example, functional and nutraceuticals foods, optimum nutrition, and food synergy (Sultan et al., 2009; Yang et al., 2009).

Consumer awareness was the guiding force behind the success of such healthy foods that have taken hold of the global nutrition market (Siró et al., 2008). People consuming a diet rich in functional or bioactive components are at lower risk of chronic illnesses (Vina et al., 2006; Jenkins et al., 2008). Functional foods that are predominant in the market include green tea, soybean, flax, broccoli, grape juice, cabbage, tomatoes, raspberry, watermelon, psyllium, oats and barley, onion, garlic, etc. (Butt et al., 2008; Mateos-Aparicio et al., 2008; Wang et al., 2009). Some culinary commodities like garlic, onion, ginger, fenugreek, etc., are being used for giving specific taste, aroma, and flavor to the meals. Such plants have a rich phytochemistry correlated with their health-promoting potential (Bárta et al., 2006; Espín et al., 2007). Ginger is one of the most commonly consumed herbs with an array of applications in traditional medicines like Chinese medicine, Ayurveda, and Unani-Tibb (Rong et al., 2009). It is generally considered safe and it possesses various pharmacological activities including cardiovascular protection, antioxidant, anti-inflammatory, glucose lowering, anti-cancer activities, etc. (Shukla and Singh, 2007; Nicoll and Henein, 2009). This review provides a decisive insight on the phytochemistry and health-promoting

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Table 1 Botanical classification

Kingdom:	Plantae
Subkingdom	Tracheobionta – Vascular plants
Super-division	Spermatophyta – Seed plants
Class	Monocotyledons
Subclass	Zingiberidae
Order:	Zingiberales
Family:	Zingiberaceae (Ginger Family)
Genus:	Zingiber
Species:	Officinale

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potential of ginger against various ailments through a diet-based regimen.

BOTANICAL CLASSIFICATION AND PHYTOCHEMISTRY

Ginger (*Zingiber officinale Rosc.*) belongs to the family *Zingiberaceae*. It originated in South-East Asia and then became widespread in many ecological zones; the botanical classification is cited in Table 1. It has been cultivated since long as a spice and condiment to add flavor to Indian food (Park and Pizzuto, 2002). Often the ginger rhizome is used to serve all these purposes; however, some times fresh ginger is also used as a cooking aid (Altman and Marcussen, 2001).

Besides its extensive use as a spice, the rhizome of ginger has also been used in traditional oriental herbal medicine. The health-promoting perspective of ginger is often attributed to its rich phytochemistry (Shukla and Singh, 2007). The constituents of ginger are numerous and vary depending on the place of origin and form of rhizomes, e.g., fresh or dry. The ginger rhizome contains several components of interest, i.e., carbohydrates, minerals, phytochemicals, etc. It contains proximate components like moisture, proteins, fats, fiber, ash, and carbohydrates. It also contains appreciable amounts of vitamins and minerals as well as some enzymes, for example, a potent proteolytic enzyme called zingibain. Additionally, extractable oleoresins and waxes are its fundamental constituents or functional ingredients. In a research investigation, Onyenekwe and Hashimoto (1999) determined the essential oil of ginger using gas chromatography and gas chromatography-mass spectrometry techniques. The results showed that it carries 2.4% of essential oil mainly composed of 64.4% sesquiterpene, 6.6% carbonyl compounds, 5.6% alcohols, and 2.4% monoterpene hydrocarbons. The identified components are listed in Table 2.

Jolad et al. (2004) identified more than 60 compounds in fresh ginger grouped into two broader categories, i.e., volatiles and non-volatiles, contributing to specific pungency in different ways. Volatiles include sesquiterpene and monoterpenoid hydrocarbons providing the distinct aroma and taste of ginger. On the contrary, non-volatile pungent compounds include gingerols, shogaols, paradols, and zingerone. Likewise, Gong et al. (2004) analyzed both fresh and dried ginger using GC-MS and observed varying results, and the number of components that were reported was 140 and 136, respectively. Its main volatile

Table 2 Phytochemicals density

Sr. #	Category	Components
1	Monoterpenoids	Geraniol, curcumene b-phellandrene, (+)-camphene, 1,8-cineole, citral, terpineol, borneol, linalool, neral
2	Sesquiterpenoids	Zerumbone, a-zingiberene, b-sesquiphellandrene, b-bisabolene, (E-E)-a-farnesene, arcurcumene, zingiberol.
3	Non-volatile pungent components	Gingerols, shogaols, paradols, zingerone
4	Miscellaneous	Zingibain

Langner et al., 1998.

components are α-zingiberene (22.29%), β-sesquiphellandrene (8.58%), α-farnesene (3.93%), β-bisabolene (3.87%), α-curcumene (2.63%), with [6]-gingerol (9.38%) and [6]-shogaol (7.59%) being the promising pungent compounds. Moreover, zingerones (9.24%) are also present in a significant amount as they are produced during thermal degradation of gingerols or shogaols (Zhan et al., 2008).

Gingerols are of prime importance. They are a homologous series of phenols differing in their unbranched alkyl chains length and mainly attributed for ginger-specific pungency (Govindarajan, 1982). The quantity of [6]-gingerol in the fresh ginger rhizome was 104–965 mug/g (Nigam et al., 2009). They are hydrated compounds that further convert to shogaols and conversion is dependent on temperature and the pH dependence. Wohlmuth et al. (2005) and Bhattarai et al. (2001) have already described this phenomenon. Hydrogenation of shogaols further leads to the formation of paradol and allied derivatives and these are implicated for the pharmacological properties of ginger (Jiang et al., 2006).

Owing to the aforementioned phytochemistry, ginger has been widely used in Chinese, Ayurvedic, and Unani-Tibb medicines. Ginger has enormous health-promoting potential as is evident when using it for treating a number of ailments including degenerative disorders (arthritis and rheumatism), digestive health (indigestion, constipation and ulcer), cardiovascular disorders (atherosclerosis and hypertension), diabetes mellitus, and cancer. It also has anti-inflammatory properties, and these properties are beneficial in controlling the process of aging. Also, it is recommended for sore throat and vomiting. Moreover, it has antimicrobial potential as well which can help in treating infectious diseases and helminthiasis (Jiang et al., 2006; Shukla and Singh, 2007; Ali et al., 2008; Nicoll and Henein, 2009). Its health benefits have been discussed in subsequent sections.

GINGER AND ANTIOXIDANTS

The rich phytochemistry of ginger includes components that scavenge free radicals produced in food chains or biological systems. Some free radicals generated during the process of oxidation are essential for energy production (Ramaa et al., 2006). Increased production of free radicals and reduction in cellular homeostasis results in a condition known as oxidative stress that can lead to DNA damage (Hussein et al., 2005).

In such circumstances of imbalance, extra antioxidant supplementation through dietary modules is essential for organism vitality (Bárta et al., 2006). Ginger is one of the richest sources of antioxidants that paved the way for its utilization to scavenge free radicals and allied health discrepancies. The active ingredients of ginger include gingerols, which exhibit antioxidant activity as determined through in vitro studies (Kikusaki and Nakatani, 1993). Furthermore, enzymes such as xanthine oxidase are involved in the generation of reactive species and their inhibition has been documented regarding gingerols (Chang et al., 1994). The bioactive molecules of ginger like gingerols have shown antioxidant activity in various modules (Dugasani et al., 2010).

At times, in experimental rodents, chemicals have been used to initiate the production of free radicals in the body. Rat modeling showed that ginger significantly lowered induced lipid peroxidation and raised the levels of antioxidant enzymes, together with serum glutathione (El-Sharaky et al., 2009). Kota et al. (2008) studied the effects of ginger at 0.5, 1, and 5 and their findings indicated significant reduction in MDA in liver and kidney tissues. The appropriate justifications regarding these effects include enhancement of the antioxidant status of the host tissue or inhibition of oxidative products. Likewise, a synthetic analogue of zingerone (Dehydrogingerone) showed mild inhibition of lipid peroxidation by scavenging free radicals (Rajkumar and Rao, 1993). Additionally, feeding dietary ginger at 1% w/w during administration of malathion (20 ppm) for 4 weeks significantly attenuated malathion-induced lipid peroxidation and oxidative stress in rats (Ahmed et al., 2000). Later, concomittant dietary feeding of ginger (1%w/w) significantly attenuated lindane-induced lipid peroxidation, accompanied by the modulation of OFR-scavenging enzymes as well as reduced glutathione (GSH) and the GSH-dependent enzymes glutathione peroxidase (Gpx), glutathione reductase (GR), and glutathione-S-transferase (GST) (Ahmed et al., 2008).

The functional ingredients of ginger like gingerols possess substantial antioxidant activity as determined by various antioxidants assays. In the antioxidant activity assay, [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol exhibited substantial scavenging activities with IC_{50}values of 26.3, 19.47, 10.47, and 8.05 muM against DPPH radical. IC_{50} values of 4.05, 2.5, 1.68, and 0.85 muM against superoxide radical and IC_{50} values of 4.62, 1.97, 1.35, and 0.72 muM against hydroxyl radical, respectively (Dugasani et al., 2010). In vitro, zingerone scavenged O_2- and OH and suppressed lipid peroxidation. The effects of zingerone treatment in this model suggest possible value in the treatment of Parkinson's disease (Kabuto et al., 2005). Likewise, [6]-shogaol also attenuated the lipopolysaccharide-induced upexpression of iNOS and COX-2 in murine macrophages (Pan et al., 2008).

The antioxidative properties of ginger and its components have been explored in various in vitro and in vivo test systems.

Strengthening the body's defenses by improving the antioxidant status will undoubtedly protect against the oxidative stress involved in the etiology of many chronic diseases (Shukla and Singh, 2007).

CANCER INSURGENCE AND GINGER

There are many reasons for the pathogenesis and progression of cancer; however, it is hypothesized that cancer insurgence can be minimized through diets rich in bioactive molecules (Butt and Sultan, 2009). A number of research investigations unveiled the therapeutic role of culinary herbs against malignancy, including garlic, black cumin, etc. (Butt et al., 2009; Butt and Sultan, 2010). Despite the potential efficacy of ginger in chemoprevention, the mechanism by which it affects this chemoprevention remains a matter of conflict among researchers. Ginger, owing to its functional ingredients like [6]-gingerol, [6]-shogaol, [6]-paradol, and zerumbone, exhibits anti-inflammatory and antitumorigenic activities (Jeong et al., 2009; Hung et al., 2009). Ginger and its bioactive molecules are effective in controlling the extent of colorectal, gastric, ovarian, liver, skin cancers (Ishiguro et al., 2008; Sung et al., 2008; Brown et al., 2009; Kim et al., 2009; Jeong et al., 2009). Some recent works related to anticancer perspectives have been presented in Table 3. Furthermore, several research investigations also support the fact that ginger can cure breast and prostate cancers (Lee et al., 2008; Sung et al., 2009).

Colorectal cancer is more prevalent in vegetarians and the intake of ginger has been found to be effective in reducing the extent of this menacing disease. Manju and Nalini (2005) studied the efficacy of ginger against 1,2 dimethylhydrazine (DMH)-induced colon cancer. They observed that ginger supplementation at 50 mg/kg body weight/day suppresses colon carcinogenesis by enhancing the activities of various enzymes, e.g., glutathione peroxidase (GPX), glutathione-S-transferase (GST), and glutathione reductase (GR). In this context, Jeong et al. (2009) further showed that [6]-gingerol is effective in suppressing in vivo tumor growth in nude mice, an effect that was mediated by the inhibition of LTA(4)H activity in HCT116 colorectal cancer cells (Lee et al., 2008; Brown et al., 2009). Likewise, Kim et al. (2009) administered Zerumbone (ZER) at 100, 250, and 500 ppm orally in preclinical mouse models and observed inhibition in multiplicity of colonic adenocarcinomas along with suppressing colonic inflammation in a dose-dependent manner. The mode of action includes inhibition of proliferation, induction of apoptosis, and suppression of NF-κB and heme oxygenase (HO)-1 expression. It also stems cIAP1 expression that is helpful in the induction of apoptosis. In an earlier study by Nakamura et al. (2004) significant increase in glutathione S-transferase concentrations was observed because of ZER treatment. They further reported that ZER induces nuclear localization of the transcription factor Nrf2, which holds the ability to bind the antioxidant response element (ARE) of the phase II enzyme genes. This suggests that ZER is a potential activator of the Nrf2/ARE-dependent detoxification pathway helpful in the chemo-preventive potential of ginger against colorectal cancer (Chung et al., 2009). Earlier, Murakami et al. (2002) reported that ZER inhibits the proliferation of human colonic adenocarcinoma cell lines in a dose-dependent manner and brings apoptosis in COLO205 cells, as detected by dysfunction of the mitochondria transmembrane, Annexin V-detected translocation of phosphatidylserine, and chromatin condensation. Likewise, [6]-shogaol inhibits the growth of human colon cancer cells (COLO 205) and induces apoptosis through modulation of mitochondrial function regulated by reactive oxygen species (ROS), preceding cytochrome c release, caspase activation, and DNA fragmentation. They also observed [6]-that shogaol-treated COLO 205 cells exhibited up-regulation of Bax,

Table 3 Recent evidences for anticancer perspectives of ginger

Sr. #	Research Group and Year	Cancer Types	Model used	Component of interest	Mechanism of action
1	Jeong et al., 2009	Colon cancer	In vivo in nude mice	[6]-Gingerol	Inhibition of LTA(4)H activity
2	Hung et al., 2009	Lungs cancer	Cell culture study	6-Shogaol	Inhibition of AKT
3	Yodkeeree et al., 2009	Colon cancer	Human colon cancer cells	Zerumbone	Activation of extracellular signal-regulated kinase 1/2 p38 mitogen-activated protein kinase leading to DR4 and DR5
4	Nigam et al., 2009	Skin cancer	Mouse model	[6]-gingerol	Apoptotic potential
5	Sung et al., 2009	Osteoclastogenesis	Mouse monocyte	Zerumbone	Block RANKL-induced NF-kappaB activation
6	Habib et al., 2008	Liver cancer	Male Wistar rats	Ginger extract	Reduced the elevated expression of NF-κB and TNF-α
7	Kim et al., 2008	Colon and lung cancer	Preclinical mouse models	Zerumbone	Suppresses modulatory mechanisms of growth and induce apoptosis Reduce expression of NF-κB and HO-1
8	Ishiguro et al., 2007	Gastric cancer	Gastric cancer cells	6-gingerol 6-shogaol	6-gingerol inhibit TRAIL-induced NF-κB activation 6-shogaol alone reduces viability by damaging microtubules
9	Lee et al., 2008	Breast cancer	Human cell lines	[6]-Gingerol	Inhibits cell adhesion invasion motility and activities of MMP-2 and MMP-9
10	Rhode et al., 2007	Ovarian cancer	Human ovarian cancer cell lines	Ginger and [6]-Gingerol	Inhibition of NF-κB activation

Fas, and FasL, with concurrent down-regulation of Bcl-2 and Bcl-X (Pan et al., 2008).

In gastric cancer, the tumor necrosis factor-related apoptosis-inducing ligand (TRIALS) plays a critical role by inducing apoptosis. Cascades of caspase proteins activate and deactivate owing to ginger and its functional components (Yodkeeree et al., 2009). The major component of ginger, [6]-gingerol, increased the TRAIL-induced apoptosis and activation of caspase-8 that further triggers the release of Cyt-c from mitochondria leading to caspase-9 activation. The mode of action in such cases also includes inhibition of NF-κB via impairment p65 nuclear translocation (Wei et al., 2005). Accordingly, Ishiguro et al. (2007) introduced a model for [6]-gingerol and [6]-shogaol action against gastric cancer cells. They observed that [6]-gingerol inhibits TRAIL-induced NF-κB activation by impairing the nuclear translocation of NF-κB, suppresses cIAP1 expression, and increases TRAIL-induced caspase-3/7 activation. On the other hand, [6]-shogaol damages microtubules, arrests cell cycle in G2+M phases, and reduces viability in a casepase-3/7 independent manner. Despite all efforts, skin cancer incidence and prevalence is constantly on the increase and a search for newer and better agents for protection and treatment is required. [6]-gingerol leads to up-regulation of Cytochrome-c and Apaf-1 subsequently culminating in triggering of the caspase cascade. These firmly suggest that [6]-gingerol can effectively be used for the treatment of gastric cancer (Ishiguro et al., 2007).

Yagihashi et al. (2008) reported that [6]-gingerol inhibited both proliferation and invasion of hepatoma cells in a dose-dependent manner at concentrations of 6.25–200 muM (proliferation) and 50–200 muM (invasion). Suppression of hepatoma cell proliferation by [6]-gingerol may be due to cell cycle arrest and apoptosis induction. The cell cycle arrest is also dependent upon microtubules. Previous studies have indicated that the microtubule damage affects activities of various protein kinases and the expression of upstream genes of apoptosis, leading to apoptosis via a caspase-3/7-dependent or independent pathway (Ishiguro et al., 2007). Similarly, Chen et al. (2007) indicated that [6]-shogaol induces apoptosis by depleting glutathione (GSH) in Mahlavu cells, a human hepatoma subline. Later, Habib et al. (2008) suggested that ginger extract (100 mg/kg body weight) holds the ability to reduce the elevated expression of NF-κB and TNF-alpha in rats with liver cancer.

Though tumor promotion is closely associated with inflammation and oxidative stress, it is likely that a compound with a strong inhibitory effect on the arachidonic acid metabolism would have anti-tumor promoting potential. For example, topical application of ginger extract 30 min prior to TPA leads to dramatic protection against DMBA-initiated skin carcinogenesis in SENCAR mice and suppressed TPA-caused induction of epidermal ODC and its mRNA expression, as well as cyclooxygenase COX, and lipoxygenase activities (Katiyar et al., 1996; Park et al., 1998). Inhibition of angiogenesis through suppression of IjB degradation in the mouse skin proved ginger useful in the treatment of skin cancer (Kim et al., 2005). [6]-Gingerol treatment at 250, 300, and 350 μM exhibited considerable cytotoxicity as indicated by the growth inhibition of human epidermoid carcinoma A431 cells mediated via reactive oxygen species (ROS) induced apoptosis of 16.27, 20.54, and 29.52%, respectively. As these effects decreased in mitochondrial membrane potential (MMP), further leading to subsequent apoptosis of cancerous cells, they became more pronounced (Nigam et al., 2009). In this regard, Lee et al. (2008) suggested that ingestion of ginger at 250 mg/day can/may provide substantial quantities of [6]-gingerol and its derivatives, namely 10 μM, that may be useful for preventing or treating breast cancer. Likewise, [6]-Paradol is another principle component attributed to anticancer perspectives against skin cancer as it attenuates carcinogenesis and TPA-induced ear edema in female ICR mice (Surh et al., 1999; Keum et al., 2002).

The effectiveness of ginger and its functional ingredients has been demonstrated in a number of research investigations like for ovarian cancer. Vijaya Padma et al. (2007) attributed such properties to ROS production. Similarly, Rhode et al. (2007) found that in vitro, ginger inhibits NF-κB activation as well as diminished the secretion of VEGF and IL-8 helping in the treatment and prevention of ovarian cancer via inhibition of growth and modulation of angiogenic factors. Kyung et al. (2006) have reported that [6]-shogaol mitigates apoptosis in the experimental spinal cord injury. Azoxymethane-induced intestinal carcinogenesis in rats was significantly suppressed by dietary administration of gingerols (Yoshimi et al., 1992). CXC chemokine receptor 4 (CXCR4) mediates the proliferation of tumor cells to specific organs. The down-regulation of CXCR4 expression would have potential against cancer metastasis. The zerumbone down-regulated CXCR4 owing to transcriptional modifications, i.e., it down-regulated mRNA expression, inhibited NF-κB activity, and suppressed chromatin immunoprecipitation activity. Suppression of CXCR4 expression by zerumbone correlated with the inhibition of CXCL12-induced invasion of both breast and pancreatic cancer cells (Sung et al., 2008). ZER is also an effective blocker of the receptor activator of nuclear factor-kappaB (NF-kappaB) ligand (RANKL)-induced NF-kappaB activation and of osteoclastogenesis induced by RANKL and tumor cells, suggesting its potential as a therapeutic agent for osteoporosis and cancer-associated bone loss (Sung et al., 2009). β-elemene is another component of ginger reported to hold anticancer potential. It enhances the caspase-3, -7, and -9 activities, and decreases Bcl-2 expression, thereby resulting in cytochrome c release in non-small-cell lung cancer (NSCLC) and all these processes lead to apoptosis (Wang et al., 2005).

Ginger may act as an anti-cancer and anti-inflammatory agent by inactivating NF-κB through the suppression of the pro-inflammatory TNF-alpha. Evidence pertaining to anticancer properties of ginger and its components are quite conclusive. The molecular targets involved in chemoprevention like inhibition of NF-κB activation via impairing nuclear translocation, suppresses cIAP1 expression, increases caspase-3/7 activation, arrests cell cycle in G2 + M phases, up-regulates Cytochrome-c, Apaf-1, activates PI3K/Akt/I kappaB kinases IKK, suppresses cell proliferation, and induces apoptosis and chromatin

condensation. Its functional ingredients like gingerols, shogaol, and paradols are the valuable ingredients which can prevent various cancers. However, results pertaining to anticancer perspective have mostly been taken from cell-culture studies or animal models, therefore urgent studies are needed to elucidate the exact mechanism of action and their relevance for their potential application to prevent and cure cancers in humans.

GINGER AND IMMUNONUTRITION

Dietary patterns are major influential factors involved in the proper functionality of the immune system. Among some newer concepts in the domain of nutrition, immunonutrition is linked with the role of certain nutrients in bringing a balance in the human immune system. Immunonutrition, often based on the principle to have a diet that can improve the immune system, maintains homeostasis, and helps to fight against foreign and malignant cells. Many studies have indicated that diet influences the various intrinsic and extrinsic factors of the immune system (Lin and Karin, 2007; Bourgeon et al., 2007). Chronic (or acute) inflammation is a multi-step process mediated by activated inflammatory or immune cells (Grip et al., 2003). The hallmark of most immune boosters remained in their anti-inflammatory perspectives and reduction in the toxicity of certain ingested chemicals (Butt et al., 2009).

In ancient times medical practitioners focused on herbs and spices for improving the body systems. In many cultures ginger and its products when consumed boost the immune system. In addition, it has many other proclaimed beneficial effects. (Bárta et al., 2006). The anti-inflammatory potential of ginger has been demonstrated in a number of scientific investigations. In this context, Guh et al. (1995) reported concentration-dependent inhibition of arachidonic acid-induced platelet aggregation and formation of thromboxane B. Gingerol, shogaol, and other structurally-related substances in ginger inhibit prostaglandin and leukotriene biosynthesis through suppression of 5-lipoxygenase or prostaglandin synthetase. Ginger also holds the ability to inhibit synthesis of IL-1, TNF-α, and IL-8, considered as pro-inflammatory cytokines. The mechanism behind this inhibition involves genes encoding (Tjendraputra et al., 2001; Verma et al., 2004). In another investigation, Pan et al. (2008) showed that [6]-shogaol down-regulates inflammatory iNOS and COX-2 gene expression in macrophages by inhibiting the activation of NF-κB by interfering with the activation PI3K/Akt/I kappaB kinases IKK and MAPK.

Inflammation results in the onset of several maladies, for example, gout and neurogeneative disorders. These ailments result in enhanced production of several inflammatory cytokines and prostaglandins. It is possible to control excess production of such metabolites with the help of ginger and its active ingredients. Jung et al. (2009) indicated that Rhizome hexane fraction extract of Zingiber officinale Roscoe (ginger hexan extract or GHE) significantly inhibited the excessive production of NO, PGE(2), TNF-alpha, and IL-1beta in LPS-stimulated BV2 cells. The molecular mechanisms that underlie GHE-mediated attenuation are related to the inhibition of the phosphorylation of three mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinases 1 and 2 (ERK1/2), p38 MAPK, and c-Jun N-terminal kinase (JNK), and the activation of NF-κB. Ginger rhizome contains potent compounds capable of inhibiting allergic reactions and may be useful for the treatment and prevention of allergic diseases (Chen et al., 2009). The activation of NF-κB is linked to a variety of inflammatory diseases, including cancer, atherosclerosis, myocardial infarction, diabetes, allergy, asthma, arthritis, Crohn's disease, multiple sclerosis, Alzheimer's disease, osteoporosis, psoriasis, septic shock, and AIDS (Aggarwal and Shishodia, 2006). Its inactivation or balanced expression is essential for the proper functioning of the immune system. Ginger and its components have been reported to possess the ability of reduced expression via modulation of protein kinases, etc. (Zhou et al., 2006). Lee et al. (2009) used lipopolysaccharide (LPS)-stimulated macrophages to study the anti-inflammatory effects of 6-gingerol. They observed that its reduction could decrease inducible nitric oxide synthase and TNF-a expression through suppression of I-jBa phosphorylation, NF-jB nuclear activation, and PKC-a translocation.

Gout is a rheumatic disease of joints and the functional ingredients of ginger including [6]-shogaol, owing to its strong anti-inflammatory and antioxidant effects, can be used as curative agents (Grzanna et al., 2005; Sabina et al., 2010). Likewise, intraperitoneal injections of ginger extract decreased the number of eosinophils along with diminished levels of IL-4, IL-5, and eotaxin levels in the lungs (Ahui et al., 2009). Further evidence can also be presented in this regard and intraperitoneal administration of [6]-gingerol (25 mg/kg-50 mg/kg) produced an inhibition of acetic acid-induced writhing response and formalin-induced licking time in the late phase. However, higher doses of [6]-gingerol (50 mg/kg-100 mg/kg) inhibited paw edema induced by carrageenin (Young et al. 2005). Ginger essential oil recovered the humoral immune response in immunosuppressed mice (Carrasco et al., 2009).

The immune system also helps the body by protecting it from the hazardous effects of chemicals. In this regard, ethanol-induced toxicity is of prime importance. In rat modeling studies, some chemicals like bromobenzene have been employed to induce hepatotoxicity. In one such study, the pretreatment of ginger extract prior to chemical-induced toxicity alleviated its toxic effects. The ginger extract improved the activities of the antioxidant enzymes like SOD, GPx, and the GSH level. Additionally, reduction in the activities of GR and GSTs and Cyt P450 also supported the hypothesis that ginger and its functional ingredients are helpful in overcoming the toxicity arising due to chemicals via modulation of enzymes (El-Sharaky et al., 2009). In this context, excessive consumption of alcohol is also a risk factor contributing to many disorders like liver necrosis. Shati and Elsaid (2009) postulate that water extracts of ginger have detoxifying and antioxidant effects, and these help to overcome alcohol-induced liver toxicity. Thus it

can be observed that ginger and its components possess anti-inflammatory activities and can reduce the chemical toxicity in organs like liver.

A conclusive approach drawn from this section of the paper is that anti-inflammatory responses of ginger components include inhibition of prostaglandin and leukotriene biosynthesis and suppression of 5-lipoxygenase. Furthermore, inhibition of phosphorylation of three mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinases 1 and 2 (ERK1/2), and c-Jun N-terminal kinase (JNK) are also important. The results are of significant importance in treating disorders like asthma, gout, arthritis, etc. However, cohort studies and controlled trails need to be conducted as these would be helpful for dieticians to warrant the pharmacological applications of ginger.

GINGER AND CARDIOVASCULAR PROTECTION

Cardiovascular disorders (CVD) are a major cause of morbidity and mortality in the world. The changing lifestyles and dietary patterns are major contributory factors in the prevalence and pathogenesis of CVD (Matsuura et al., 2008). Ginger and its functional ingredients play many roles in improving the cardiovascular health of individuals. At a molecular level, it reduces retinoid binding protein (RBP) mRNA expression levels in the liver and visceral fat resulting in improved lipid metabolism (Matsuda et al., 2009).

Epidemiological studies have indicated that elevated blood pressure is one of the major risk factors for stroke and coronary heart disease (CHD). In recent years, several herbal remedies are in use and ginger and its combinations with other herbs are of significant importance (Chen et al., 2009). Ghayur et al. (2005) demonstrated in a research study that the aqueous extract of fresh ginger lowers BP via endothelium-dependent (cholinergic) and endothelium-independent (CCB) vasodilator pathways. They reported the emergence of some cardiotonic component due to ginger supplementation that was sensitive to the blockade of Ca++ release in the presence of the cholinergic receptor blockade. Previous studies showed that the cholinergic component is usually concentrated in the aqueous while the CCB component is concentrated in the less polar extracts (Ghayur and Gilani, 2005; Abdel-Aziz et al., 2006).

Apart from ginger itself, some of the pure compounds of ginger, [6]-gingerol and [6]-shogaol, have been studied for their effects on BP in laboratory animals and both produced a depressant effect. Later reports revealed that the peripheral pressor effect of [6]-shogaol in rats is caused by the release of a peptide-like substance from the sympathetic nerve endings (Suekawa et al., 1984).

Ansari et al. (2006) reported that treatment with an ethanolic extract of ginger in isoproterenol-treated rats increased the levels of endogenous myocardial antioxidants (catalase, superoxide dismutases, and tissue glutathione), decreased the levels of serum marker enzymes (LDH, creatinine kinase, aspartate aminotransferase, and alanine aminotransferase), and increased myocardial lipid peroxides. The cardioprotective property of ginger, further confirmed by histological examination, demonstrated that ginger treatment largely protected rats from isoproterenol-induced myocardial injury.

Some of the known pungent constituents of ginger including [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol hold vasodilator activity; [6]-shogaol exhibited only a mild vasodilator effect as compared to gingerols (Kimura et al., 1988). It is possible that the cholinergic-mediated vascular effects of ginger are due to sesquiterpenes such as zingiberene, bisabolene, camphene, and phellandrene (Langner et al., 1998). Alizadeh-Navaei et al. (2008) evaluated the potential of ginger in improving lipid profile and according to their observation, 3 g/day in three equal doses resulted in marked decrease in triglyceride, cholesterol, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL). There were several compounds, including [6]-gingerol, [8]-gingerol, [6]-shogaol, and [10]-gingerol, that bound to the thrombocytes, and all had shown anti-platelet aggregation activities (Nie et al., 2008). Dias et al. (2006) contradicted the findings of other scientists and observed that ginger supplementation did not improve lipid profile significantly. The improvement in lipid profile as a function of ginger is dependent on reduced cholesterol biosynthesis in liver and stimulated the conversion of cholesterol to bile acids and the excretory system (Verma et al., 2004).

The present discussion concludes that ginger is of significant importance in improving lipid profile and its blood pressure lowering ability is indeed imperative in controlling the extent of hypertension, arthrosclerosis, and allied cardiovascular disorders.

GINGER FOR DIGESTIVE HEALTH

It facilitates the transport of nutrients and phytochemicals into the blood stream for their delivery to body cells. Dietary factors also influence the frequency and severity of gastrointestinal disorders including gastro-esophageal reflux disease (GERD), diverticular disease, and Crohn's disease. The balanced diets improve the health of individuals, and herbs/spices are important in this regard. It has also been reported that ginger can interfere with the activities of some digestive enzymes. Ramakrishna Rao et al. (2003) demonstrated that ginger enhanced the activity of pancreatic lipase and amylase.

Since times immemorial, ginger and its formulations have been used as traditional remedies for gastric disturbances. Research investigations in the domain of pharmaceuticals and nutrition explored the significant association of ginger and its role in improving the functionality of the gastrointestinal tract. Nanjundaiah et al. (2009) studied the ulcer-preventive properties of the aqueous extract of ginger rhizome at 200 mg kg^{-1} body weight; it reduces the swim stress-/ethanol stress-induced ulcers up to 77–86% and its effects were similar to that of lansoprazole (80%) at 30 mg kg^{-1} body weight. Ulcerative colitis is one

gastrointestinal ailment characterized with inflammatory responses. Tumor necrosis factor-α (TNF-α) amplifies the inflammatory response by activating a cascade of immune responses (Ardizzone and Bianchi, 2005). This cytokine also stimulates the production of other cytokines, arachidonic acid metabolites, and proteases (Jainu et al., 2006). Inhibition of PGE2, on the other hand, may follow that of TNF-α or may result from GE ability to inhibit cycloxygenase enzymes. El-Abhar et al. (2008) stated that ginger extract can indeed reduce the onset of ulcerative colitis owing to its functional ingredients (Young et al., 2005; Grzanna et al., 2005).

Ginger also helps in enhancing the growth of bacteria residing in the gastrointestinal tract. Recently, Sutherland et al. (2009) showed that aqueous extracts of garlic significantly enhanced the growth of *L. reuteri* while inhibiting both pathogenic strains of E. coli. The results are quite conclusive that ginger helps in improving the health of gastrointestinal tracts.

MISCELLANEOUS HEALTH BENEFITS

In the last few years, the health-promoting potential of ginger has been largely explored and it is considered to be safe as a herbal medicine. Diabetes mellitus and its complications are one of the leading causes of death in the world. According to one estimate, at the end of the year 2030, this disease will affect approximately 376 million people worldwide (Wild et al., 2004; Lapshina et al., 2006). Some research studies have presented the effectiveness of ginger against diabetes and its complications. Weidner and Sigwart (2000) conducted an acute (64 days) experimental study and suggested that a patented ginger extract (25–100 mg/kg) with a high content of gingerols and shogaols did not induce significant changes in blood glucose, blood coagulation, blood pressure, and heart rate in normal male rats. However, the effects have been more pronounced in hyperglycemic rats, for example, in animals that are diabetic, deficient in the apolipoprotein E gene or those that have been fed a high lipid diet. In these animals, ginger significantly lowered blood glucose, serum total cholesterol, LDL, VLDL, and triglycerides, and raised HDL (Fuhrman et al., 2000).

Later, Bhandari et al. (2005) postulated that ethanolic extract of Zingiber officinale (200 mg/kg) fed orally for 20 days produced a significant antihyperglycaemic effect ($P < 0.01$) in diabetic rats and the results were comparable to a standard antihyperglycaemic agent, namely gliclazide (25 mg/kg, orally). Likewise Han et al. (2005) demonstrated that an aqueous extract of ginger inhibited the hydrolysis of triolein emulsified with phosphatidylcholine by pancreatic lipase in vitro and reduced the elevation of rat plasma triacylglycerol levels after oral administration of a lipid emulsion containing corn oil. Furthermore, Nammi et al. (2009) assert that the ethanolic extract of ginger at 100, 200, and 400 mg/kg body weight reduced body weights and levels of glucose, insulin, total cholesterol, LDL cholesterol, triglycerides, free fatty acids, and phospholipids in high-fat diets (Ojewole, 2006). Recently Heimes et al. (2009) supported the hypoglycemic potential of ginger. Islam and Choi (2008) suggested that ginger has insulinoptropic properties that are mainly attributed to its glucose-lowering potential (Sekiya et al., 2004; Goyal and Kadnur, 2006; Heimes et al., 2009).

Herbal remedies are becoming important in pregnancy-induced disorders such as nausea, vomiting, insomnia, and morning sickness. Although, the pharmaceuticals are in use yet many people prefer herbal remedies owing to their safe status (Holst et al., 2009). According to Ozgoli et al. (2009), ingestion of 1000 mg of ginger/daily can serve as a means to decrease pregnancy-induced nausea and vomiting. Moreover, ginger, along with higher amounts of protein intake, can delay the onset of nausea in pregnancy and chemoprevention (Levine et al., 2009). In this regard, Ensiyeh and Sakineh (2009) stated that ginger is more effective than other nutritional therapies, for instance, vitamin B6, for relieving the severity of nausea and vomiting episodes in pregnancy.

Ginger and its preparations are rich in antioxidant compounds that are effective in reducing the extent of diabetes mellitus, pregnancy-induced maladies, arthritis, etc. It is considered a safe herbal medicine with only a few and insignificant adverse/side effects. More studies are required in animals and humans to study the kinetics of functional ingredients of ginger. Additionally, the safety studies should be carried out over extended period of time thus to present comprehensive evidences for meticulousness.

CONCLUSIONS

Natural products are gaining attention owing to their rich phytochemistry and risk-free use. The plant-based functional and neutraceutical foods enriched with biomolecules have been capturing a major share of the global nutrition market. A number of plants are explored in this context; ginger holds a unique composition and FDA ranked it in the GRAS list. The health-promoting perspectives of ginger are well known. It can treat a wide range of ailments including immunonutrition and anti-inflammatory responses. Likewise, the anticancer potential of ginger is well documented and its molecular aspects embrace induction of Phase 2 enzymes, inhibition of post-translational modification, angiogenesis and metastasis, induction of apoptosis, and inhibition of cell-cycle progression. Besides these, it improves cardiovascular disorders, diabetes mellitus, and gastrointestinal health. Undoubtedly, we have presented a great deal of evidence in this article and it seems to favor ginger but some ambiguities necessitate further research before claiming its efficacy.

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