Medicinal and nutritional qualities of Zingiber officinale

Chapter · December 2016
DOI: 10.1016/B978-0-12-802972-5.00025-1
CHAPTER OUTLINE

Introduction 525
Ginger in Traditional Use 527
   Essential oil 528
Nutrient Composition 528
Bioactive Components of Ginger 529
   Gingerol homologues 529
Analgesic Effect 534
Cardiovascular Effects 536
Gastrointestinal Effects 537
Effect on Migraine/Retinopathy 539
Metabolism of Ginger 540
Future Prospects 542
References 543

INTRODUCTION

The word “nutraceuticals” was coined by Stephan L. De Felice for the bioactive compounds that are found in foods, dietary supplements, and herbal products having health benefits. The word encompasses nutrition and pharmaceutical properties of the plant/molecule. Therefore, nutraceuticals are those molecules/plants which have health-promoting, disease-preventing medicinal properties. They are accredited to improve health, delay
CHAPTER 25 Medicinal and nutritional qualities of Zingiber officinale

Age progression, prevent persistent diseases, and increase life expectancy by supporting the structure or function of the body. However, they differ from pharmaceutics in having a natural origin. Nowadays, considerable interest is being generated in nutraceuticals because of their potential nutritional, safety, and therapeutic effects with no/less side effects, as compared to modern system of medicine. Traditional systems of medicine of several Asian countries have been using plant as a source of medicines for general well-beings (Afzal et al., 2001). Not only whole plant but plant-derived bioactives including phytoestrogens, terpenoids, carotenoids, limonoids, phytosterols, glucosinolates, polyphenols, flavonoids, isoflavonoids, and anthocyanidins are also being used as nutraceuticals (Gupta and Sharma, 2014). Modern science has demonstrated that these phytochemicals/extracts have a specific pharmacological role in promoting human health. It could be as antiinflammatory, antiallergic, antioxidants, antibacterial, antifungal, antispasmodic role, or they may have chemopreventive, hepatoprotective, hydropelidemic, neuroprotective, hypotensive, and antiaging properties (Afzal et al., 2001). Literature cites several examples of plants having anti-diabetic, antiosteoporotic, anticancer, and apoptosis-inducing properties (Gupta and Sharma, 2014). In the present chapter, we extend our focus to highlight the medicinal and nutritional qualities of Zingiber officinale (ginger) in the prevention and treatment of diseases. Ginger has a distinction of being among those few herbs that are used as food, culinary, and also as medicine (Badreldin et al., 2008). According to USFDA, it is categorized as GRAS (generally regarded as safe). Ginger is among the 20 top selling herbal supplements in the United States. Its retail sales in mainstream US market (including food stores, drug stores, and mass market retail sales) in 2001 amounted to US$1.2 million. In Germany, ginger products are marketed for the treatment of dyspepsia and prophylaxis of motion sickness. Today, pharmacopoeias of a number of different countries list ginger extract for various diseases (World Health Organization (WHO), 2000a). This chapter also underlines the related pharmacological research to give an insight of the scientific background to the traditional medicinal applications.

Ginger (Z. officinale Rosc.), a member of Zingiberaceae family, is grown in tropical and subtropical regions for spice and medicinal purposes, since decades. With 53 genera and over 1200 species, the Zingiberaceae is the largest of the eight families of the order (Kress, 1990). It is a member of a plant family that includes highly valued premium spices like cardamom and turmeric. The plant has long history of cultivation in the Asian subcontinent, probably originating from South East Asia (Ravindran and Nirmal, 2005). It is cultivated on a large scale in India, China, Bangladesh, Taiwan, Jamaica, and Nigeria from where it is exported to other countries of the world (Dedov et al., 2002). The plant is cultivated throughout
the humid tropics, with India being the largest producer (Pandotra et al., 2013). Indians and Chinese are believed to have produced ginger as a tonic root for over 5000 years to treat several ailments. Ginger was an important article of trade and was exported from India to the Roman Empire over 2000 years ago, where it was especially valued for its medicinal properties. Ginger continued to be a highly sought after commodity in Europe even after the fall of the Roman Empire, with Arab merchants controlling the trade in ginger and other spices for centuries. In the 13th and 14th centuries, the value of a pound of ginger was equivalent to the cost of a sheep (Ravindran and Nirmal, 2005). By medieval times, it was being imported in preserved form to be used in sweets. The importance of ginger can be summarized in the invention of the “gingerbread man” by Queen Elizabeth I of England, which became a popular Christmas treat.

Morphologically, ginger plant has a perennial, tuberous root, or rhizome having erect annual stem invested by smooth sheaths of leaves, 2–3 ft in height. The rhizome, which is the horizontal stem from which the roots grow, is the main portion of ginger that is consumed as a spice in dried, preserved, and green forms (Pandotra et al., 2013). Dried-ginger-derived products (oil and oleoresins) are used in nutraceuticals and pharmaceuticals and are valued more in international trade than either of the other two forms. Its spicy aroma is mainly due to presence of ketones, especially the gingerols, which appear to be the primary component of ginger studied in much of the health-related scientific research. It is widely used as flavoring agent in great variety of food preparations. The roots contain polyphenolic compounds (gingerol homologs and shogaols), which have a high antioxidant activity (Bartley and Jacobs, 2000). In addition, ginger is also reported as detoxifying agent against alcohol abuse (Stoilova et al., 2007) and bromobenzene intoxication. The rhizome is also known to have anti-diabetic, antihyperlipidemic, and hepatic anticancer effects (Hamed et al., 2012; Bordia et al., 1997; Akimoto et al., 2015).

**GINGER IN TRADITIONAL USE**

Ginger is an important plant with several medicinal, ethnomedicinal, and nutritional attributes. Traditionally, in Indian, Chinese, and Tibetan system of medicines, ginger is being used since ancient times, for the treatment of catarrh, rheumatism, nervous diseases, gingivitis, toothache, asthma, stroke, constipation, diabetes, cough and cold, motion sickness, menstrual cramps, cancer, and many more (Shukla and Singh, 2007). In Ayurveda, ginger is called “maha aushadhi,” meaning the “great medicine” and recommended for use as carminative, diaphoretic, expectorant, peripheral circulatory stimulant, astringent, appetite stimulant, and diuretic and digestive
aid (Ghosh et al., 2011). Studies have shown that ginger induces increase in the pancreatic and intestine lipase, when given in animal diets (Patel and Srinivasan, 2000). Some active components of ginger have been reported to increase the muscular activity of the digestive tract, thereby stimulating digestion, absorption, and relieving constipation and flatulence (Wu et al., 1990, 2008). It has been observed that ginger and its metabolites accumulate in the gastrointestinal tract; therefore, many of its effects are manifested in the gastrointestinal areas.

Compositional analysis has revealed the presence of carbohydrates, fats, vitamins, minerals, and extractable oleoresins (Shukla and Singh, 2007). Ginger contains 9% of lipids or glycolipids and 5–8% of oleoresin (Chrubasik et al., 2005). Literature survey divulged that, as seen in several medicinal herbs, most of the information on uses of ginger has been handed down by word of mouth with little demonstrable scientific evidence to support the numerous claims. However, in the last few years, more organized scientific investigations have focused on the mechanisms and targets of ginger and its various components. To comprehend the evident medicinal and nutritional qualities of ginger rhizome, understanding of the underlying scientific mechanism will provide a better insight of its qualities. Here, we will be discussing few of them in the later part of the chapter.

**Essential oil**

The aroma and flavor of ginger are determined by the composition of its steam volatile essential oil (1–2.5%), which is primarily comprised of monoterpenes, oxygenated monoterpenes, and sesquiterpenes. The major essential oil components are zingiberene (30–70%), β-sesquiphellandrene (15–20%), β-bisabolene (10–15%), and α-farnesene (Govindarajan, 1982). However, camphene, β-phellandrene, curcumene, geranyl acetate, borneol, geraniol, limonene, and linalool were also found in appreciable quantity (Gupta et al., 2011). Many of these volatile oil constituents contribute to the distinct aroma and taste of ginger. Both oil and oleoresins are used in many food items, soft drinks, beverages, pickles, and many types of medicinal preparations (Gurdip et al., 2008). Experiments have shown that ginger essential oil enhanced improvement in humoral immune response in immune suppressed mice (Carrasco et al., 2009).

**NUTRIENT COMPOSITION**

Ginger rhizome is a rich source of minerals like, iron, calcium, phosphorous, and vitamins such as thiamine, riboflavin, niacin, and vitamin C. Not
only the rhizome-derived components, but the powdered rhizome also has nutritional components like fatty oil (3–6%), protein (9%), carbohydrates (60–70%), crude fiber (3–8%), and about 8% ash. Ginger rhizomes also contain a potent proteolytic enzyme called zingibain. Their composition varies with the type, variety, agronomic conditions, curing methods, and drying and storage conditions (Agrahari, 2015). Vitamin C and total carotenoids content were found to be 10.97 and 92.96 mg per 100 g, respectively, in ginger rhizome. Jeevani Osadee Wijekoon et al. (2011) evaluated the nutritional quality of torch ginger (Etlingera elatior Jack.) inflorescence and found the presence of high amounts of dietary fiber, unsaturated fatty acids (palmitoleic acid, linoleic acid, and oleic acid), and essential amino acids (leucine and lysine) (Jeevani Osadee Wijekoon et al., 2011). The study revealed that inflorescence of torch ginger is a rich source of essential minerals such as K (1589 mg/100 g), Ca (775 mg/100 g), Mg (327 mg/100 g), P (286 mg/100 g), and S (167 mg/100 g) with lower levels of heavy metal contaminants (Cd, As, Pb, Hg, Ni). This was also corroborated by Pandotra et al. (2015) in ginger germplasm, collected from north western Himalayan India (World Health Organization (WHO), 2000a). In this study, the ionome of the ginger rhizome suggested raw ginger to be a good source of beneficial elements/minerals like Mg, Ca, Mn, Fe, Cu, and Zn (Gupta et al., 2010). Evaluation of Malaysian ginger rhizome and ginger sourced from Nigeria revealed higher moisture (90.9% vs 76.9%), crude fiber (3.8 g/100 g), and lower carbohydrate content (6.3 g/100 g sample) than the USDA database (USDA Nutrient Database, 2013). An inductively coupled plasma-mass spectrometry based multielemental profiling to assess the quantitative complement of elements and nutritional quality in ginger rhizome showed abundance of 18 elements quantified (Gupta et al., 2010). The acid digested rhizomes was having K > Mg > Fe > Ca > Na > Mn > Zn > Ba > Cu > Cr > Ni > Pb > Co > Se > As > Be > Cd metals in that order of abundance. Chemometric of the data showed positive correlation among most of the elements. It is generally believed that paradol, formed on hydrogenation of shogoal, in ginger plant possess considerable antioxidant content which produces protective health benefits in various diseases (Badreldin et al., 2008).

**BIOACTIVE COMPONENTS OF GINGER**

**Gingerol homologues**

At least 115 constituents in fresh and dried ginger varieties have been identified by a variety of analytical processes. Chemical profiling of the methanolic crude extracts of fresh ginger rhizome has revealed at least 31 gingerol-related compounds (Jiang et al., 2005); homologs were found
to be the major constituents (%) present in the solvent extract of ginger rhizome and attribute pungency to the rhizome. The concentrations of gingerols were found to be reduced in dried ginger, whereas the concentrations of shogaols, which are the major gingerol dehydration products, are more abundant (Jolad et al., 2004) in dried ginger. Ginger homologs are the biologically active pungent principles of ginger that significantly contributes toward medicinal applications of ginger (Sanwal et al., 2010). Ginger has been fractionated into at least 14 bioactive compounds, including [4]-gingerol, [6]-gingerol, [8]-gingerol, [10]-gingerol, [6]-paradol, [14]-shogaol, [6]-shogaol, 1-dehydro-[10]-gingerdione, [10]-gingerdione, hexahydrocurcumin, tetrahydrocurcumin, gingerenone A, 1,7-bis-(4′ hydroxyl-3′ methoxyphenyl)-5-methoxyheptan-3-one, and methoxy-[10]-gingerol (Koh et al., 2009). Their proportion in the ginger depends on the habitat, processing mechanism, and the harvest stage of the ginger (Singh and Gupta, 2013). Of the four main bioactive pungent components of Jamaican ginger, including [6]-, [8]-, and [10]-gingerols and [6]-shogaol, [6]-gingerol appears to be the most abundant compound, in most of the oleoresin samples studied (Bailey-Shaw et al., 2008). Although phylogenetic analysis has shown that all the Z. officinale samples, from widely different geographical origins, are genetically indistinguishable, their metabolic profiling showed quantitative variation. 6-Gingerol has been shown to have a number of pharmacological activities such as antipyretic, anti-tussive, hypotensive (Suekawa et al., 1986), cardiotonic (Kobayashi et al., 1988), antiplatelet (Guh et al., 1995), neural protectant (Kim et al., 2014), antiinflammatory, analgesic (Lantz et al., 2007), cytotoxic, apoptotic (We et al., 2005), antitumor (Chan et al., 2012), anticancer (Yusof et al., 2008), antioxidant (Masuda et al., 2004), antihepatotoxic (Haniadka et al., 2013), antifungal (Ficker et al., 2003a), vanilloid receptor agonistic (Dedov et al., 2002), cholangic (Yamahara et al., 1985), and antiemetic activities (Micklefield et al., 1999). Ginger is good for the respiratory system to fight against colds and flu (Langmead and Rampton, 2001). It relieves headaches, pains, and helps to clear sore throats (Gupta and Sharma, 2014). It is very effective as a cleansing agent through the bowels and kidneys and also through the skin (Uz et al., 2009).

It has been observed that consuming ginger regularly leads to decreased pain levels in people suffering from osteoarthritis or rheumatoid arthritis along with improvements in their mobility. The antiinflammatory property of gingerols is thought to have a role in these joint problems (Funk et al., 2009). One of the mechanisms by which ginger exerts its ameliorative effects could be related to inhibition of prostaglandin and leukotriene biosynthesis. Ginger not only stimulates the muscles of the gastric tract, but
consumption of ginger is seen to stimulate heart muscles also, resulting in better blood circulation throughout the body and increased cellular metabolic activity. It also helps to reduce blood pressure and cardiac workload (Shoji et al., 1982).

Ginger has been found to be anticarcinogenic mediated by multiple pathways (Yusof et al., 2008; Chen et al., 2007) and reported to have colon cancer chemopreventive activity (Bode, 2003). Gingerols, the active phytonutrients in ginger, kill ovarian cancer cells by inducing apoptosis (programmed cell death) and autophagocytosis (self-digestion) (Rhode et al., 2006). A pro-inflammatory state is considered to be an important contributing factor in the development of ovarian cancer. In the presence of ginger, a number of key indicators of inflammation (vascular endothelial growth factor, interleukin-8 (IL-8), and prostaglandin E2) were found in lesser amount in the ovarian cancer cells (Rhode et al., 2006). It has been observed that the combined treatment with 6-shogaol and tumor necrosis factor (TNF)-related apoptosis-inducing ligand induces apoptosis in various cancer cells like renal carcinoma Caki cells, breast carcinoma MDA-MB-231 cells, and glioma U118MG cells, but not in normal mesangial cells and normal mouse kidney cells. 6-Shogaol also has the capability to reduce the mitochondrial membrane potential and released cytochrome c from mitochondria to cytosol via Bax activation. It is also involved in down-regulation of c-FLIP(L) expression at the posttranslational levels (Qazi et al., 2014). Gingerol also inhibited the growth of human colorectal cancer cells (Bode, 2003). The efficacy of ginger in mice was found to be significant in both cases, when the mice were fed with ginger before and after tumor cells were injected. The effects of chronic treatment with hot water extract of ginger rhizome on spontaneous mammary tumorigenesis in mice demonstrated that when mice had ginger extract (0.125%) in drinking water, the development of mammary tumors was significantly inhibited (Rhode et al., 2006). Tumor development and progressions are multistep processes incorporating genetic and metabolic changes (Qazi et al., 2014). The extract of ginger (Z. officinale Rosc.) and its major pungent components, that is 6-shogaol and 6-gingerol, have shown antiproliferative effect on several tumor cell lines in vitro. Moreover, a cytotoxic or cytostatic effect, mediated by apoptosis, was found for 6-gingerol and 6-paradol in human promyelocytic leukemia HL-60 cells (Lee and Surh, 1998), and also for four diarylheptanoids and two shogaols (We et al., 2005). On the basis of molecular target-based virtual screening of phytochemicals, several ingredients of ginger, including 6-shogaol, 6-paradol, and 6-gingerol, have been found as potential candidates for the prevention and therapy of nonsmall cell lung carcinoma (NSCLC).
Among the above mentioned compounds, 6 gingerols were found to be most effective in suppressing the proliferation of NSCLC cells (Yusof et al., 2008). Ginger and its constituents are also effective against pancreatic cancer (Akimoto et al., 2015). Besides, ginger extract inhibited cell proliferation and subsequently induced the autotic death of pancreatic cancer. It has been found that whole ginger extract or its constituents may have clinical implications for therapeutic intervention against pancreatic cancer (Patel and Srinivasan, 2000). Importantly, ginger has attracted attention for the chemoprevention of colorectal cancer. The suppression of tumor growth in colon cancer was found to be linked with the inhibition of leukotriene A4 hydrolase activity. Hexahydrocurcumin extracted from ginger was also found to be cytotoxic to colorectal cancer cells. It has been observed that treatment of SW480 colon cancer cells with hexahydrocurcumin (100μM) resulted in apoptosis indicating its potential as anticancer agent (Lee and Surh, 1998). Besides ginger rhizome, treatment with ginger leaves induce apoptosis and reduction of cell viability, followed by the increased ATF3 expression via activating ATF3 promoter in human colorectal cancer cells (Park et al., 2014). Furthermore, in vitro studies revealed that ginger components are effective against liver cancer. In a study, 6-shogaol has been reported to induce apoptotic cell death of Mahlavu hepatoma cells via an oxidative stress-mediated caspase-dependent mechanism (Chen et al., 2011). The major components of ginger, 6-shogaol and 6-gingerol, have shown to exert antiinvasive activity against hepatoma cells. In animal model, ginger suppresses ethionine-induced liver carcinogenesis by scavenging the free radical formation and by reducing lipid peroxidation, thus preventing rat hepatocarcinogenesis (Mansour et al., 2010). An ethanolic ginger extract applied topically to mouse skin provided a highly significant protective effect against the development of skin tumors. This was found to be associated with the inhibition of 12-O-tetradecanoylphorbol-13-acetate-caused induction of epidermal ornithine decarboxylase, cyclooxygenase (COX), and lipoxygenase activities (Katiyar et al., 1996).

Drug resistance is growing worldwide and it is consider as a main offender in the failure of treatment. The use of antibiotics against microorganism is effective mode of treatment but also causes adverse complications. Consumption of ginger produces heat in body that promotes healthy sweating, which assists detoxification of the body through skin and conferring protection against invading microorganisms. Ginger has been traditionally exploited for having broad range of antimicrobial activity against both gram-positive and gram-negative bacteria and fungi. In vitro studies have shown that active constituents of ginger inhibit multiplication
of colon bacteria. These bacteria are responsible for fermentation of undigested carbohydrates causing flatulence which can be counteracted with ginger (Habsah et al., 2000). It inhibits the growth of *Escherichia coli*, *Proteus* sp., *Staphylococci*, *Streptococci*, and *Salmonella* (Azu and Onyeagba, 2007). Earlier investigators have shown that ginger and its constituents play a vital role in the prevention of microbial growth or act as antimicrobial agents (Kumar et al., 2011). Ginger rhizome contains several constituents which have antibacterial and antifungal effects. The gingerol and shogaol are identified as more active agents (Atai et al., 2009). 10-Gingerol from Ginger extracts has demonstrated antimicrobial activity against a wide range of pathogenic microorganisms including gram-positive and gram-negative bacteria and the yeast *Candida albicans* (Chairgulprasert et al., 2005). Of particular interest is an in vitro study showing that a crude methanolic extract (minimum inhibitory concentration (MIC) 6–50µg/mL) and a gingerol-containing fraction significantly inhibited the growth of 19 strains of *Helicobacter pylori*, the microorganism associated with peptic ulcer disease as well as gastric and colon cancers (Mahady et al., 2003). Various studies demonstrating time-dependent anthelmintic activity of crude powder and crude aqueous extract of dried ginger (1–3 g/kg) in sheep naturally infected with mixed species of gastrointestinal nematodes are reported (Iqbal et al., 2006). Ginger inhibits *Aspergillus* sp., a fungus known for the production of carcinogenic aflatoxin (Ficker et al., 2003a). Study on ginger rhizome afforded three lipophilic analogues: 6-gingerol, 8-gingerol, and 10-gingerol that exhibited antimicrobial activity (Ficker et al., 2003a). The lipophilic analogues (8-gingerol and 10-gingerol) were more active, with MIC values of 25–50µg/mL exhibiting toward *Mycobacterium tuberculosis* H37Rv and *Mycobacterium avium*. Besides, 6-gingerol and 12-gingerol, isolated from ginger rhizome, showed antibacterial activity against periodontal bacteria (Miri et al., 2008). Thus, ginger which is a normal ingredient of our routine food preparations can provide protection against our natural enemies like bacterial and fungal pathogens.

Limited studies have observed the possible immunomodulatory action of ginger. Experiments have shown that mice fed a 50% ethanolic ginger extract (25mg/kg) for 7 days had higher hemagglutinating antibody titer and plaque-forming cell counts and improved humoral immunity (Puri et al., 2000). In vitro study found that ginger suppressed lymphocyte proliferation mediated by decreased IL-2 and IL-10 production (Wilasrusmee et al., 2002) and aqueous ginger extract significantly increased the production of IL-1β, IL-6, and TNF-α in activated peritoneal mouse macrophages (Ryu and Kim, 2004). Aqueous ginger extract also stimulated splenocyte
proliferation and cytokine production in a concentration-dependent manner in mice. Recently, study has shown the immunomodulatory effects of zerumbone on antigen-presenting dendritic cells in vitro and antiallergic effect via modulation of Th1/Th2 cytokines in an asthmatic mouse model (Shieh et al., 2015).

**ANALGESIC EFFECT**

Various studies have assessed for the analgesic effect of ginger and its constituents. It has a vigorous analgesic action and act by COX-1 inhibition. Gingerol and its derivatives, particularly 8-paradol, have been reported to be more effective antiplatelet and COX-1 inhibitors than aspirin (Nurtjahja-Tjendraputra et al., 2003). Inhibition of the arachidonic acid (AA) metabolism cascade via the COX-1/thromboxane synthase system by these phenolic compounds may highlight the mechanism of their action for peripheral and possible antiinflammatory action. Besides, 6-shogaol inhibits the release of substance P by stimulation of the primary afferents from their central terminal and hence shares this site of action with capsaicin (Onogi et al., 1992) while gingerols act as vanilloid receptor (VR1) agonists (Dedov et al., 2002). The VR1 has been shown to integrate chemical and thermal nociceptive stimuli (Ma and Quirion, 2007). This finding bears significance as direct activation or deactivation of the VR1 at the painful site recommends a new strategy for the development of a new class of peripheral analgesics devoid of the well-characterized side effects of currently available analgesics and antiinflammatory drugs.

The polyphenols present in ginger roots extracts contain compounds which possess high antioxidant activity. The antioxidants inhibit the reactive oxygen species, which are capable of causing damage to DNA, coronary heart disease, and many other health problems related to advancing age (Patel and Srinivasan, 2000). Antioxidant compounds are commonly used to counter the free-radical-mediated oxidative stress in the cell. The free radical assembly is stabilized by the antioxidative defense system of our body (Shyur et al., 2005). [6]-Gingerol is recognized as a strong antioxidant component comparable with its antiinflammatory and antiapoptotic action both in vivo and in vitro studies (Kim et al., 2007) Experiment performed on rats indicated extracts of red and white ginger protect the brain through their antioxidant activity, Fe$^{2+}$ chelating and OH$^-$ scavenging ability and prevents oxidative stress (Oboh et al., 2012a). Ginger provides number of antioxidants helping in the reduction of the lipid oxidation and inhibiting the pathogenesis of diseases. The polyphenolic compounds show high antioxidant activity due to the presence of secondary metabolites that includes flavones, flavonoids,
coumarin, lignans, isoflavones, anthocyanin, catechins, and isocatechins (El-Ghorab et al., 2010). Experimentally, the total phenolic content in the alcoholic extract of the dried rhizome of ginger has been found 870.1 mg/g extract exhibiting 90.1% of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity with the IC$_{50}$ value of 0.64 μg/mL (Bartley and Jacobs, 2000). Recently, there are growing evidences displaying ginger leaves have higher antioxidant activity than rhizomes and flowers (Eric Chan et al., 2011). The antioxidant property of ginger is an extremely significant activity being used as a preventive agent against a number of diseases. More than 50 compounds with antioxidant activity from ginger rhizome have been identified (Masuda et al., 2004). They belonged to either related to gingerols or diarylheptanoids. Structure–activity relationship studies of the gingerol-like compounds proposed that substitution on and the length of the alkyl chain contribute to the antioxidant activity. A glucoside of 6-gingerdial has also been reported to exhibit strong antioxidant activity in vitro (Sekiwa et al., 2000). Several in vivo studies have also established the antioxidant activity of ginger on animal models, where lipid peroxidation was significantly lowered in rats fed on ginger (1%). Here, it was observed that the activities of the antioxidant enzymes, that is superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase were insistent, with significantly increased blood glutathione content. Besides, it was found that rats on a high fat diet complemented with ginger at 35 and 70 mg/kg had lowered levels of tissue thiobarbituric acid reactive substances and hydroperoxides, higher SOD and CAT activities, and raised levels of reduced glutathione in the kidney, intestine, and liver, compared with controls group (Jeyakuma et al., 1999). Also, rats noshed with dried ginger (1%) showed significant attenuated oxidative stress and lipid peroxidation when exposed to the organophosphorous pesticide malathion for 4 weeks (20 ppm) (Ahmed et al., 2000). Furthermore, atherosclerotic, apolipoprotein E-deficient mice fed on ginger extract showed a significant drop in the low-density lipoprotein (LDL) basal oxidative state, with reduced susceptibility to oxidation and aggregation (Fuhrman et al., 2000). Curcumin, another active component present in ginger, was found to be an antioxidant and an antiinflammatory agent and induced heme oxygenase-1 and protect endothelial cells against oxidative stress (Gurdip et al., 2008; Habsah et al., 2000; Kim et al., 2007). Antioxidants act as free radical scavengers and inhibit lipid peroxidation and other free radical-mediated processes; thereby helping to protect the human body from several diseases attributed to the reactions of radicals. Ginger is a good source of antioxidant and most of the antioxidant components exhibit higher activities in alcoholic media (Fuhrman et al., 2000; Ojewole, 2006). Hence, apart from its medicinal properties, ginger can also be used as an antioxidant supplement for preventive agent against a number of diseases.
In traditional system of medicine, ginger has been used for hyperglycemia and dyslipidemia (Bordia et al., 1997; Ojewole, 2006; Mascolo et al., 1989). Modern science has confirmed the role of ginger as antidiabetic (Hamed et al., 2012). Experiments have shown that ginger has the potential protective effect of oxidative damage to pancreatic β cells in rats. Studies have shown that, the long-term dietary intake of ginger has hypoglycemic and hypolipidemic effects (Akhani et al., 2004). Experiments have proved that fresh juice of ginger (4 mL/kg body weight) produced a significant time-dependent decrease in blood glucose level in streptozotocin-induced diabetic rats. The juice of ginger was also reported to control type I diabetes (Srivastava, 1984). Treatment with aqueous extract (500 mg/kg body weight) for a period of 7 weeks significantly decreased the serum glucose, cholesterol, and triacylglycerol levels in the treated diabetic rats compared with the control diabetic rats (Bordia et al., 1997). Reports point to the therapeutic usefulness of ginger extracts also with regard to diabetes and diabetic complications (Lantz et al., 2007; Mascolo et al., 1989). This was confirmed in a pilot study which was done to investigate the protective potential of ginger in a model of cytotoxic conditions imposed by diabetes in β cells.

**CARDIOVASCULAR EFFECTS**

Ginger, in traditional Chinese medicine, is used to monitor the movement of body fluids. It exhibited a dominant stimulatory effect on the heart muscles by diluting blood and thereby exciting blood circulation all over the body (Shoji et al., 1982). Enhanced circulation improved the cellular metabolic activity thereby relieving cramps and tension (Kobayashi et al., 1988). Besides, reports from Japanese group have shown that the blood pressure and cardiac workload could be declined due to certain active constituents in ginger. Additionally, ginger reduced the formation of pro-inflammatory prostaglandins and thromboxane thereby lowering the clotting ability of the blood (Bordia et al., 1997). The inhibition of platelet aggregation by ginger is more than the alike effects studied with garlic and onion (Pancho et al., 1989). One of the most important properties of ginger is that it be capable of averting increased cholesterol levels, following intake of cholesterol-rich diet (Haniadka et al., 2013). The ginger extracts as well as 6- and 8-gingerols have been shown to modulate eicosanoid responses in smooth vascular muscles ex vivo (Suekawa et al., 1986). These analogues were found to inhibit AA-induced serotonin release by human platelets in a dose range similar to the effective dose of aspirin and their aggregation. Importantly, 6-gingerol and 6-shogaol, at the doses of 10–100 μg/kg, not only lowered systemic blood pressure in anesthetized rats but also caused
bradycardia when administered intravenously (Gayur and Gilani, 2005). Several evidences, mostly from experiments performed on rats, have suggested that ginger exerts many direct and indirect effects on blood pressure and heart rate (Afzal et al., 2001) showing a dose-dependent (0.3–3 mg/kg) fall in the arterial blood pressure of anesthetized rats. The Ca\(^{2+}\) channel-blocking activity of gingerols was found to be similar to the effect of verapamil, indicating that it acts at both the membrane-bound and the intracellular Ca\(^{2+}\) channels. Recent study has also confirmed the blood pressure lowering effect of ginger is mediated through blockade of voltage-dependent calcium channels (White, 2007) through a dual inhibitory effect mediated via stimulation of both muscarinic receptors and blockade of Ca\(^{2+}\) channels. This group noted that the different constituents of ginger might have opposing actions on the reactivity of blood vessels. For example, an atropine-resistant and L-NAME (NG-nitro-L-arginine methyl ester)-sensitive vasodilator activity was also noted for the ginger phenolic constituents 6-, 8-, and 10-gingerols, while 6-shogaol showed a mild vasodilator effect (Gayur et al., 2005). Experiments have shown inconclusive and contradictory results in anticoagulating potential of ginger. Lumb (1994) and Bordia et al. (1997) found no effect of ginger on platelet count, bleeding time, platelet aggregation, fibrinolytic activity, or fibrinogen levels. Ginger has been shown to inhibit platelet aggregation (Mahady et al., 2003) and to decrease platelet thromboxane production in vitro (Guh et al., 1995). 8-Gingerol, 8-shogaol, 8-paradol, and gingerol analogues exhibited antiplatelet activities (Nurtjahja-Tjendraputra et al., 2003), but Verma et al. (1993) found ginger to decrease platelet aggregation. Similarly, Janssen et al. (1996) showed no effect of oral ginger on platelet thromboxane B2 production, while Srivastava (1989) found thromboxane levels to be decreased by ginger ingestion in a small study. These studies demand a thorough evaluation of activity with respect to anticoagulant effect.

GASTROINTESTINAL EFFECTS

Peptic ulcer is a major health problem worldwide in both males and females having several factors triggering its effect including food ingredients, stress, \textit{H. pylori}, and drugs. In traditional system of medicine, medicinal plants and its constituents have shown antiulcer effect in various ways, but their exact mechanism is not fully understood (Akhani et al., 2004). Ginger and its constituents show a vital role in ulcer prevention via increasing mucin secretion. Earlier findings have shown antiulcerative effects of ginger in experimental gastric ulcer models (Yamahara et al., 1988). Studies have demonstrated 6-gingerol and 6-shogaol suppressed gastric contraction in situ, with 6-shogaol having more intensive
effect (Suekawa et al., 1986). It was found that acetone, 50% ethanolic extracts (100–500 mg/kg), and ginger juice (2–4 mL/kg) reversed cisplatin-induced delay in gastric emptying in rats when given orally (Sharma and Gupta, 1998). The effect on gastric motility may be partially explained by the antiemetic properties of ginger. Several experiments on the effect of ginger on gastric motility have supported this observation. Ginger is found to stimulate bile secretion, intestinal lipase, trypsin, chymotrypsin, amylase, sucrase, and maltase activities in rats, with 6- and 10-gingerols being chiefly responsible for this activity (Patel and Srinivasan, 2000).

These findings support the traditional use of ginger as a digestive stimulant. Traditionally, ginger is probably best utilized in alleviating symptoms of nausea and vomiting, and several controlled studies have reported that ginger is generally effective as an antiemetic (Quimby, 2007). But its mechanism of action remains uncertain. However, there are several proposed mechanisms. The components in ginger that are responsible for the antiemetic effect are thought to be the gingerols, shogaols, and galanolactone, a diterpenoid of ginger (Mascolo et al., 1989). Animal models and in vitro studies have demonstrated that ginger extract possesses antiserotonergic and 5-HT3 receptor antagonism effects, which play an important role in postoperative nausea and vomiting (Lumb, 1993). The effectiveness of ginger as an antiemetic has been attributed to its carminative effect, which helps to break up and expel intestinal gas. This idea was supported by the results of a randomized, double-blind trial in which healthy volunteers reported ginger effectively accelerated gastric emptying and stimulated antral contractions (Wu et al., 2008). Contrary to this in another randomized, placebo-controlled, crossover trial of 16 healthy volunteers, ginger (1 g orally) had no effect on gastric emptying (Phillips et al., 1993). However, this is also true that nausea and vomiting during pregnancy affects most pregnant women, and over the years, ginger has been used to alleviate the condition (Tripathi et al., 2007). At least one survey indicated that the overall use of dietary supplements in pregnant women appears to be low, but ginger is commonly recommended and used to prevent nausea (Tsui et al., 2001). Several double-blind, randomized, placebo-controlled clinical trials have indicated that ginger consumption is effective and safe in helping to prevent nausea and vomiting during pregnancy (Willetts et al., 2003; Yamahara et al., 1990).

Ginger may also increase the conversion of cholesterol into bile acids by increasing the activity of hepatic cholesterol-7-α-hydroxylase, the rate-limiting enzyme of bile acid biosynthesis (Sambaiah and Srinivasan, 1991). There is evidence that ginger rhizome (root) increases stomach acid production thereby interfering with antacids, sucralfate (Carafate),
H2 antagonists, or proton pump inhibitors. Interestingly (Ravindran and Nirmal, 2005), shogaol, generally being more potent than (6)-gingerol, has shown inhibitory intestinal motility in intravenous preparations and facilitatory gastrointestinal motility in oral preparations. A number of animal studies have demonstrated hypocholesterolemic action of ginger and ginger extracts by decreased lipid peroxidation and increased fibrinolytic activity. These studies have shown decreased levels of total cholesterol, LDL-cholesterol, very low-density-lipoprotein-cholesterol and triglycerides, and increased levels in high-density-lipoprotein-cholesterol (Fuhrman et al., 2000). In a more recent study, air-dried ginger powder (100 mg/kg orally daily) fed to rabbits with experimentally induced atherosclerosis for 75 days, inhibited atherosclerotic changes in the aorta and coronary arteries by about 50% (Verma et al., 1993). It is evident from these findings that ginger has demonstrated potential of being an antiatherosclerotic agent in animal studies, but as yet this promise has not been confirmed in human trials. Experimentally, it has found that ethanolic extract of ginger show antipyretic effect comparable to that of acetylsalicylic acid at the same dose (Akhani et al., 2004). This antipyretic activity may be mediated by COX inhibition. Furthermore, studies have shown that the ginger crude extract and the paracetamol drug have the same level of efficacy in lowering body temperature (Magdale et al., 2014). Further studies on this aspect will be a welcome step.

**EFFECT ON MIGRAINE/RETINOPATHY**

Migraine is considered as a neurological disorder with little convincing evidence of the involvement of some vascular phenomenon. Recent understanding of the mechanisms behind migraine pain generation and perception has considerably helped the development of modern migraine drugs. Evidences of ginger manifesting relief from migraine was shown when ginger powder, at dose of 500–600 mg, was administered for 3–4 days (Mustafa and Srivastava, 1990). Ginger is reported in Ayurvedic and Tibetan systems of medicine to be useful in neurological disorders. It is proposed that administration of ginger may exert abortive and prophylactic effects in migraine headache without any side effects. Considering the role of ginger in diabetes management, effect of ginger on retinopathy, a diabetes associated disease was investigated. It was found that ginger lowers intraocular pressure (IOP) in rabbits’ eyes and could be useful in reducing IOP in humans as well. It has been proposed that ginger could be a useful medication for the prevention of blindness due to diabetes, as IOP increase is the major predisposing factor for the manifestation of glaucoma which is the second major cause of blindness in the world (Saraswat et al., 2009). Report has shown
that an extract of ginger with dose 0.1 and 1.0 mg/mL reduced carboxymethyllysine-keyhole limpet haemocyanin (CML-KLH) and methylglyoxal (MGO)-derived advanced glycation end products (AGE) by 60–80% and glucose-derived AGE products by 50–60% (Akpalaba et al., 2009). Further evidences in this area may lead to ginger as medicine. It will be highly beneficial as ginger is cheap, readily available, and relatively nontoxical.

**METABOLISM OF GINGER**

Very limited information is available on the metabolism or metabolites of ginger. Evaluation of the bioactivity of ginger becomes obligatory for completely understanding its mechanism of action and potential therapeutic effects, as it is widely consumed. For investigating the fate of a metabolite, in blood plasma, method for identification and quantification of the desired molecule is a critical step. Several methods for the simultaneous quantification of [6]-, [8]-, and [10]-gingerols and [6]-shogaol in rat plasma are available in literature. The investigators were able to identify a glucuronide of [6]-gingerol following hydrolysis of β-glucuronidase and the intestinal glucuronidation (Wang et al., 2009a). The study facilitated pharmacokinetics, tissue distribution, and excretion of 6-gingerol, after oral or intraperitoneal administration in rats (Wang et al., 2009b). This type of experiments provides insight into the pharmacokinetic of the molecules, which in turn present the connecting link between traditional medicinal properties and scientific proof of concept. Several studies demonstrating maximum absorption time, site of absorption, and amount absorbed of the target molecule give insight to site of action and its mechanism. For example, several metabolites of [6]-gingerol, following its oral administration (50 mg/kg) in rats, have been identified (Nakazawa and Ohsawa, 2002). A primary metabolite, (S)-[6]-gingerol-4′-O-β-glucuronide, was detected in the bile and several minor metabolites were found in β-glucuronidase-treated urine, suggesting conjugation and oxidation of phenolic side chain of [6]-gingerol (Nakazawa and Ohsawa, 2002). Studies have shown that gingerol is rapidly cleared from rat plasma following intravenous administration (3 mg/kg) and it was reported to be metabolized enzymatically in a stereospecific reduction to gingerdiol (Chan et al., 2012). Studies have also demonstrated that oral intake of ginger extract in rats, having approximately 53% [6]-gingerol, revealed its maximum absorption into the plasma, with a maximal concentration (4.23 μg/mL) being reached after 10 min (Jiang et al., 2008). Also, it was found distributed in various tissues, but gastrointestinal tract had the maximum concentration. Its peak concentrations, in most tissues, were after about 30 min, and the concentration in tissues was higher than that in plasma (Jiang et al., 2008). Based on the
success of several experiments, at least one clinical trial focusing on the pharmacokinetics of [6]-, [8]-, and [10]-gingerols and [6]-shogaol along with their respective conjugate metabolites (Zick et al., 2008), was conducted. In this case, human volunteers were given ginger at doses ranging from 100mg to 2g and blood samples were taken at 15min to 72h after a single oral dose. Results indicated that the free forms of [6]-, [8]-, and [10]-gingerols or [6]-shogaol were not detectable, whereas the respective glucuronide of each compound was detected, suggesting that these ginger components are readily absorbed after oral consumption and can be detected as glucuronide conjugates (Zick et al., 2008). Although progress in determining the active components and metabolites of ginger and understanding their pharmacokinetics has been made, however, more work is required in this direction.

Several in vitro and animal studies and one in vitro study employing human hepatic and intestinal microsomes have investigated the metabolism of the major pungent compound in ginger, 6-gingerol. The pharmacology and therapeutic use of ginger has been the subject of several recent reviews (Grzanna et al., 2005). Studies conducted in vitro have shown gingerols act as agonists of the vanilloid receptor (VR1) (Dedov et al., 2002), which are also activated by capsaicin, the major pungent principle in cayenne and chilli pepper, probably because of being structurally similar to the gingerols. Herbal products are extensively used in many Asian, African, and western countries in the complementary and alternative systems of medicine. According to a survey conducted by the World Health Organization (WHO), 60–80% of the world population relies on nonconventional or alternative medicines, mainly of botanical origin, as their primary form of health care (Chrubasik et al., 2005). However, not all herbal sources are safe. Rapid industrialization, population explosion, ineffective and insufficient pollution control, and indiscriminate use of chemical fertilizers and pest control agents have led to heavy metal contamination in agricultural soils and environment. Plants are being grown in the contaminated soil, most of the time unknowingly; toxic heavy metals from these polluted soil may accumulate in the plant and vegetables grown in them (especially underground part) thereby entering into the human food chain. It is a well-known fact that human health is directly affected by the food they consume and environment they live in. Thus monitoring of toxic heavy metals in the rhizome of ginger becomes important for protecting public health against the hazards of metal toxicity. Reports of heavy metal contaminations from Asia, Africa, and western countries have illustrated the presence of toxic metals in the plant-derived products. The WHO has also emphasized the need for safety assessment and quality assurance of plant products using
modern techniques with suitable standards (World Health Organization, 2000b). Measurement of toxicity and lethal dose level is important before using herbs in health management. Several studies were performed to check the safe dose in animal model study. The dose and toxicity of ginger has been checked and recommended by various earlier investigators. Most of the studies have found that ginger extract was nontoxic in mice in different dosages (100, 333, and 1000 mg/kg) in pregnant rats (Weidner and Sigwart, 2001). Further, no teratogenicity effect of ginger on pregnant rats could be seen but embryo toxicity was detected when 20 or 50 g/L ginger tea via their drinking water was administered (Wilkinson, 2000). A patented ginger extract, when tested for teratogenic potential in pregnant rats (Weidner and Sigwart, 2001), caused neither maternal nor developmental toxicity at daily doses of up to 1 g/kg body weight. However, few earlier studies did find adverse effects of ginger-like involuntary contractions of skeletal muscle, gastrointestinal spasm, hypothermia, diarrhea, and anorexia (Akhani et al., 2004). Norethandrolone and oxandrolone were investigated for their genotoxic effect on human lymphocyte chromosomes using chromosomal aberrations and sister chromatid exchanges as parameters and subsequently Genistein and 6-gingerol were used as antigenotoxic agents to ameliorate the genotoxicity induced by the steroids. Genistein and 6-gingerol proved to be effective in reducing genotoxic damage at appropriate doses (Wilkinson, 2000). Studies have shown that 6-shogaol was much less mutagenic than 6-gingerol (Nakamura and Yamamoto, 1983). Besides, 6-gingerol and to a far lesser extent 6-shogaol were shown to have mutagenic properties in an assay using E. coli Hs30 as an indicator strain of mutagenesis (Nakamura and Yamamoto, 1983). Despite this pronouncement, ginger is not considered a mutagenic substance, apparently due to its long history of harmless use.

It is clear from the above that the current state of knowledge of the pharmacokinetics of ginger compounds in humans is embryonic. Expanding this knowledge and including information about oral bioavailability of compounds with known pharmacological activity should be a priority and ought to precede further clinical trials of ginger for inflammatory conditions.

**FUTURE PROSPECTS**

The use of ginger in human health has been documented since ancient times and they provide a useful source of new therapeutics. Scientific evidences have further confirmed its importance, not only as food, nutraceutical, spice but also as medicine. Now the time has come that time-tested
traditionally employed herbs backed by scientific inputs should take a front seat as herbal nutraceuticals. These will not only alleviate the disease but also avoid it with no aftereffects.

REFERENCES


CHAPTER 25  Medicinal and nutritional qualities of *Zingiber officinale*


Gupta, S., Pandotra, P., Gupta, A.P., Dhar, J.K., Sharma, G., Ram, G., et al., 2010. Volatile (As and Hg) and non-volatile (Pb and Cd) toxic heavy metals analysis in rhizome of Zingiber officinale collected from different locations of North Western Himalayas by atomic absorption spectroscopy. Food Chem. Toxicol. 48, 2966–2971.


