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# Chapter 7 The Amazing and Mighty Ginger

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## 7.1. INTRODUCTION

The use of “natural” or alternative medicines has increased markedly over the last few years. More and more older adults (i.e., baby boomers) are using complementary and alternative medicine dietary supplements and herbal remedies without advice from a physician on the assumption that these substances will have a beneficial effect (Cohen, Ek, and Pan 2002). However, this might not be a safe or advisable practice. For example, at least one recent survey revealed a significant problem with herb-chemotherapeutic drug interactions in cancer patients and, notably, at least half of the herbal remedies taken by these patients lacked research data documenting their potential interactions (Engdal, Klepp, and Nilsen 2009). Regrettably, a great deal of the information regarding the effectiveness and safety of these remedies has been garnered from anecdotal or historical accounts, and much of the information offered is generally misleading and might even be detrimental (Ernst and Schmidt 2002).

Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) is one of the most commonly consumed dietary condiments in the world (Surh et al. 1999). The oleoresin (i.e., oily resin) from the rhizomes (i.e., roots) of ginger contains many bioactive components, such as [6]-gingerol (1-[4′-hydroxy-3′- methoxyphenyl]-5-hydroxy-3-decanone; Figure 7.1), which is the primary pungent ingredient that is believed to exert a variety of remarkable pharmacological and physiological activities. Although ginger is generally considered to be safe (Kaul and Joshi 2001), the lack of a complete understanding of its mechanisms of action suggests caution in its therapeutic use (Wilkinson 2000a). Previous reviews (Barrett, Kiefer, and Rabago 1999; Ness, Sherman, and Pan 1999; Talalay and Talalay 2001) have emphasized the importance of careful scientific research in establishing the safety and efficacy of potential therapeutic plant remedies and in defining the risks and benefits of herbal medicine. Ginger has been used for thousands of years for the treatment of numerous ailments, such as colds, nausea, arthritis, migraines, and hypertension. The medicinal, chemical, and pharmacological properties of ginger have been extensively reviewed (Surh, Lee, and Lee 1998; Ernst and Pittler 2000; Afzal et al. 2001; Bode and Dong 2004; Boone and Shields 2005; Borrelli et al. 2005; Chrubasik and Pittler 2005; Chrubasik, Pittler, and Roufogalis 2005; Grzanna, Lindmark, and Frondoza 2005; Thompson and Potter 2006; Eliopoulos 2007; Shukla and Singh 2007; White 2007; Ali et al. 2008; Nicoll and Henein 2009). Over the last few years, interest in ginger or its various components as valid preventive or therapeutic agents has increased markedly, and scientific studies focusing on verification of ginger’s pharmacological and physiological actions have likewise increased (Ali et al. 2008). The primary purpose of this chapter is to comprehensively examine the available scientific evidence regarding ginger’s proven effectiveness in preventing or treating a variety of pathologic conditions.

## 7.2. HISTORY AND ORIGIN OF GINGER

Ginger is a member of a plant family that includes cardamom and turmeric. 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. The rhizome, which is the horizontal stem from which the roots grow, is the main portion of ginger that is consumed. Ginger’s current name comes from the Middle English *gingivere*, but this spice dates back over 3000 years to the Sanskrit word *srngaveram*, meaning “horn root,” based on its appearance. In Greek, it was called *ziggiberis*, and in Latin, *zinziberi*. Interestingly, ginger does not grow in the wild and its actual

origins are uncertain.

Indians and Chinese are believed to have produced ginger as a tonic root for over 5000 years to treat many ailments, and this plant is now cultivated throughout the humid tropics, with India being the largest producer. Ginger was used as a flavoring agent long before history was formally recorded. It was an exceedingly 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 thirteenth and fourteenth centuries, the value of a pound of ginger was equivalent to the cost of a sheep. By medieval times, it was being imported in preserved form to be used in sweets. Queen Elizabeth I of England is credited with the invention of the gingerbread man, which became a popular Christmas treat.

## 7.3. USAGE, PREPARATION, AND PROCESSING

Ginger is used in numerous forms, including fresh, dried, pickled, preserved, crystallized, candied, and powdered or ground. The flavor is somewhat peppery and slightly sweet, with a strong and spicy aroma. The concentration of essential oils increases as ginger ages and, therefore, the intended use of the rhizome determines the time when it is harvested. If extracting the oil is the main purpose, then ginger can be harvested at 9 months or longer. Ginger is commonly pickled in sweet vinegar, which turns it a pink color; this form is popular with sushi. Ginger harvested at 8-9 months has a tough skin that must be removed before eating, and the root is more pungent and is used dried or pulverized into ground ginger. This is the form most commonly found in our spice racks and used in cookies, cakes, and curry mixes. Candied or crystallized ginger is cooked in sugar syrup and coated with granulated sugar. Ginger harvested at 5 months is not yet mature and has a very thin skin, and the rhizomes are tender with a mild flavor and are best used in fresh or preserved forms.

## 7.4. BIOACTIVE COMPONENTS OF GINGER

At least 115 constituents in fresh and dried ginger varieties have been identified by a variety of analytical processes. Gingerols are the major constituents of fresh ginger and are found slightly reduced in dry ginger, whereas the concentrations of shogaols, which are the major gingerol dehydration products, are more abundant (Jolad et al. 2005) in dry ginger than in fresh ginger. At least 31 gingerol-related compounds have been identified from the methanolic crude extracts of fresh ginger rhizome (Jiang, Solyom et al. 2005). 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-methoxyhepthan-3-one, and methoxy-[10]-gingerol (Koh et al. 2009). The proportion of each individual component in a sample of ginger depends on country of origin, commercial processor, and whether the ginger is fresh, dried, or processed (Schwertner, Rios, and Pascoe 2006). Of the bioactive pungent components of Jamaican ginger, including [6]-, [8]-, and [10]-gingerols and [6]-shogaol, [6]-gingerol appears to be the most abundant pungent bioactive compound in most of the oleoresin samples studied (Bailey-Shaw et al. 2008). Although phylogenetic analysis has showed that all ginger samples from widely different geographical origins are genetically indistinguishable, metabolic profiling showed some quantitative differences in the contents of [6]-, [8]-, and [10]-gingerols (Jiang et al. 2006). An examination of the concentrations of [6]-, [8]-, and [10]-gingerols and [6]-shogaol in 10 different ginger-root dietary supplements purchased randomly from a variety of pharmacies and health food stores yielded some disconcerting results (Schwertner, Rios, and Pascoe 2006). Perhaps not surprisingly, the content of these active components was found to vary extensively from none or very minute amounts to several milligrams per gram. In addition, the suggested serving size ranged from about 250 mg to 4.8 g/day (Schwertner, Rios, and Pascoe 2006). The basis for the wide range of dosing is not clear. These studies suggest that ginger contains a variety of bioactive compounds and standardization of contents is critically lacking.

## 7.5. METABOLISM OF GINGER

Although ginger is one of the most widely consumed spices in the world, not a great deal is known regarding its metabolism or metabolites. Evaluating the bioactivity of ginger is necessary for completely understanding its mechanism of action and potential therapeutic effects. Although many food-derived supplements are consumed today with little knowledge of their activity or safety, more attention is beginning to be given to addressing these issues. The most well-studied bioactive component of ginger is probably [6]-gingerol (Surh et al. 1999). The careful isolation of several metabolites of [6]-gingerol following its oral administration (50 mg/kg) to rats was reported (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 that [6]-gingerol undergoes conjugation and oxidation of its phenolic side chain (Nakazawa and Ohsawa 2002). Gingerol is rapidly cleared from rat plasma following intravenous administration (3 mg/kg; Ding et al. 1991), and it was reported to be metabolized enzymatically in a stereospecific reduction to gingerdiol (Surh and Lee 1994).

A method has been developed for the simultaneous quantification of [6]-, [8]-, and [10]-gingerol and [6]-shogaol in rat plasma in pharmacokinetic studies after oral administration of ginger oleoresin (Wang et al. 2009b). The investigators were able to identify a glucuronide of [6]-gingerol after hydrolysis of β-glucuronidase, and the intestinal glucuronidation was further confirmed by comparing plasma samples of hepatic portal vein and femoral vein (Wang et al. 2009b). This method was also used to obtain pharmacokinetics, tissue distribution, and excretion studies of 6-gingerol after oral or intraperitoneal administration in rats (Wang et al. 2009a). In a study in which a ginger extract (approximately 53% [6]-gingerol) was administered to rats by oral ingestion, [6]-gingerol was absorbed rapidly into the plasma, with a maximal concentration (4.23 μg/mL) being reached after 10 minutes (Jiang, Wang, and Mi 2008). The [6]-gingerol was distributed to various tissues and the most concentration was found in the gastrointestinal tract. Peak concentrations of [6]-gingerol were reached in most tissues at about 30 minutes, and the concentration in tissues was higher than that in plasma (Jiang, Wang, and Mi 2008).

At least one clinical trial focused on the pharmacokinetics of [6]-, [8]-, and [10]-gingerols and [6]-shogaol along with their respective conjugate metabolites (Zick et al. 2008). In this case, human volunteers were given ginger at doses ranging from 100 mg to 2 g and blood samples were taken at 15 minutes to 72 hours 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, more work is clearly needed.

## 7.6. HEALTH EFFECTS: THE SCIENTIFIC EVIDENCE

Because ginger and its metabolites appear to accumulate in the gastrointestinal tract, the consistent observations of ginger exerting many of its effects in this area are not surprising. Ginger has been purported to exert a variety of powerful therapeutic and preventive effects and has been used for thousands of years for the treatment of hundreds of ailments from colds to cancer. Like many medicinal herbs, much of the information has been handed down by word of mouth with little controlled 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. In Sections 7.6.1 through 7.6.5, the evidence for the effectiveness of ginger as an antioxidant, anti-inflammatory agent, antinausea compound, and anticancer agent as well as the protective effect of ginger against other disease conditions are reviewed (Figure 7.2).

### 7.6.1. General Antioxidant Properties of Ginger

The presence of oxidative stress is associated with numerous diseases and a common mechanism often put forth to explain the actions and health benefits of ginger is associated with its antioxidant properties (Aeschbach et al. 1994; Ahmad, Katiyar, and Mukhtar 2001). Ginger was reported to decrease age-related oxidative stress markers (Topic et al. 2002) and was suggested to guard against ethanol-induced hepatotoxicity by suppressing oxidative consequences in rats treated with ethanol (Mallikarjuna et al. 2008). Ginger root contains a very high level (3.85 mmol/100 g) of total antioxidants, surpassed only by pomegranate and some types of berries (Halvorsen et al. 2002). The phorbol ester, 12-*O*-tetradecanoylphorbol-13-acetate (TPA), promotes oxidative stress by activating the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system or the xanthine oxidase system or both. Ginger was reported to suppress TPA-induced oxidative stress in human promyelocytic leukemia (HL)-60 cells and Chinese hamster ovary AS52 cells (Kim et al. 2002). Others have shown that ginger compounds effectively inhibit superoxide production (Krishnakantha and Lokesh 1993). Several reports indicate that ginger suppresses lipid peroxidation and protects the levels of reduced glutathione (GSH; Reddy and Lokesh 1992; Ahmed, Seth, and Banerjee 2000; Ahmed, Seth, Pasha, and Banerjee 2000; Shobana and Naidu 2000; Ahmed et al. 2008; El-Sharaky et al. 2009).

Reactive nitrogen species, such as nitric oxide (NO), influence signal transduction and cause DNA damage, which contributes to disease processes. Nitric oxide is produced by inducible nitric oxide synthase (iNOS), which is stimulated in response to various stresses. [6]-gingerol was reported to dose-dependently inhibit NO production and reduce iNOS in lipopolysaccharide (LPS)-stimulated mouse macrophages (Ippoushi et al. 2003). [6]-gingerol also effectively suppressed peroxynitritemediated oxidative damage (Ippoushi et al. 2003). Ippoushi et al. (2003) later proposed that [6]-gingerol and peroxynitrite form a symmetric dimer with [6]-gingerol covalently linked at the aromatic ring of peroxynitrite, attenuating peroxynitrite-induced oxidation and nitration reactions (Ippoushi et al. 2005). [6]-shogaol, 1-dehydro-[10]-gingerdione, and [10]-gingerdione also decreased LPS-induced NO production, and [6]-shogaol and 1-dehydro-[10]-gingerdione were reported to effectively reduce iNOS expression (Koh et al. 2009). In the bromobenzene (BB)-induced hepatotoxicity model, orally given ginger extract (100 mg/kg body weight [BW]) normalized NO levels and total and reduced glutathione levels, and also decreased the level of lipid peroxidation (El-Sharaky et al. 2009). Ginger consumption has also been reported to decrease lipid peroxidation and normalize the activities of superoxide dismutase and catalase, as well as GSH and glutathione peroxidase, glutathione reductase, and glutathione-S-transferase, in rats (Ahmed et al. 2008). Ginger supplementation before ischemia/reperfusion resulted in a higher total antioxidant capacity (i.e., normalized glutathione peroxidase and superoxide dismutase activities) and lower total oxidant (lower tissue malondialdehyde, NO, and protein carbonyl contents) status levels compared to an untreated group of Wistar albino rats (Uz et al. 2009). Overall, the rats fed ginger (5%) experienced less kidney damage due to oxidative stress induced by ischemia/reperfusion (Uz et al. 2009).

Ginger extract has been reported to exert radioprotective effects in mice exposed to gamma radiation (Jagetia et al. 2003), and the effect was associated with decreased lipid peroxidation and protection of GSH levels (Jagetia, Baliga, and Venkatesh 2004). [6]-gingerol pretreatment also decreased oxidative stress induced by ultraviolet B (UVB) and activated caspase-3, -8, -9, and Fas expression (Kim et al. 2007). Evidence does seem to suggest that ginger and some of its components are effective antioxidants in vitro. However, whether the physiological activity occurs in humans in vivo is not clear, and the specific mechanism and cellular targets are still to be determined.

### 7.6.2. Anti-Inflammatory Effects of Glnger

One of the many health claims attributed to ginger is its purported ability to decrease inflammation, swelling, and pain. [6]-gingerol (Young et al. 2005), a dried ginger extract, and a dried gingerol-enriched extract (Minghetti et al. 2007) were each reported to exhibit analgesic and potent anti-inflammatory effects. Earlier animal studies suggest

that rat hind limbs perfused with [6]-gingerol showed increased heat production that was associated with increased oxygen consumption and lactate efflux (Eldershaw et al. 1992). The thermogenesis was at least partly associated with vasoconstriction independent of adrenergic receptors or secondary catecholamine release. In contrast, larger doses of ginger components inhibited oxygen consumption, which was attributed to disruption of mitochondrial function (Eldershaw et al. 1992). These results were supported in a later study in which rats that were given a single intraperitoneal injection of [6]-gingerol (2.5 or 25 mg/kg) exhibited a rapid, marked drop in body temperature and a significant decrease in metabolic rate (Ueki et al. 2008).

Data suggest that ginger may exhibit anti-inflammatory effects through the modulation of calcium levels mediated through transient receptor potential vanilloid subtype 1 (TRPV1), which is a heat-and pain-sensitive receptor that can interact with [6]-gingerol (Dedov et al. 2002). [6]-gingerol has been reported to induce a substantial rise in intracellular calcium levels in Madin-Darby canine kidney renal tubular cells by stimulating both extracellular calcium influx and thapsigargin (an endoplasmic reticulum $Ca^{2+}$ pump inhibitor)-sensitive intracellular calcium release (Chen et al. 2008). The gingerols are known to be TRPV1 agonists (Dedov et al. 2002), and the [6,8,10]-gingerols and [6,8,10]-shogaols can increase the intracellular calcium concentration in TRPV1-expressing HEK293 cells through TRPV1 (Iwasaki et al. 2006). Shogaols appear to be more potent than the gingerols, and most of the compounds cause aversive or nociceptive responses mediated by TRPV1 when applied to the eye or following subcutaneous injection to the hind paw, respectively (Iwasaki et al. 2006). In this case, most of the ginger compounds also promoted adrenal catecholamine secretion, which influences energy consumption (Iwasaki et al. 2006).

Ginger has been suggested to be effective against inflammation, osteoarthritis, and rheumatism (Reginster et al. 2000). However, inconsistencies in clinical studies have led to debate regarding the effectiveness and safety of ginger for treatment of arthritis (Marcus and Suarez-Almazor 2001). An earlier study showed that ginger oil (33 mg/kg), administered orally to rats for 26 days, caused a significant repression of paw and joint swelling associated with severe chronic adjuvant arthritis (Sharma, Srivastava, and Gan 1994). More recently, the effectiveness of a crude ginger extract was compared with a fraction containing only gingerols and derivatives to inhibit joint swelling in the streptococcal cell wall-induced arthritis animal model of rheumatoid arthritis (Funk et al. 2009). Results indicated that although both extracts could prevent joint inflammation, the crude dichloromethane extract, which also contained essential oils and more polar compounds, was more effective (when normalized to gingerol content) in preventing both joint inflammation and destruction (Funk et al. 2009). In humans, one study showed no difference between placebo and ginger in patients with osteoarthritis of the hip or knee (Bliddal et al. 2000). In contrast, patients suffering from osteoarthritis of the knee showed a consistently greater response to treatment with ginger extract compared with the control group (Altman and Marcussen 2001). In addition, relief from pain and swelling was reported in patients suffering from rheumatoid arthritis, osteoarthritis, or general muscular discomfort when using powdered ginger as a dietary supplement for 3 months to 2 years (Srivastava and Mustafa 1992). Besides pain relief from arthritis, results of a double-blind comparative clinical trial indicated that ginger (250-mg capsules) was as effective as the nonsteroidal anti-inflammatory drugs mefenamic acid (250 mg) and ibuprofen (400 mg) in relieving pain in women with primary dysmenorrhea (Ozgoli, Goli, and Moattar 2009). In contrast, consumption of 2 g of ginger before 30 minutes of cycling exercise (60% $VO_2$) had no effect on quadriceps muscle pain, rating of perceived exertion, work rate, heart rate, or oxygen uptake (Black and Oconnor 2008).

Researchers have hypothesized that the anti-inflammatory effects of ginger might be related to its ability to inhibit prostaglandin and leukotriene biosynthesis (Srivastava and Mustafa 1992). Some others have showed that gingerols actively inhibit arachidonate 5-lipoxygenase, an enzyme of leukotriene biosynthesis (Kiuchi et al. 1992). [8]-gingerol, but not [6]-gingerol, was shown to inhibit cyclooxygenase-2 (COX-2) expression, which is induced during inflammation to increase formation of prostaglandins (Tjendraputra et al. 2001). Others have also reported that

ginger extract suppresses the activation of tumor necrosis factor α (TNF-α) and expression of COX-2 in human synoviocytes (Frondoza et al. 2004). Proinflammatory cytokines such as TNF-α, interleukin (IL)-1β, and IL-12, which are produced primarily by macrophages, play an important role in sepsis, ischemia/reperfusion injury, and transplant rejection. [6]-gingerol was reported to inhibit the production of proinflammatory cytokines from LPS-stimulated peritoneal macrophages, but to have no effect on the function of antigen presenting cells (APC) or the LPS-induced expression of proinflammatory chemokines (Tripathi et al. 2007). However, this same group later reported that a ginger extract attenuated the production of IL-12, TNF-α, and IL-1β proinflammatory cytokines and RANTES (regulated upon activation, normal T cell expressed and secreted) and monocyte chemoattractant protein 1 (MCP-1) proinflammatory chemokines in LPS-stimulated murine peritoneal macrophages (Tripathi, Bruch, and Kittur 2008). In general, ginger extract inhibited macrophage activation and APC function, and indirectly suppressed T-cell activation (Tripathi, Bruch, and Kittur 2008). Other stable [6]-gingerol metabolites or analogs were reported to suppress LPS-induced NO production in murine macrophages mainly by reducing *inos* gene and iNOS protein production (Aktan et al. 2006). Some of ginger's anti-inflammatory effects appear to be associated with decreased IκBα degradation and impaired nuclear factor κB (NF-κB) nuclear translocation of p65 (Aktan et al. 2006; Lee et al. 2009). The majority of scientific evidence does seem to suggest that ginger and its various components have anti-inflammatory effects both in vitro and ex vivo. However, the data supporting ginger as an effective anti-inflammatory agent in humans in vivo are still contradictory and incomplete.

### 7.6.3. Ginger as an Antinausea Agent

The most common and well-established use of ginger throughout history is probably its utilization in alleviating symptoms of nausea and vomiting. The benefits and dangers of herbal treatment of liver and gastrointestinal distress have been reviewed (Langmead and Rampton 2001), and several controlled studies have reported that ginger is generally effective as an antiemetic (Aikins Murphy 1998; Ernst and Pittler 2000; Jewell and Young 2000, 2002, 2003; Langmead and Rampton 2001; Dupuis and Nathan 2003; Boone and Shields 2005; Borrelli et al. 2005; Bryer 2005; Mahesh, Perumal, and Pandi 2005; Chaiyakunapruk et al. 2006; Thompson and Potter 2006; Quimby 2007). 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 that ginger effectively accelerated gastric emptying and stimulated antral contractions (Wu et al. 2008). Previously, [6]-gingesulfonic acid, isolated from ginger root, was showed to be effective against HCl/ethanol-induced gastric lesions in rats (Yoshikawa et al. 1992). This compound showed weaker pungency but more potent antiulcer activity than [6]-gingerol or [6]-shogaol (Yoshikawa et al. 1994).

Ginger root is commonly recommended for preventing seasickness (Schmid et al. 1994) and is found to be superior to dimenhydrinate (Dramamine) or placebo against symptoms of motion sickness (Mowrey and Clayson 1982). A follow-up study also indicated that 1 g of ginger might be effective in reducing the subjective severity of seasickness in naval cadets on the high seas (Grontved et al. 1988). On the other hand, additional research studies showed no benefits of using ginger for treating motion sickness (Wood et al. 1988; Stewart et al. 1991), and at least one group reported that patients receiving ginger extract for treating osteoarthritis experienced more, although mild, gastrointestinal adverse events compared to a placebo-treated group (Altman and Marcussen 2001). The exact antiemetic mechanism of ginger is not clear, although some evidence suggests that it inhibits serotonin receptors and exerts its antiemetic effects directly on the gastrointestinal system and in the central nervous system (DerMarderosian and Beutler 2006). Although the antiemetic effects of ginger are the most well-studied effects of this condiment and have been reviewed extensively, the effectiveness and safety of ginger for treating nausea and vomiting have been questioned in the past because the findings reported were often contradictory (Wilkinson 2000b). At the same time, ginger continues to be recommended for alleviating nausea and vomiting associated with pregnancy, chemotherapy, and certain surgical procedures.

Nausea and vomiting during pregnancy affects most pregnant women, and over the years ginger has been used to try to alleviate the condition (Aikins Murphy 1998; Jewell and Young 2000, 2002, 2003; Fugh-Berman and Kronenberg 2003; Boone and Shields 2005; Borrelli et al. 2005; Bryer 2005; Chrubasik, Pittler, and Roufogalis 2005; White 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, Dennehy, and Tsourounis 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 (Portnoi et al. 2003; Willetts, Ekangaki, and Eden 2003). Randomized trials suggest that although ginger might not be as potent as some treatments (Jewell and Young 2000), its consumption for treating nausea or vomiting or both in early pregnancy has very few or no adverse side effects and seems to be effective (Niebyl 1992; Jackson 2001; Vutyavanich, Kraisarin, and Ruangsri 2001; Jewell and Young 2002; Niebyl and Goodwin 2002). In fact, ginger has been reported to be as effective as dimenhydrinate (i.e., Dramamine) in treating nausea and vomiting in pregnancy with fewer side effects (Pongrojpaw, Somprasit, and Chanthasenanont 2007). Women who received ginger (250-mg capsules) appeared to experience less vomiting and nausea compared to those receiving placebo (Ozgoli, Goli, and Simbar 2009), and ginger also relieved pain from primary dysmenorrhea (Ozgoli, Goli, and Simbar 2009). The effectiveness of ginger has been compared with that of vitamin B6 (another recommended therapy) in randomized, double-blind, controlled trials. Results indicated that ginger and vitamin B6 therapy were equally effective in reducing nausea and the number of vomiting episodes during pregnancy (Sripramote and Lekhyananda 2003; Smith et al. 2004). In a later randomized, double-blind, controlled trial, pregnant women were randomly divided to receive either 650 mg of ginger or 25 mg of vitamin B6 (3xd/4 days). In this case, ginger actually appeared to be more effective than vitamin B6, with only minor side effects (Chittumma, Kaewkiattikun, and Wiriyasiriwach 2007). These results were supported in an additional trial in which pregnant women with nausea were randomized into groups to receive either 1 g of ginger/day or 40 mg of vitamin B6/day for 4 days. Results of this trial indicated that compared with a baseline, nausea and vomiting in the ginger group were significantly less than those reported by the vitamin B6 group (Ensiyeh and Sakineh 2009). A systematic review of the results of other double-blind, randomized, controlled trials, uncontrolled trials, case reports, and observational studies indicated that ginger is superior to placebo and as effective as vitamin B6 in relieving the severity of nausea and vomiting, with no reported side effects or adverse effects on pregnancy (Borrelli et al. 2005). A similar review of the literature regarding the safety and efficacy of ginger in the management of nausea and vomiting during pregnancy revealed that ginger appears to be a relatively low-risk and effective treatment for these symptoms (Boone and Shields 2005). Importantly, no differences in birth weight, gestational age, or frequencies of congenital abnormalities have been observed between ginger-treated and untreated mothers (Willetts, Ekangaki, and Eden 2003). A survey of a group of obstetricians and gynecologists revealed that most of them would recommend taking an antiemetic (71.3%), and specifically ginger (51.8%), to patients suffering from moderate to severe nausea (Power, Holzman, and Schulkin 2001).

Ginger has been recommended to combat nausea associated with chemotherapy (Sharma and Gupta 1998; Grant and Lutz 2000). Gingerol was reported to reduce cisplatin (a platinum-based chemotherapy drug)-induced emesis in a vomiting model of mink possibly by inhibiting the central or peripheral increase of 5-hydroxytryptamine, dopamine, and substance P (Qian et al. 2009). In contrast, addition of ginger root powder (1 g/day) to a standard antiemetic regimen with metoclopramide had no advantage in reducing nausea or vomiting in acute or delayed phases of cisplatin-induced emesis in gynecologic cancer patients (Manusirivithaya et al. 2004). Cisplatin can cause renal oxidative and nitrosative stress and dysfunction. However, rats that were administered cisplatin and [6]-gingerol exhibited lower lipid peroxidation and conservation of GSH coupled with enhanced superoxide dismutase and catalase, which resulted in a restoration of normal renal function (Kuhad et al. 2006). Complementary intervention with ginger has also been suggested to have possible benefits in preventing acute chemotherapy-induced nausea and vomiting (CINV) in children (Dupuis and Nathan 2003). However, the results of a randomized, double-blind,

placebo-controlled trial indicated that ginger did not provide any additional benefit in reducing CINV when given with a 5-hydroxytryptamine 3 (HT3) receptor antagonist and/or aprepitant (a substance P antagonist; Zick et al. 2009). Notably, compared with a normal diet, high-protein meals with ginger consumed twice daily were reported to reduce the delayed nausea of chemotherapy and decrease the use of antiemetic medications (Levine et al. 2008).

Ginger was suggested to be an effective postoperative prophylactic antiemetic (Phillips, Ruggier, and Hutchinson 1993) that is not associated with effects on gastric emptying (Phillips, Ruggier, and Hutchinson 1993). However, the effectiveness of ginger in preventing postoperative nausea and vomiting has been disputed (Visalyaputra et al. 1998). One study indicated that pretreatment with ginger extracts reversed experimentally induced delay in gastric emptying in rats (Gupta and Sharma 2001), and ginger was also reported to reduce food transit time in experimental rats, an effect that might have implications in the prevention of colon cancer or constipation (Platel and Srinivasan 2001). The digestive stimulatory effects of ginger and other spices might be associated with positive effects on trypsin and pancreatic lipase (Platel and Srinivasan 2000) and ginger's ability to increase gastric motility (Micklefield et al. 1999).

Several groups have studied the effectiveness of ginger in preventing nausea associated with gynecological laparoscopy. Patients who took ginger (1 g) appeared to experience less nausea incidence, especially within 2-4 hours of the procedure, and some reported less vomiting also (Pongrojpaw and Chiamchanya 2003). These results were supported by a later study involving 60 patients who received either 3 g of ginger or placebo 1 hour before the procedure. Although nausea was less in the ginger group at 2 hours postprocedure, vomiting did not vary between the two groups (Apariman, Ratchanon, and Wiriyasirivej 2006). However, at 6 hours, patients who had received ginger reported significantly less nausea and vomiting than the placebo group (Apariman, Ratchanon, and Wiriyasirivej 2006). Results of another similar trial indicated that ginger (1 g) taken 1 hour before major gynecologic surgery decreased nausea and vomiting at 2 and 6 hours postsurgery compared to placebo, and had no adverse side effects (Nanthakomon and Pongrojpaw 2006). In contrast, at least one trial indicated that ginger was not effective in reducing the incidence of postoperative nausea and vomiting in patients undergoing gynecologic laparoscopy (Eberhart et al. 2003). Finally, a systematic review and meta-analysis of randomized, controlled trials comparing ginger with placebo in preventing postoperative nausea and vomiting revealed that a fixed dose of at least 1 g of ginger appears to be more effective than placebo (Chaiyakunapruk et al. 2006). Overall, these results suggest that ginger is probably fairly effective in alleviating nausea and vomiting associated with a variety of conditions. Although the mechanism is not clear, ginger appears to have no adverse side effects and never seems to worsen nausea and vomiting.

### 7.6.4. Anticarcinogenic Activities of Ginger

A great deal of interest by numerous research groups, including our own, is now being focused on the cancer-preventive and potential cancer therapeutic applications of ginger and its various components. Several aspects of the chemopreventive effects of numerous phytochemical dietary and medicinal substances, including ginger, have been reviewed previously (Surh, Lee, and Lee 1998; Surh 1999, 2002; Bode and Dong 2004; Shukla and Singh 2007; Aggarwal et al. 2008). Studies focused on the anticancer activities of various forms of ginger from a crude or partially purified extract to gingerols, especially [6]-gingerol; shogaols, especially [6]-shogaol; and zerumbone, a sesquiterpene compound derived from ginger and a number of minor components and metabolites. The effectiveness of ginger in preventing or suppressing cancer growth has been examined in a variety of cancer types, including lymphoma, hepatoma, colorectal cancer, breast cancer, skin cancer, liver cancer, and bladder cancer. The mechanisms proposed to explain the anticancer activities of ginger and its components include antioxidant activity and the ability to induce apoptosis, decrease proliferation, cause cell-cycle arrest, and suppress activator protein 1 (AP-1) and NF-κB/COX-2 signaling pathways (Figure 7.3).

The anticancer activities of [6]-gingerol and zerumbone have been associated with their antioxidant activities. Several ginger components were reported to have effective anticancer promoter activity based on their ability to inhibit TPA-induced Epstein-Barr virus early antigen (EBV-EA) in Raji cells (Vimala, Norhanom, and Yadav 1999; Kapadia et al. 2002). [6]-gingerol was reported to suppress the reactive oxygen species-potentiated invasive capacity of ascites hepatoma AH109A cells by reducing peroxide levels (Yagihashi, Miura, and Yagasaki 2008). In normal RL34 rat liver epithelial cells, zerumbone was found to induce glutathione S-transferase and the nuclear localization of the transcription factor Nrf2, which binds to the antioxidant response element (ARE) of phase II enzyme genes (Nakamura et al. 2004). Zerumbone potentiated the expression of several Nrf2/ARE-dependent phase II enzyme genes, including Y-glutamyl-cysteine synthetase, glutathione peroxidase, and hemeoxygenase-1 (Nakamura et al. 2004). Others have reported that zerumbone decreases TPA-induced hydrogen peroxide formation and edema corresponding to enhanced levels of various antioxidant enzymes (Murakami et al. 2004). These types of changes have been linked with lower 7,12-dimethylbenz[a]anthracene (DMBA)-initiated/TPA-promoted tumor incidence, number of tumors per mouse, and tumor volume (Murakami et al. 2004).

Zerumbone has also been reported to downregulate CXC chemokine receptor 4 (CXCR4), which is highly expressed in various tumors, including breast, ovary, prostate, gastrointestinal, head and neck, bladder, brain, and melanoma tumors (Sung et al. 2008). Because the CXCR4 mediates homing of tumor cells to specific organs that express its ligand, CXCL12, zerumbone was suggested as a potential suppressor of cancer metastasis and was effective in suppressing CXCR4 in a variety of cancers, including those of the pancreas, lung, kidney, and skin (Sung et al. 2008). Furthermore, zerumbone effectively attenuated osteoclast formation induced by human breast tumor cells and by multiple myeloma and decreased osteolysis dose-dependently in MDA-MB-231 breast cancer tumor-bearing athymic nude mice, suggesting that it might be effective in preventing cancer-associated bone loss or osteoporosis (Sung et al. 2009). [6]-gingerol has also been reported to suppress adhesion, invasion, motility, matrix metalloproteinase (MMP)-2, and MMP-9 messenger ribonu-cleic acid (mRNA) expression and protein activities in MDA-MB-231 human breast cancer cell lines (Lee, Seo, Kang, and Kim 2008).

Ginger and its constituents have been reported to inhibit tumor promotion in mouse skin (Katiyar, Agarwal, and Mukhtar 1996). In particular, [6]-gingerol has been reported to be highly effective as an anticancer agent in skin in vivo in the two-stage initiation-promotion mouse skin model. In this model, tumors are initiated by a one time application of DMBA followed by repeated topical applications of TPA beginning a few days later. Topical application of [6]-gingerol on the shaved backs of female ICR mice decreased the incidence of DMBA-initiated/TPA-promoted skin papilloma formation and also suppressed TPA-induced epidermal ornithine decarboxylase activity and inflammation (Park et al. 1998). Results of a similar study indicated that in the DMBA/TPA skin tumor model, topical application of [6]-paradol or [6]-dehydroparadol prior to the application of TPA significantly decreased both the number of tumors per mouse and the number of mice exhibiting tumors (Chung et al. 2001).

Earlier studies suggest that gingerol is an effective inhibitor of azoxymethane-induced intestinal carcinogenesis in rats (Yoshimi et al. 1992). Ginger supplementation (50 mg/kg BW) was reported to suppress the number of tumors as well as the incidence of 1, 2-dimethylhydrazine (DMH)-induced colon cancer (Manju and Nalini 2005). The effect was attributed to decreased oxidative damage associated with enhanced catalase, superoxide dismutase, glutathione peroxidase, and glutathione transferase activities as well as increased GSH (Manju and Nalini 2005). This group later reported that administration of ginger to DMH-treated rats significantly decreased the incidence and number of tumors as well as the activity of microbial enzymes, β-glucuronidase, and mucinase (Manju and Nalini 2006). Finally, Wistar rats that were fed a ginger extract (1% mixed in diet) exhibited significantly lower multiplicity of urothelial lesions (hyperplasia and neoplasia) than untreated groups (Ihlaseh et al. 2006).

Studies suggest that ginger compounds suppress proliferation of human cancer cells through the induction of

apoptosis (Lee et al. 1998; Lee and Surh 1998; Thatte, Bagadey, and Dahanukar 2000). A saline extract prepared from ginger extract suppressed the proliferation of HEp-2 cells by inducing cytotoxic effects and DNA fragmentation (Vijaya Padma, Arul Diana Christie, and Ramkuma 2007). Ginger extract and especially [6]-gingerol were reported to effectively decrease proliferation of YYT colon cancer cells and the angiogenic potential of endothelial cell tubule formation in immortalized MS1 endothelial cells (Brown et al. 2009). [10]-gingerol was reported to cause a significant and prolonged increase in intracellular calcium and cytotoxicity in human colorectal cancer SW480 cells (Chen, Li, and Kuo 2009). [6]-gingerol was reported to inhibit both proliferation and invasion of ascites hepatoma AH109A cells and appeared to act by causing an S-phase arrest, elongated doubling time of hepatoma cells, and an increased rate of apoptosis (Yagihashi, Miura, and Yagasaki 2008). This compound also induced cell-cycle arrest and suppressed the growth of human pancreatic cancer cell lines, human pancreatic adenocarcinoma (HPAC) cells, which express wild-type p53 and BxPC-3 cells that express a mutant p53 protein (Park et al. 2006). Interestingly, [6]-gingerol appeared to be most effective in inducing apoptosis in p53-mutant cells and induced arrest, but not apoptosis, in p53-expressing cells (Park et al. 2006). [6]-gingerol was further reported to suppress proliferation and induce apoptosis or G1 cell-cycle arrest in several colorectal cell lines, including HCT116, SW480, HT29, LoVo, and Caco2 cells (Lee, Cekanova, and Baek 2008). These effects were associated with a decreased abundance of cyclin D1 (a proto-oncoprotein that is overexpressed in cancer) and increased expression of a nonsteroidal anti-inflammatory drug (NSAID)-activated gene (NAG-1), a proapoptotic and antitumorigenic protein (Lee, Cekanova, and Baek 2008).

Through the comparison of promotion-sensitive ($P^+$) and promotion-resistant ($P^-$) derivatives of the mouse epidermal JB6 cell lines, AP-1 was reported to have a critical role in tumor promotion (Huang, Ma, Bowden, and Dong 1996; Huang, Ma, and Dong 1996). In addition, blocking the tumor promoter–induced activation of AP-1 inhibited neoplastic transformation (Dong et al. 1994). Epidermal growth factor (EGF) is known to induce a relatively high level of AP-1 activity and cell transformation (Huang, Ma, and Dong 1996). We previously investigated the effect of two structurally related compounds of the ginger family, [6]-gingerol and [6]-paradol, on EGF-induced cell transformation and AP-1 activation (Bode et al. 2001). Our results provided the first evidence that both compounds block EGF-induced cell transformation, but by different mechanisms. [6]-gingerol appeared to act by directly inhibiting AP-1 DNA binding activity and transactivation, whereas [6]-paradol appeared to act by inducing apoptosis (Bode et al. 2001). Others report that [6]-gingerol causes DNA fragmentation and suppresses Bcl-2 expression in promyelocytic leukemia HL-60 cells (Wang et al. 2003), and also induces growth inhibition and caspase-mediated apoptosis in human epidermoid carcinoma A431 cells (Nigam et al. 2009). [6]-paradol and other structurally related derivatives, such as [10]-paradol, [3]-dehydroparadol, [6]-dehydroparadol, and [10]-dehydroparadol, inhibited proliferation of KB oral squamous carcinoma cells in a time-and dose-dependent manner (Keum et al. 2002). [6]-dehydroparadol (75 μM) was more potent than the other compounds tested, and it induced apoptosis through a caspase-3-dependent mechanism (Keum et al. 2002).

[6]-shogaol [1-(4-hydroxy-3-methoxyphenyl)-4-decen-3-one], an alkanone from ginger, exhibited the most potent cytotoxicity against human A549, SK-OV-3, SK-MEL-2, and HCT15 tumor cells, compared to [4]-, [6]-, [8]-, and [10]-gingerols (Kim et al. 2008). This compound also inhibited proliferation of several transgenic mouse ovarian cancer cell lines, including C1 and C2 (Kim et al. 2008). Further, [6]-shogaol was reported to inhibit the growth of and induce apoptosis in COLO 205 cells (Pan et al. 2008). Treatment with [6]-shogaol, but not [6]-gingerol, induced DNA fragmentation in COLO 205 colon cancer cells. Apoptosis was mediated by activation of caspase-9, -3, and -8, resulting in the release of mitochondrial cytochrome *c*, upregulation of proapoptotic Bax, and downregulation of antiapoptotic Bcl2, and the induction of growth arrest and DNA damage (GADD)-inducible transcription factor 153 (GADD153) mRNA and protein (Pan et al. 2008). [6]-shogaol induced apoptosis of hepatoma cells mediated by activation of caspase-3 and -7 (Chen et al. 2007). The compound was also reported to reduce the viability of gastric cancer cells by directly damaging microtubules and inducing mitotic arrest (Ishiguro et al. 2007).

NF-κB is a rapidly induced stress-responsive transcription factor that functions to intensify the transcription of a variety of genes, including cytokines, growth factors, and acute response proteins (Baldwin 1996). Its activation is also linked to mitogen-activated protein (MAP) kinase signaling pathways (Schulze-Osthoff et al. 1997). The mechanism for NF-κB activation is well known. In its inactive form, NF-κB is found in the cytosol bound to an inhibitory protein called inhibitory kappa B (IκB). When stimulated, IκB is phosphorylated by an IκB kinase, which releases it from NF-κB and is subsequently degraded. Following its separation from IκB, NF-κB is translocated into the nucleus, where it activates gene transcription by binding to its specific DNA sequence found in certain genes. Importantly, NF-κB activation is associated with initiation or acceleration of tumorigenesis (Gilmore 1997), and in JB6 cells, inhibition of NF-κB also blocks tumor promoter-induced cell transformation (Li et al. 1997). [6]-gingerol might exert its effects by suppressing the NF-κB/COX-2 pathway. This idea is supported by data indicating that the reduction of UVB-induced expression and transactivation of COX-2 by [6]-gingerol was associated with the suppression of IκBα phosphorylation (Ser32) resulting in a decreased translocation of NF-κB from cytosol to nucleus in HaCaT cells (Kim et al. 2007). A ginger extract fed to rats with experimentally induced liver cancer resulted in decreased NF-κB and TNF-α expression (Habib et al. 2008). [6]-gingerol was reported to suppress TNF related apoptosis induced ligand (TRAIL)-induced NF-κB activation, resulting in apoptosis mediated by caspase-3 or -7 activation, which was associated with the down-regulation of clAP1, a negative regulator of these caspases (Ishiguro et al. 2007).

Zerumbone has been reported to suppress NF-κB activation induced by a variety of stimuli, including tumor necrosis factor (TNF), cigarette smoke condensate, and hydrogen peroxide (Takada, Murakami, and Aggarwal 2005). It also suppressed IκBα kinase phosphorylation and degradation, resulting in a downregulation of constitutively active NF-κB and many of its regulated gene targets, such as COX-2, cyclin D1, Bcl2, and other antiapoptotic genes, thereby enhancing apoptosis induced by chemotherapeutic agents (Takada, Murakami, and Aggarwal 2005). Zerumbone was also reported to suppress receptor activator of NF-κB ligand (RANKL) activity in mouse monocytes (osteoclast precursor cells) by inhibiting IκBα kinase activity, phosphorylation, and degradation (Sung et al. 2009). Oral administration of zerumbone (100, 250, or 500 ppm) to ICR mice decreased inflammation and the multiplicity of colon adenocarcinomas induced by intraperitoneal injection of azoxymethane (AOM, 10 mg/kg BW; Kim et al. 2009). Additionally, zerumbone (250 or 500 ppm) effectively suppressed 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung adenoma formation in female A/J mice (Kim et al. 2009). This ginger derivative appeared to exert its effects by inhibition of proliferation, induction of apoptosis, and suppression of NF-κB and heme oxygenase expression in both colon and lung cancer tissues (Kim et al. 2009). In an earlier study, [6]-gingerol was reported to inhibit both the vascular endothelial growth factor (VEGF)-and basic fibroblast growth factor (bFGF)-induced proliferation of human endothelial cells and cause cell-cycle arrest in the G1 phase (Kim, Min et al. 2005). [6]-gingerol also blocked capillary-like tube formation by endothelial cells in response to vascular endothelial growth factor (VEGF), and strongly inhibited sprouting of endothelial cells in the rat aorta and formation of new blood vessels in the mouse cornea in response to VEGF (Kim, Min et al. 2005).

Investigators suggested that the effectiveness of ginger might be related to its ability to inhibit prostaglandin and leukotriene biosynthesis (Srivastava and Mustafa 1992). Some researchers showed that gingerol actively inhibits arachidonate 5-lipoxygenase, an enzyme of leukotriene biosynthesis (Kiuchi et al. 1992). The leukotriene A4 hydrolase (LTA4H) protein is regarded as a relevant target for cancer therapy, and our *in silico* prediction using a reverse-docking approach revealed that LTA4H might be a potential target for [6]-gingerol (Jeong et al. 2009). Our prediction was supported by work showing that [6]-gingerol suppresses anchorage-independent cancer cell growth by binding to LTA4H and inhibiting LTA4H activity in HCT116 colorectal cancer cells. We further found that [6]-gingerol effectively suppressed tumor growth in vivo in nude mice, an effect that was mediated by the inhibition of LTA4H activity. Collectively, these findings indicate a crucial role of LTA4H in cancer and also support the

anticancer efficacy of [6]-gingerol targeting of LTA4H for the prevention of colorectal cancer (Jeong et al. 2009). Importantly, these are the first results that identify a direct target of [6]-gingerol to explain its anticancer activity.

Cyclooxygenase-2 is an important enzyme in prostaglandin biosynthesis, and is regarded as a promising molecular target for many anti-inflammatory as well as chemopreventive agents. Topical application of [6]-gingerol was reported to suppress TPA-induced COX-2 expression, p38 phosphorylation, and NF-κB DNA binding activity in mouse skin (Kim et al. 2004). These results were further expanded to show that pretreatment of mouse skin with [6]-gingerol resulted in decreased TPA-induced NF-κB DNA binding and transcriptional activity by suppressing both IκBα phosphorylation and degradation and p65 phosphorylation and nuclear translocation (Kim, Kundu et al. 2005). The interaction of phosphorylated p65 (Ser536) with CREB (cAMP response element binding) protein, a transcriptional coactivator of NF-κB, was prevented by [6]-gingerol, and the inhibitory effect of [6]-gingerol on p38 phosphorylation, an upstream mediator of COX-2 activation, was observed (Kim, Kundu et al. 2005).

Treatment of cultured ovarian cancer cells with [6]-shogaol caused a marked growth inhibition that was associated with suppression of NF-κB activation as well as the diminished secretion of angiogenic factors, VEGF and IL-8 (Rhode et al. 2007), suggesting a role for this compound in preventing angiogenesis in cancer. In contrast to most reports, dietary consumption of ginger (0.5% or 1.0%) did not suppress aberrant crypt foci (ACF) formation or reduce the number of crypts per ACF in DMH-treated rats compared to untreated control rats (Dias et al. 2006). Dietary ginger did not significantly change the proliferative or apoptotic indexes of the colonic crypt cells induced by DMH (Dias, 2006). In marked contrast to many studies, ginger extract was not able to inhibit the development of *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine (BBN)/*N*-methyl-*N*-nitrosourea (MNU)-induced bladder cancer in male Swiss mice. In fact, in BBN/MNU/2% ginger-treated mice, the incidence of grade 2 transitional cell carcinoma was increased (Dias et al. 2006; Bidinotto et al. 2006).

### 7.6.5. Cardiovascular and Other Disease-Preventive Effects of Ginger

In addition to its effects in relation to cancer, some evidence supports a protective role for ginger in cardiovascular function and a number of other disease conditions. Ginger has gained interest for its potential to treat various aspects of cardiovascular disease, and the in vitro and animal data supporting the anti-inflammatory, antioxidant, antiplatelet, hypotensive, and hypolipidemic effects of this condiment have been reviewed (Nicoll and Henein 2009). However, human trials are less convincing and more investigations are needed (Nicoll and Henein 2009). Caution when taking ginger and other herbal extracts has been suggested because of an apparent association of ginger with reported incidences of increased risk of bleeding following surgery (Chang and Whitaker 2001; Pribitkin and Boger 2001) or if taken with anticoagulant drugs such as warfarin (Heck, DeWitt, and Lukes 2000). However, the data are not conclusive (Vaes and Chyka 2000). At least one study indicates that ginger has no effect on blood pressure, heart rate, or coagulation parameters and does not interact with anticoagulant drugs such as warfarin (Weidner and Sigwart 2000). These findings were supported in a later study in which ginger was reported to have no effect on clotting status or the pharmacokinetics or pharmacodynamics of warfarin in healthy subjects (Jiang, Williams et al. 2005). An aqueous ginger extract was reported to induce a dose-dependent decrease in arterial blood pressure in a variety of animal models (Ghayur and Gilani 2005a,b).

At least one group found that administration or consumption of standardized ginger extract decreased aortic atherosclerotic lesion areas, plasma triglycerides and cholesterol, low-density lipoprotein (LDL)-associated lipid peroxides, and LDL aggregation in mice (Fuhrman et al. 2000). In rabbits that were fed a high-cholesterol diet, administration of ginger extract resulted in a significant antihyperlipidemic effect and a lower degree of atherosclerosis compared to the group that was fed cholesterol alone (Bhandari, Sharma, and Zafar 1998). Importantly, ginger powder (3 g/day in 1-g capsule 3xd) significantly lowered lipid levels in volunteer patients in a double-blind, controlled clinical trial study (Alizadeh-Navaei et al. 2008). Triglyceride and cholesterol were

substantially decreased as was LDL levels compared to placebo group. Notably, the high-density lipoprotein (HDL) level of the ginger group was higher than that of the placebo group, whereas the very-low-density lipoprotein (VLDL) level of the placebo group was higher than that of the ginger group (Alizadeh-Navaei et al. 2008). Dried ginger powder (0.1 g/kg BW, per oral administration [p.o.] for 75 days) significantly lowered (50%) the development of atheroma in the aorta and coronary arteries of rabbits that were fed cholesterol (Verma et al. 2004). This effect was associated with decreased lipid peroxidation and increased fibrinolytic activity with ginger, but blood lipid levels were not different from control animals (Verma et al. 2004). Another compound isolated from ginger, (E)-8 β,17-epoxylabd-12-ene-15,16-dial, was reported to inhibit cholesterol biosynthesis (Tanabe et al. 1993), and ginger meal (1%) decreased serum cholesterol levels significantly (Dias et al. 2006). Ginger was also reported to slightly reduce retinoid-binding protein mRNA expression levels in liver and visceral fat in male rats that were fed cholesterol to induce hyperlipidemia (Matsuda et al. 2009). These results hint that ginger consumption might improve lipid metabolism (Matsuda et al. 2009).

Antiplatelet therapy is an effective approach for preventing coronary heart disease. Ginger components are suggested as a potential new class of platelet-activation inhibitors without the potential side effects of aspirin, which is most commonly used in this approach. In a comparison of gingerols and analogs with aspirin, ginger compounds were found to be less potent compared to aspirin in inhibiting arachidonic acid-induced platelet release and aggregation and COX activity (Koo et al. 2001). However, several analogs had a significant inhibitory effect, suggesting that further development of more potent gingerol analogs might have value as an alternative to aspirin therapy in preventing ischemic heart disease (Koo et al. 2001). Consumption of ginger (5 g) inhibited platelet aggregation induced in men who consumed 100 g of butter daily for 7 days (Verma et al. 1993), and a later study showed that ginger enhanced fibrinolytic activity (Verma and Bordia 2001). An evaluation of the antiplatelet activity of 20 pungent constituents of ginger revealed that [8]-paradol was the most potent COX-1 inhibitor and antiplatelet aggregation agent (Nurtjahja-Tjendraputra et al. 2003). [8]-gingerol and [8]-shogaol were also found to be effective antiplatelet aggregation agents (Nurtjahja-Tjendraputra et al. 2003). Ginger and nifedipine (a calcium-channel blocker) were reported to have a synergistic effect on antiplatelet aggregation in normal human volunteers and hypertensive patients (Young et al. 2006). Ginger oil (24% citral) effectively lowered spontaneous or prostoglandin F2-alpha (PGF2-alpha)-2α-induced rat myometrial (uterus) contractility, and increases in external calcium concentration reversed the relaxant effects of ginger oil (Buddhakala et al. 2008). Ginger compounds have been reported to directly stimulate myocardial sarcoplasmic reticulum (SR) calcium uptake (Antipenko, Spielman, and Kirchberger 1999; Maier et al. 2000), but its therapeutic use in treating heart failure has not been advocated (Maier et al. 2000). Ginger is also used to treat asthma, diabetes, and other conditions.

Asthma is a chronic disease characterized by inflammation and hypersensitivity of airway smooth muscle cells to different substances that induce spasms, and ginger has been used for centuries in treating respiratory illnesses. Components of ginger rhizomes are reported to contain potent compounds capable of suppressing allergic reactions and might be useful for the treatment and prevention of allergic diseases (Chen et al. 2009). Ghayur, Gilani, and Janssen (2008) reported that a ginger extract inhibits airway contraction and associated calcium signaling, possibly by blocking plasma membrane calcium channels. In a mouse model of Th2-mediated pulmonary inflammation, an intraperitoneal injection of a ginger extract mainly comprised of gingerols markedly decreased the recruitment of eosinophils to the lungs in ovalbumin-sensitized mice and also suppressed the Th2 cell-driven response to allergen (Ahui et al. 2008).

Ginger has been suggested to have antidiabetic effects. In the streptozotocin-induced diabetic rat model, rats that were fed ginger exhibited better glucose tolerance and higher serum insulin levels than untreated rats, suggesting that it can help control blood sugar levels (Islam and Choi 2008). Treatment with a ginger extract produced a significant reduction in fructose-induced elevation in lipid levels, body weight, hyperglycemia, and hyperinsulinemia associated

with insulin resistance (Kadnur and Goyal 2005). An aqueous extract of raw ginger (administered daily, 500 mg/kg intraperitoneally) to streptozotocin-induced diabetic rats lowered serum glucose, cholesterol, and triacylglycerol levels; decreased urine protein levels, water intake, and urine output; and prevented the weight loss associated with diabetes in this model (Al-Amin et al. 2006). [6]-gingerol has also been found to enhance differentiation of 3T3-L1 preadipocytes and to enhance insulin-sensitive glucose uptake (Sekiya, Ohtani, and Kusano 2004). A later study showed that [6]-shogaol or [6]-gingerol significantly inhibited TNF-α-mediated downregulation of adiponectin expression in 3T3-L1 adipocytes (Isa et al. 2008). [6]-shogaol appeared to function as a peroxisome proliferator-activated receptor (PPAR)γ agonist, whereas [6]-gingerol acted by suppressing TNF-α-induced JNKs signaling (Isa et al. 2008). These results give some suggestion that ginger might be valuable in managing the effects of diabetes in humans.

Dried ginger may have beneficial effects in treating dementia, including Alzheimer's disease (Ghayur, Gilani, Ahmed, Khalid, Nawaz, Agbedahunsi, Choudhary, and Houghton 2008). Ulcerative colitis is a chronically recurrent inflammatory bowel disease of unknown origin, and in rats, ginger extract alleviated the symptoms of acetic acid-induced ulcerative colitis (El-Abhar, Hammad, and Gawad 2008).

## 7.7. SAFETY, EFFICACY, AND CONTRAINDICATIONS

Ginger is recognized by the U.S. Food and Drug Administration (FDA) as a food additive that is "generally recognized as safe." However, and notably, in 1930, thousands of Americans were poisoned and paralyzed by an illicit extract of Jamaican ginger (jake) that was used to circumvent Prohibition laws. The extract had been adulterated with a neurotoxic organophosphate compound, triorthocresyl phosphate (TOCP; Crandall 1931; Morgan and Penovich 1978). The extract was banned in 1931.

Early studies suggest that ginger extract increased the mutagenesis ability of 2(2-furyl)-3(5-nitro-2-fury)acryl amide (AF2) or *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (NTG), and [6]-gingerol was determined to be an active mutagen (Nakamura and Yamamoto 1982). A later study suggests that [6]-shogaol is much less mutagenic than [6]-gingerol and that the active part of [6]-gingerol is the aliphatic chain moiety containing a hydroxyl group (Nakamura and Yamamoto 1983). To our knowledge, these studies have not been confirmed nor repeated, and no recent evidence suggests that ginger or its components are mutagenic.

Oral administration of a ginger extract (1000 mg/kg) was reported to be tolerated well by pregnant rats, and it exerted no adverse effects on the mothers or in the development of fetuses (Weidner and Sigwart 2001). This result is somewhat in contrast to an earlier study, in which administration of ginger tea to pregnant rats resulted in twice the loss of embryos but heavier surviving fetuses compared to untreated controls (Wilkinson 2000a). Ginger rhizome extract (0.5-10.0 g/kg) administered intraperitoneally to mice was reported to have no clastogenic effects compared to ginger oil, which produced some chromosomal irregularities (Mukhopadhyay and Mukherjee 2000).

Most recently, male and female rats that were fed ginger powder (500, 1000, or 2000 mg/kg BW) by gavage for 35 days did not exhibit any overall mortalities or abnormalities in behavior, growth, or food and water consumption (Rong et al. 2009). No overt organ abnormalities were observed and hematological and blood biochemical parameters in treated and untreated control animals were similar. The only real difference observed was a slightly decreased absolute and relative weight of the testes only at the highest dose (2000 mg/kg; Rong et al. 2009). Observational studies in humans suggest no evidence of teratogenicity from treatments for early pregnancy nausea that included ginger (Jewell and Young 2003). These results were confirmed in a similar trial showing that administration of ginger beginning at the first trimester of pregnancy did not appear to increase the rates of major malformations above the baseline rate of 1-3% (Portnoi et al. 2003). Overall, these data indicate that ginger consumption appears to be very safe with very limited side effects.

## 7.8. SUMMARY AND CONCLUSIONS

Ginger is not only an extremely popular dietary condiment used for flavoring food but also an herb that has been used for thousands of years as a medicinal herb to treat a variety of ailments. Chemical and metabolic analyses have revealed that ginger comprises hundreds of compounds and metabolites. The most extensively studied bioactive components include gingerols and shogaols, especially [6]-gingerol and [6]-shogaol, respectively. The content of each component is clearly dependent on the source and preparation of the ginger rhizome. Research interest in determining the role of natural compounds in preventing disease has increased markedly over the last few years. In spite of the abundance of research studies, many of the results are phenomenon based and provide data that are descriptive and observational rather than mechanistic. More studies are needed in animals and humans on the kinetics of ginger and its constituents and on the effects of consumption over a long period of time. Specific molecular targets and mechanisms of action need to be identified. Ginger clearly has a vast number of components and metabolites, many of which have not been studied in detail. The lack of standardization of ginger supplements is disconcerting, and whether consumption of high levels of isolated components (e.g., [6]-gingerol) is advisable is uncertain. [6]-gingerol or other ginger components might require inter-reactivity or dependency on other components in the whole food source to exert their positive effects.

Research data indicate that ginger and its constituents accumulate in the gastrointestinal tract, which supports the many observations of ginger’s effectiveness as an antinausea agent and as a possible colon cancer-preventing compound. Ginger acts as a potent antioxidant in vitro and ex vivo, but the data are not obvious for in vivo application and specific targets and mechanisms are lacking. Ginger appears to exert anti-inflammatory effects by suppressing COX-2 with subsequent inhibition of prostaglandin and leukotriene biosynthesis. On the other hand, the data supporting the effectiveness of ginger in alleviating pain and swelling associated with arthritis are somewhat conflicting. The most common use of ginger is to alleviate the vomiting and nausea associated with pregnancy, chemotherapy, and some types of surgery. The clinical data undoubtedly indicate that ginger is at least as effective, and may be better, than vitamin B6 in treating these symptoms. Again, mechanisms are lacking, but no reports indicate that ginger has any adverse side effects or that it can worsen illness in pregnant women or patients. Interest in ginger as an anticancer agent has markedly increased over the last few years and a direct protein target has been identified in colon cancer. Ginger also appears to reduce cholesterol and improve lipid metabolism, thereby helping to decrease the risk of cardiovascular disease and diabetes.

In summary, ginger has been reported to possess diverse pharmacological properties, although its specific biological targets are largely unknown and remain to be determined. However, in spite of the lack of specific mechanistic information, use of ginger appears to be safe and its effects are mighty and amazing in its many applications.

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## REFERENCES

1. Aeschbach R, Loliger J, Scott B. C, Murcia A, Butler J, Halliwell B, Aruoma O. I. Antioxidant actions of thymol, carvacrol, [6]-gingerol, zingerone and hydroxytyrosol. Food Chem Toxicol. 1994;32(1):31–6. [PubMed: 7510659]
2. Afzal M, Al-Hadidi D, Menon M, Pesek J, Dhami M. S. Ginger: An ethnomedical, chemical and pharmacological review. Drug Metabol Drug Interact. 2001;18(3-4):159–90. [PubMed: 11791883]
3. Aggarwal B. B, Kunnumakkara A. B, Harikumar K. B, Tharakan S. T, Sung B, Anand P. Potential of spice-derived phytochemicals for cancer prevention. Planta Med. 2008;74(13):1560–9. [PubMed: 18612945]

4. Ahmad N, Katiyar S.K, Mukhtar H. Antioxidants in chemoprevention of skin cancer. Curr Probl Dermatol. 2001;29:128–39. [PubMed: 11225193]
5. Ahmed R. S, Seth V, Banerjee B. D. Influence of dietary ginger (Zingiber officinales Rosc.) on antioxidant defense system in rat: Comparison with ascorbic acid. Indian J Exp Biol. 2000;38(6):604–6. [PubMed: 11116533]
6. Ahmed R. S, Seth V, Pasha S. T, Banerjee B. D. Influence of dietary ginger (Zingiber officinales Rosc.) on oxidative stress induced by malathion in rats. Food Chem Toxicol. 2000;38(5):443–50. [PubMed: 10762730]
7. Ahmed R. S, Suke S. G, Seth V, Chakraborti A, Tripathi A. K, Banerjee B. D. Protective effects of dietary ginger (Zingiber officinales Rosc.) on lindane-induced oxidative stress in rats. Phytother Res. 2008;22(7):902–6. [PubMed: 18389491]
8. Ahui M. L, Champy P, Ramadan A, editors. et al. Ginger prevents Th2-mediated immune responses in a mouse model of airway inflammation. Int Immunopharmacol. 2008;8(12):1626–32. [PubMed: 18692598]
9. Aikins Murphy P. Alternative therapies for nausea and vomiting of pregnancy. Obstet Gynecol. 1998;91(1):149–55. [PubMed: 9464741]
10. Aktan F, Henness S, Tran V. H, Duke C. C, Roufogalis B. D, Ammit A. J. Gingerol metabolite and a synthetic analogue Capsarol inhibit macrophage NF-kappaB-mediated iNOS gene expression and enzyme activity. Planta Med. 2006;72(8):727–34. [PubMed: 16732525]
11. Al-Amin Z. M, Thomson M, Al-Qattan K. K, Peltonen-Shalaby R, Ali M. Anti-diabetic and hypo-lipidaemic properties of ginger (Zingiber officinale) in streptozotocin-induced diabetic rats. Br J Nutr. 2006;96(4):660–6. [PubMed: 17010224]
12. Ali B. H, Blunden G, Tanira M. O, Nemmar A. Some phytochemical, pharmacological and toxicological properties of ginger (Zingiber officinale Roscoe): A review of recent research. Food Chem Toxicol. 2008;46(2):409–20. [PubMed: 17950516]
13. Alizadeh-Navaei R, Roozbeh F, Saravi M, Pouramir M, Jalali F, Moghadamnia A. A. Investigation of the effect of ginger on the lipid levels. A double blind controlled clinical trial. Saudi Med J. 2008;29(9):1280–4. [PubMed: 18813412]
14. Altman R. D, Marcussen K. C. Effects of a ginger extract on knee pain in patients with osteoarthritis. Arthritis Rheum. 2001;44(11):2531–8. [PubMed: 11710709]
15. Antipenko A. Y, Spielman A. I, Kirchberger M. A. Interactions of [6]-gingerol and ellagic acid with the cardiac sarcoplasmic reticulum $Ca2^{+}$-AT Pase. J Pharmacol Exp Ther. 1999;290(1):227–34. [PubMed: 10381780]
16. Apariman S, Ratchanon S, Wiriyasirivej B. Effectiveness of ginger for prevention of nausea and vomiting after gynecological laparoscopy. J Med Assoc Thai. 2006;89(12):2003–9. [PubMed: 17214049]
17. Bailey-Shaw Y. A, Williams L. A, Junor G. A, Green C. E, Hibbert S. L, Salmon C. N, Smith A. M. Changes in the contents of oleoresin and pungent bioactive principles of Jamaican ginger (Zingiber officinale Roscoe) during maturation. J Agric Food Chem. 2008;56(14):5564–71. [PubMed: 18564850]
18. Baldwin A. S. Jr. The NF-kappa B and I kappa B proteins: New discoveries and insights. Annu Rev Immunol. 1996;14:649–83. [PubMed: 8717528]
19. Barrett B, Kiefer D, Rabago D. Assessing the risks and benefits of herbal medicine: An overview of scientific evidence. Altern Ther Health Med. 1999;5(4):40–9. [PubMed: 10394673]
20. Bhandari U, Sharma J. N, Zafar R. The protective action of ethanolic ginger (Zingiber officinale) extract in cholesterol fed rabbits. J Ethnopharmacol. 1998;61(2):167–71. [PubMed: 9683348]
21. Bidinotto L. T, Spinardi-Barbisan A. L, Rocha N. S, Salvadori D. M, Barbisan L. F. Effects of ginger (Zingiber officinale Roscoe) on DNA damage and development of urothelial tumors in a mouse bladder carcinogenesis model. Environ Mol Mutagen. 2006;47(8):624–30. [PubMed: 16878317]

22. Black C. D, Oconnor P. J. Acute effects of dietary ginger on quadriceps muscle pain during moderate-intensity cycling exercise. Int J Sport Nutr Exerc Metab. 2008;18(6):653–64. [PubMed: 19164834]
23. Bliddal H, Rosetzsky A, Schlichting P, editors. et al. A randomized, placebo-controlled, cross-over study of ginger extracts and ibuprofen in osteoarthritis. Osteoarthritis Cartilage. 2000;8(1):9–12. [PubMed: 10607493]
24. Bode A. M, Dong Z. Ginger. Packer L, Ong C.N, Halliwell B. New York: Marcel Dekker; Herbal and Traditional Medicine: Molecular Aspects of Health. 2004
25. Bode A. M, Ma W. Y, Surh Y. J, Dong Z. Inhibition of epidermal growth factor-induced cell trans-formation and activator protein 1 activation by [6]-gingerol. Cancer Res. 2001;61(3):850–3. [PubMed: 11221868]
26. Boone S. A, Shields K. M. Treating pregnancy-related nausea and vomiting with ginger. Ann Pharmacother. 2005;39(10):1710–3. [PubMed: 16131535]
27. Borrelli F, Capasso R, Aviello G, Pittler M. H, Izzo A. A. Effectiveness and safety of ginger in the treatment of pregnancy-induced nausea and vomiting. Obstet Gynecol. 2005;105(4):849–56. [PubMed: 15802416]
28. Brown A. C, Shah C, Liu J, Pham J. T, Zhang J. G, Jadus M. R. Ginger's (Zingiber officinale Roscoe) inhibition of rat colonic adenocarcinoma cellsproliferation and angiogenesis in vitro. Phytother Res. 2009;23(5):640–5. [PubMed: 19117330]
29. Bryer E. A literature review of the effectiveness of ginger in alleviating mild-to-moderate nausea and vomiting of pregnancy. J Midwifery Womens Health. 2005;50(1):e1–3. [PubMed: 15637501]
30. Buddhakala N, Talubmook C, Sriyotha P, Wray S, Kupittayanant S. Inhibitory effects of ginger oil on spontaneous and PGF2alpha-induced contraction of rat myometrium. Planta Med. 2008;74(4):385–91. [PubMed: 18484528]
31. Chaiyakunapruk N, Kitikannakorn N, Nathisuwan S, Leeprakobboon K, Leelasettagool C. The efficacy of ginger for the prevention of postoperative nausea and vomiting: A meta-analysis. Am J Obstet Gynecol. 2006;194(1):95–9. [PubMed: 16389016]
32. Chang L. K, Whitaker D. C. The impact of herbal medicines on dermatologic surgery. Dermatol Surg. 2001;27(8):759–63. [PubMed: 11493302]
33. Chen C. Y, Chen C. H, Kung C. H, Kuo S. H, Kuo S. Y. [6]-gingerol induces Ca2+ mobilization in Madin-Darby canine kidney cells. J Nat Prod. 2008;71(1):137–40. [PubMed: 18181576]
34. Chen C. Y, Li Y. W, Kuo S. Y. Effect of [10]-gingerol on $[Ca2^{+}]_{i}$ and cell death in human colorectal cancer cells. Molecules. 2009;14(3):959–69. [PubMed: 19255554]
35. Chen C. Y, Liu T. Z, Liu Y. W, editors. et al. [6]-shogaol (alkanone from ginger) induces apoptotic cell death of human hepatoma p53 mutant Mahlavu subline via an oxidative stress-mediated caspase-dependent mechanism. J Agric Food Chem. 2007;55(3):948–54. [PubMed: 17263498]
36. Chen B. H, Wu P. Y, Chen K. M, Fu T. F, Wang H. M, Chen C. Y. Antiallergic potential on RBL- 2H3 cells of some phenolic constituents of Zingiber officinale (ginger) J Nat Prod. 2009;72:950–3. [PubMed: 19271742]
37. Chittumma P, Kaewkiattikun K, Wiriyasiriwach B. Comparison of the effectiveness of ginger and vitamin B6 for treatment of nausea and vomiting in early pregnancy: A randomized double-blind controlled trial. J Med Assoc Thai. 2007;90(1):15–20. [PubMed: 17621727]
38. Chrubasik S, Pittler M. H. Addendum to a recent systematic review on ginger. Forsch Komplementarmed Klass Naturheilkd. 2005;12(3):168. author reply 168-9. [PubMed: 16060051]
39. Chrubasik S, Pittler M. H, Roufogalis B. D. Zingiberis rhizoma: A comprehensive review on the ginger effect and efficacy profiles. Phytomedicine. 2005;12(9):684–701. [PubMed: 16194058]
40. Chung W. Y, Jung Y. J, Surh Y. J, Lee S. S, Park K. K. Antioxidative and antitumor promoting effects of

[6]-paradol and its homologs. Mutat Res. 2001;496(1-2):199–206. [PubMed: 11551496]
41. Cohen R. J, Ek K, Pan C. X. Complementary and alternative medicine (CAM) use by older adults: A comparison of self-report and physician chart documentation. J Gerontol A Biol Sci Med Sci. 2002;57(4):M223–7. [PubMed: 11909887]
42. Crandall F. G. Paralysis-from spurious Jamaica ginger extract: Report on Los Angeles county outbreak. Cal West Med. 1931;35(3):180–2. [PMC free article: PMC1657957] [PubMed: 18741869]
43. Dedov V. N, Tran V. H, Duke C. C, Connor M, Christie M. J, Mandadi S, Roufogalis B. D. Gingerols: A novel class of vanilloid receptor (VR1) agonists. Br J Pharmacol. 2002;137(6):793–8. [PMC free article: PMC1573550] [PubMed: 12411409]
44. DerMarderosian A, Beutler J. A. The Review of Natural Products. St. Louis, MO: Wolters Kluwer; 2006.
45. Dias M. C, Spinardi-Barbisan A. L, Rodrigues M. A, de Camargo J. L, Teran E, Barbisan L. F. Lack of chemopreventive effects of ginger on colon carcinogenesis induced by 1,2-dimethylhydrazine in rats. Food Chem Toxicol. 2006;44(6):877–84. [PubMed: 16442687]
46. Ding G. H, Naora K, Hayashibara M, Katagiri Y, Kano Y, Iwamoto K. Pharmacokinetics of [6]-gingerol after intravenous administration in rats. Chem Pharm Bull (Tokyo) 1991;39(6):1612–4. [PubMed: 1934184]
47. Dong Z, Birrer M. J, Watts R. G, Matrisian L. M, Colburn N. H. Blocking of tumor promoter- induced AP-1 activity inhibits induced transformation in JB6 mouse epidermal cells. Proc Natl Acad Sci. 1994;91(2):609–13. [PMC free article: PMC42998] [PubMed: 8290571]
48. Dupuis L. L, Nathan P. C. Options for the prevention and management of acute chemotherapy- induced nausea and vomiting in children. Paediatr Drugs. 2003;5(9):597–613. [PubMed: 12956617]
49. Eberhart L. H, Mayer R, Betz O, editors. et al. Ginger does not prevent postoperative nausea and vomiting after laparoscopic surgery. Anesth Analg. 2003;96(4):995–8. [PubMed: 12651648]
50. El-Abhar H. S, Hammad L. N, Gawad H. S. Modulating effect of ginger extract on rats with ulcerative colitis. J Ethnopharmacol. 2008;118(3):367–72. [PubMed: 18571884]
51. El-Sharaky A. S, Newairy A. A, Kamel M. A, Eweda S. M. Protective effect of ginger extract against bromobenzene-induced hepatotoxicity in male rats. Food Chem Toxicol. 2009;47(7):1584–90. [PubMed: 19371770]
52. Eldershaw T. P, Colquhoun E. Q, Dora K. A, Peng Z. C, Clark M. G. Pungent principles of gin-ger (Zingiber officinale) are thermogenic in the perfused rat hind limb. Int J Obes Relat Metab Disord. 1992;16(10):755–63. [PubMed: 1330955]
53. Eliopoulos C. Ginger: More than a great spice. Director. 2007;15(1):46–7. [PubMed: 19348054]
54. Engdal S, Klepp O, Nilsen O. G. Identification and exploration of herb-drug combinations used by cancer patients. Integr Cancer Ther. 2009;8(1):29–36. [PubMed: 19174505]
55. Ensiyeh J, Sakineh M. A. Comparing ginger and vitamin B6 for the treatment of nausea and vomiting in pregnancy: a randomised controlled trial. Midwifery. 2009;25:649–53. [PubMed: 18272271]
56. Ernst E, Pittler M. H. Efficacy of ginger for nausea and vomiting: A systematic review of randomized clinical trials. Br J Anaesth. 2000;84(3):367–71. [PubMed: 10793599]
57. Ernst E, Schmidt K. Health risks over the Internet: Advice offered by “medical herbalists” to a pregnant woman. Wien Med Wochenschr. 2002;152(7-8):190–2. [PubMed: 12017746]
58. Frondoza C. G, Sohrabi A, Polotsky A, Phan P. V, Hungerford D. S, Lindmark L. An in vitro screening assay for inhibitors of proinflammatory mediators in herbal extracts using human synoviocyte cultures. Vitro Cell Dev Biol Anim. 2004;40(3-4):95–101. [PubMed: 15311968]
59. Fugh-Berman A, Kronenberg F. Complementary and alternative medicine (CAM) in reproductive- age women: A review of randomized controlled trials. Reprod Toxicol. 2003;17(2):137–52. [PubMed: 12642146]
60. Fuhrman B, Rosenblat M, Hayek T, Coleman R, Aviram M. Ginger extract consumption reduces plasma

cholesterol, inhibits LDL oxidation and attenuates development of atherosclerosis in atherosclerotic, apolipoprotein E-deficient mice. J Nutr. 2000;130(5):1124–31. [PubMed: 10801908]

61. Funk J. L, Frye J. B, Oyarzo J. N, Timmermann B. N. Comparative effects of two gingerol- containing Zingiber officinale extracts on experimental rheumatoid arthritis. J Nat Prod. 2009;72:403–7. [PMC free article: PMC2837120] [PubMed: 19216559]
62. Ghayur M. N, Gilani A. H. Ginger lowers blood pressure through blockade of voltage-dependent calcium channels. J Cardiovasc Pharmacol. 2005a;45(1):74–80. [PubMed: 15613983]
63. Ghayur M. N, Gilani A. H. Pharmacological basis for the medicinal use of ginger in gastrointestinal disorders. Dig Dis Sci. 2005b;50(10):1889–97. [PubMed: 16187193]
64. Ghayur M. N, Gilani A. H, Ahmed T, Khalid A, Nawaz S. A, Agbedahunsi J. M, Choudhary M. I, Houghton P. J. Muscarinic, Ca(+ +) antagonist and specific butyrylcholinesterase inhibitory activity of dried ginger extract might explain its use in dementia. J Pharm Pharmacol. 2008;60(10):1375–83. [PubMed: 18812031]
65. Ghayur M. N, Gilani A. H, Janssen L. J. Ginger attenuates acetylcholine-induced contraction and $Ca2^{+}$ signalling in murine airway smooth muscle cells. Can J Physiol Pharmacol. 2008;86(5):264–71. [PubMed: 18432287]
66. Gilmore T. D. Clinically relevant findings. J Clin Invest. 1997;100(12):2935–6. [PMC free article: PMC508501] [PubMed: 9399935]
67. Grant K. L, Lutz R. B. Ginger. Am J Health Syst Pharm. 2000;57(10):945–7. [PubMed: 10832493]
68. Grontved A, Brask T, Kambskard J, Hentzer E. Ginger root against seasickness: A controlled trial on the open sea. Acta Otolaryngol. 1988;105(1-2):45–9. [PubMed: 3277342]
69. Grzanna R, Lindmark L, Frondoza C. G. Ginger-an herbal medicinal product with broad anti-inflammatory actions. J Med Food. 2005;8(2):125–32. [PubMed: 16117603]
70. Gupta Y. K, Sharma M. Reversal of pyrogallol-induced delay in gastric emptying in rats by ginger (Zingiber officinale) Methods Find Exp Clin Pharmacol. 2001;23(9):501–3. [PubMed: 11876024]
71. Habib S. H, Makpol S, Abdul Hamid N. A, Das S, Ngah W. Z, Yusof Y. A. Ginger extract (Zingiber officinale) has anti-cancer and anti-inflammatory effects on ethionine-induced hepatoma rats. Clinics (Sao Paulo) 2008;63(6):807–13. [PMC free article: PMC2664283] [PubMed: 19061005]
72. Halvorsen B. L, editor. et al. A systematic screening of total antioxidants in dietary plants. J Nutr. 2002;132(3):461–71. [PubMed: 11880572]
73. Heck A. M, De Witt B. A, Lukes A. L. Potential interactions between alternative therapies and warfarin. Am J Health Syst Pharm. 2000;57(13):1221–7. [PubMed: 10902065]
74. Huang C, Ma W, Bowden G. T, Dong Z. Ultraviolet B-induced activated protein-1 activation does not require epidermal growth factor receptor but is blocked by a dominant negative PKC lambda/iota. J Biol Chem. 1996;271(49):31262–8. [PubMed: 8940130]
75. Huang C, Ma W. Y, Dong Z. Requirement for phosphatidylinositol 3-kinase in epidermalgrowth factor-induced AP-1 transactivation and transformation in JB6 P+ cells. Mol Cell Biol. 1996;16(11):6427–35. [PMC free article: PMC231644] [PubMed: 8887671]
76. Ihlaseh S. M, de Oliveira M. L, Teran E, de Camargo J. L, Barbisan L. F. Chemopreventive property of dietary ginger in rat urinary bladder chemical carcinogenesis. World J Urol. 2006;24(5):591–6. [PubMed: 17021826]
77. Ippoushi K, Azuma K, Ito H, Horie H, Higashio H. [6]-gingerol inhibits nitric oxide synthesis in activated J774.1 mouse macrophages and prevents peroxynitrite-induced oxidation and nitration reac-tions. Life Sci. 2003;73(26):3427–37. [PubMed: 14572883]
78. Ippoushi K, Ito H, Horie H, Azuma K. Mechanism of inhibition of peroxynitrite-induced oxidation and nitration by [6]-gingerol. Planta Med. 2005;71(6):563–6. [PubMed: 15971130]

79. Isa Y, Miyakawa Y, Yanagisawa M, editors. et al. [6]-shogaol and [6]-gingerol, the pungent of ginger, inhibit TNF-alpha mediated downregulation of adiponectin expression via different mechanisms in 3T3-L1 adipocytes. Biochem Biophys Res Commun. 2008;373(3):429–34. [PubMed: 18577375]
80. Ishiguro K, Ando T, Maeda O, Ohmiya N, Niwa Y, Kadomatsu K, Goto H. Ginger ingredients reduce viability of gastric cancer cells via distinct mechanisms. Biochem Biophys Res Commun. 2007;362(1):218–23. [PubMed: 17706603]
81. Islam M. S, Choi H. Comparative effects of dietary ginger (Zingiber officinale) and garlic (Allium sativum) investigated in a type 2 diabetes model of rats. J Med Food. 2008;11(1):152–9. [PubMed: 18361751]
82. Iwasaki Y, Morita A, Iwasawa T, Kobata K, Sekiwa Y, Morimitsu Y, Kubota K, Watanabe T. A nonpungent componentof steamed ginger-[10]-shogaol-increases adrenaline secretion via the activation of TRPV1. Nutr Neurosci. 2006;9(3-4):169–78. [PubMed: 17176640]
83. Jackson E. A. Is ginger root effective for decreasing the severity of nausea and vomiting in early pregnancy? J Fam Pract. 2001;50(8):720. [PubMed: 11509171]
84. Jagetia G, Baliga M, Venkatesh P. Ginger (Zingiber officinale Rosc.), a dietary supplement, protects mice against radiation-induced lethality: Mechanism of action. Cancer Biother Radiopharm. 2004;19(4):422–35. [PubMed: 15453957]
85. Jagetia G. C, Baliga M. S, Venkatesh P, Ulloor J. N. Influence of ginger rhizome (Zingiber officinale Rosc.) on survival, glutathione and lipid peroxidation in mice after whole-body exposure to gamma radiation. Radiat Res. 2003;160(5):584–92. [PubMed: 14565823]
86. Jeong C. H, Bode A. M, Pugliese A, editors. et al. [6]-gingerol suppresses colon cancer growth by targeting leukotriene A4 hydrolase. Cancer Res. 2009;69(13):5584–91. [PubMed: 19531649]
87. Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev. 2000;(2) CD000145. [PubMed: 10796155]
88. Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy (Cochrane Review) Cochrane Database Syst Rev. 2002;(1) CD000145. [PubMed: 11869567]
89. Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev. 2003;(4) CD000145. [PubMed: 14583914]
90. Jiang H, Solyom A. M, Timmermann B. N, Gang D. R. Characterization of gingerol-related compounds in ginger rhizome (Zingiber officinale Rosc.) by high-performance liquid chromatography/electrospray ionization mass spectrometry. Rapid Commun Mass Spectrom. 2005;19(20):2957–64. [PubMed: 16189817]
91. Jiang S. Z, Wang N. S, Mi S. Q. Plasma pharmacokinetics and tissue distribution of [6]-gingerol in rats. Biopharm Drug Dispos. 2008;29(9):529–37. [PubMed: 19051331]
92. Jiang X, Williams K. M, Liauw W. S, Ammit A. J, Roufogalis B. D, Duke C. C, Day R. O, McLachlan A. J. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol. 2005;59(4):425–32. [PMC free article: PMC1884814] [PubMed: 15801937]
93. Jiang H, Xie Z, Koo H. J, McLaughlin S. P, Timmermann B. N, Gang D. R. Metabolic profiling and phylogenetic analysis of medicinal Zingiber species: Tools for authentication of ginger (Zingiber officinale Rosc) Phytochemistry. 2006;67(15):1673–85. [PubMed: 16169024]
94. Jolad S. D, Lantz R. C, Chen G. J, Bates R. B, Timmermann B. N. Commercially processed dry ginger (Zingiber officinale): Composition and effects on LPS-stimulated PGE2 production. Phytochemistry. 2005;66(13):1614–35. [PubMed: 15996695]
95. Kadnur S. V, Goyal R. K. Beneficial effects of Zingiber officinale Roscoe on fructose induced hyperlipidemia and hyperinsulinemia in rats. Indian J Exp Biol. 2005;43(12):1161–4. [PubMed: 16359128]
96. Kapadia G. J, Azuine M. A, Tokuda H, Hang E, Mukainaka T, Nishino H, Sridhar R. Inhibitory effect of herbalremedies on 12 -O -tetradecanoylphorbol-13-acetate-promoted Epstein-Barr virus early antigen activation. Pharmacol Res. 2002;45(3):213–20. [PubMed: 11884218]

97. Katiyar S. K, Agarwal R, Mukhtar H. Inhibition of tumor promotion in SENCAR mouse skin by ethanol extract of Zingiber officinale rhizome. Cancer Res. 1996;56(5):1023–30. [PubMed: 8640756]
98. Kaul P. N, Joshi B. S. Alternative medicine: Herbal drugs and their critical appraisal-part II. Prog Drug Res. 2001;57:1–75. [PubMed: 11727999]
99. Keum Y. S, Kim J, Lee K. H, editors. et al. Induction of apoptosis andcaspase-3 activation by chemopreventive [6]-paradol and structurally related compounds in KB cells. Cancer Lett. 2002;177(1):41–7. [PubMed: 11809529]
100. Kim S. O, Chun K. S, Kundu J. K, Surh Y. J. Inhibitory effects of [6]-gingerol on PMA- induced COX-2 expression andactivation of NF-kappaB and p38 MAPK in mouse skin. Biofactors. 2004;21(1-4):27–31. [PubMed: 15630166]
101. Kim J. K, Kim Y, Na K. M, Surh Y. J, Kim T. Y. [6]-gingerol prevents UVB-induced ROS production and COX-2 expression in vitro and in vivo. Free Radic Res. 2007;41(5):603–14. [PubMed: 17454143]
102. Kim S. O, Kundu J. K, Shin Y. K, Park J. H, Cho M. H, Kim T. Y, Surh Y. J. [6]-gingerol inhibits COX-2 expression by blocking the activation of p38 MAP kinase and NF-kappaB in phorbol ester-stimulated mouse skin. Oncogene. 2005;24(15):2558–67. [PubMed: 15735738]
103. Kim J. S, Lee S. I, Park H. W, editors. et al. Cytotoxic components from the dried rhizomes of Zingiber officinale Roscoe. Arch Pharm Res. 2008;31(4):415–8. [PubMed: 18449496]
104. Kim E. C, Min J. K, Kim T. Y, editors. et al. [6]-gingerol, a pungent ingredient of ginger, inhibits angiogenesis in vitro and in vivo. Biochem Biophys Res Commun. 2005;335(2):300–8. [PubMed: 16081047]
105. Kim M, Miyamoto S, Yasui Y, Oyama T, Murakami A, Tanaka T. Zerumbone, a tropical ginger sesquiterpene, inhibits colon and lung carcinogenesis in mice. Int J Cancer. 2009;124(2):264–71. [PubMed: 19003968]
106. Kim H. W, Murakami A, Nakamura Y, Ohigashi H. Screening of edible Japanese plants for suppressive effects on phorbol ester-induced superoxide generation in differentiated HL-60 cells and AS52 cells. Cancer Lett. 2002;176(1):7–16. [PubMed: 11790448]
107. Kiuchi F, Iwakami S, Shibuya M, Hanaoka F, Sankawa U. Inhibition of prostaglandin and leukotriene biosynthesis by gingerols and diarylheptanoids. Chem Pharm Bull (Tokyo) 1992;40(2):387–91. [PubMed: 1606634]
108. Koh E. M, Kim H. J, Kim S, editors. et al. Modulation of macrophage functions by compounds isolated from Zingiber officinale. Planta Med. 2009;75(2):148–51. [PubMed: 19031369]
109. Koo K. L, Ammit A. J, Tran V. H, Duke C. C, Roufogalis B. D. Gingerols and related analogues inhibit arachidonic acid-induced human platelet serotonin release and aggregation. Thromb Res. 2001;103(5):387–97. [PubMed: 11553371]
110. Krishnakantha T. P, Lokesh B. R. Scavenging of superoxide anions by spice principles. Indian J Biochem Biophys. 1993;30(2):133–4. [PubMed: 8394839]
111. Kuhad A, Tirkey N, Pilkhwal S, Chopra K. [6]-gingerol prevents cisplatin-induced acute renal failure in rats. Biofactors. 2006;26(3):189–200. [PubMed: 16971750]
112. Langmead L, Rampton D. S. Review article: Herbal treatment in gastrointestinal and liver disease-benefits and dangers. Aliment Pharmacol Ther. 2001;15(9):1239–52. [PubMed: 11552894]
113. Lee S. H, Cekanova M, Baek S. J. Multiple mechanisms are involved in [6]-gingerol-induced cell growth arrest and apoptosis in human colorectal cancer cells. Mol Carcinog. 2008;47(3):197–208. [PMC free article: PMC2430145] [PubMed: 18058799]
114. Lee T. Y, Lee K. C, Chen S. Y, Chang H. H. [6]-gingerol inhibits ROS and iNOS through the sup-pressionof PKC-alpha and NF-kappaB pathways in lipopolysaccharide-stimulated mouse macrophages. Biochem Biophys Res Commun. 2009;382(1):134–9. [PubMed: 19268427]

115. Lee E, Park K. K, Lee J. M, Chun K. S, Kang J. Y, Lee S. S, Surh Y. J. Suppression of mouse skin tumor promotion and induction of apoptosis in HL-60 cells by Alpinia oxyphylla Miquel (Zingiberaceae) Carcinogenesis. 1998;19(8):1377–81. [PubMed: 9744532]
116. Lee H. S, Seo E. Y, Kang N. E, Kim W. K. [6]-gingerol inhibits metastasis of MDA-MB-231 human breast cancer cells. J Nutr Biochem. 2008;19(5):313–9. [PubMed: 17683926]
117. Lee E, Surh Y. J. Induction of apoptosis in HL-60 cells by pungent vanilloids, [6]-gingerol and [6]-paradol. Cancer Lett. 1998;134(2):163–8. [PubMed: 10025876]
118. Levine M. E, Gillis M. G, Koch S. Y, Voss A. C, Stern R. M, Koch K. L. Protein and ginger for the treatment of chemotherapy-induced delayed nausea. J Altern Complement Med. 2008;14(5):545–51. [PubMed: 18537470]
119. Li J. J, Westergaard C, Ghosh P, Colburn N. H. Inhibitors of both nuclear factor-kappaB and activator protein-1 activation block the neoplastic transformation response. Cancer Res. 1997;57(16):3569–76. [PubMed: 9270030]
120. Mahesh R, Perumal R. V, Pandi P. V. Cancer chemotherapy-induced nausea and vomiting: Role of mediators, development of drugs and treatment methods. Pharmazie. 2005;60(2):83–96. [PubMed: 15739895]
121. Maier L. S, Schwan C, Schillinger W, Minami K, Schutt U, Pieske B. Gingerol, isoproterenol and ouabain normalize impaired post-rest behavior but not force-frequency relation in failing human myocardium. Cardiovasc Res. 2000;45(4):913–24. [PubMed: 10728417]
122. Mallikarjuna K, Sahitya Chetan P, Sathyavelu Reddy K, Rajendra W. Ethanol toxicity: Rehabilitation of hepatic antioxidant defense system with dietary ginger. Fitoterapia. 2008;79(3):174–8. [PubMed: 18182172]
123. Manju V, Nalini N. Chemopreventive efficacy of ginger, a naturally occurring anticarcinogen during the initiation, post-initiation stages of 1,2 dimethylhydrazine-induced colon cancer. Clin Chim Acta. 2005;358(1-2):60–7. [PubMed: 16018877]
124. Manju V, Nalini N. Effect of ginger on bacterial enzymes in 1,2-dimethylhydrazine induced experi-mental colon carcinogenesis. Eur J Cancer Prev. 2006;15(5):377–83. [PubMed: 16912565]
125. Manusirivithaya S, Sripramote M, Tangjitgamol S, Sheanakul C, Leelahakorn S, Thavaramara T, Tangcharoenpanich K. Antiemetic effect of ginger in gynecologic oncology patients receiving cisplatin. Int J Gynecol Cancer. 2004;14(6):1063–9. [PubMed: 15571611]
126. Marcus D. M, Suarez-Almazor M. E. Is there a role for ginger in the treatment of osteoarthritis? Arthritis Rheum. 2001;44(11):2461–2. [PubMed: 11710700]
127. Matsuda A, Wang Z, Takahashi S, Tokuda T, Miura N, Hasegawa J. Upregulation of mRNA of retinoid binding protein and fattyacid binding protein by cholesterol enriched-diet and effect of ginger on lipid metabolism. Life Sci. 2009;84(25-26):903–7. [PubMed: 19379761]
128. Micklefield G. H, Redeker Y, Meister V, Jung O, Greving I, May B. Effects of ginger on gastroduodenalmotility. Int J Clin Pharmacol Ther. 1999;37(7):341–6. [PubMed: 10442508]
129. Minghetti P, Sosa S, Cilurzo F, editors. et al. Evaluation of the topical anti-inflammatory activity of ginger dry extracts from solutions and plasters. Planta Med. 2007;73(15):1525–30. [PubMed: 18058610]
130. Morgan J. P, Penovich P. Jamaica ginger paralysis: Forty-seven-year follow-up. Arch Neurol. 1978;35(8):530–2. [PubMed: 666613]
131. Mowrey D. B, Clayson D. E. Motion sickness, ginger, and psychophysics. Lancet. 1982;1(8273):655–7. [PubMed: 6121968]
132. Mukhopadhyay M. J, Mukherjee A. Clastogenic effect of ginger rhizome in mice. Phytother Res. 2000;14(7):555–7. [PubMed: 11054851]
133. Murakami A, Tanaka T, Lee J. Y, editors. et al. Zerumbone, a sesquiterpene in subtropical ginger, suppresses skin tumor initiation and promotion stages in ICR mice. Int J Cancer. 2004;110(4):481–90.

[PubMed: 15122579]
134. Nakamura H, Yamamoto T. Mutagen and anti-mutagen in ginger. Zingiber officinale. Mutat Res. 1982;103(2):119–26. [PubMed: 7035917]
135. Nakamura H, Yamamoto T. The active part of the [6]-gingerol molecule in mutagenesis. Mutat Res. 1983;122(2):87–94. [PubMed: 6361533]
136. Nakamura Y, Yoshida C, Murakami A, Ohigashi H, Osawa T, Uchida K. Zerumbone, a tropical ginger sesquiterpene, activates phase II drug metabolizing enzymes. FEBS Lett. 2004;572(1-3):245–50. [PubMed: 15304356]
137. Nakazawa T, Ohsawa K. Metabolism of [6]-gingerol in rats. Life Sci. 2002;70(18):2165–75. [PubMed: 12002808]
138. Nanthakomon T, Pongrojpaw D. The efficacy of ginger in prevention of postoperative nausea and vomiting after major gynecologic surgery. J Med Assoc Thai. 2006;89 Suppl.4:S130–6. [PubMed: 17725149]
139. Ness J, Sherman F. T, Pan C. X. Alternative medicine: What the data say about common herbal therapies. Geriatrics. 1999;54(10):33–8. 40, 43. [PubMed: 10542859]
140. Nicoll R, Henein M. Y. Ginger (Zingiber officinale Roscoe): A hot remedy for cardiovascular disease? Int J Cardiol. 2009;131(3):408–9. [PubMed: 18037515]
141. Niebyl J. R. Drug therapy during pregnancy. Curr Opin Obstet Gynecol. 1992;4(1):43–7. [PubMed: 1543829]
142. Niebyl J. R, Goodwin T. M. Overview of nausea and vomiting of pregnancy with an emphasis on vitamins and ginger. Am J Obstet Gynecol. 2002;185 (5 Suppl Understanding:S253–5. [PubMed: 12011896]
143. Nigam N, Bhui K, Prasad S, George J, Shukla Y. [6]-gingerol induces reactive oxygen species regulated mitochondrial cell death pathway in human epidermoid carcinoma A431 cells. Chem Biol Interact. 2009;181:77–84. [PubMed: 19481070]
144. Nurtjahja-Tjendraputra E, Ammit A. J, Roufogalis B. D, Tran V. H, Duke C. C. Effective anti-platelet and COX-1 enzyme inhibitors from pungent constituents of ginger. Thromb Res. 2003;111(4-5):259–65. [PubMed: 14693173]
145. Ozgoli G, Goli M, Moattar F. Comparison of effects of ginger, mefenamic acid, and ibuprofen on pain in women with primary dysmenorrhea. J Altern Complement Med. 2009;15:129–32. [PubMed: 19216660]
146. Ozgoli G, Goli M, Simbar M. Effects of ginger capsules on pregnancy, nausea, and vomiting. J Altern Complement Med. 2009;15(3):243–6. [PubMed: 19250006]
147. Pan M. H, Hsieh M. C, Kuo J. M, Lai C. S, Wu H, Sang S, Ho C. T. [6]-shogaol induces apopto- sis in human colorectal carcinoma cells via ROS production, caspase activation, and GADD 153 expres-sion. Mol Nutr Food Res. 2008;52(5):527–37. [PubMed: 18384088]
148. Park K. K, Chun K. S, Lee J. M, Lee S. S, Surh Y. J. Inhibitory effects of [6]-gingerol, a major pungent principle of ginger, on phorbol ester-induced inflammation, epidermal ornithine decarboxylase activity and skin tumor promotionin ICR mice. Cancer Lett. 1998;129(2):139–44. [PubMed: 9719454]
149. Park Y. J, Wen J, Bang S, Park S. W, Song S. Y. [6]-gingerol induces cell cycle arrest and cell death of mutant p53-expressing pancreatic cancer cells. Yonsei Med J. 2006;47(5):688–97. [PMC free article: PMC2687755] [PubMed: 17066513]
150. Phillips S, Hutchinson S, Ruggier R. Zingiber officinale does not affect gastric emptying rate: A randomised, placebo-controlled, crossover trial. Anaesthesia. 1993;48(5):393–5. [PubMed: 8317647]
151. Phillips S, Ruggier R, Hutchinson S. E. Zingiber officinale (ginger)-an antiemetic for day case surgery. Anaesthesia. 1993;48(8):715–7. [PubMed: 8214465]
152. Platel K, Srinivasan K. Influence of dietary spices and their active principles on pancreatic diges-tiveenzymes in albino rats. Nahrung. 2000;44(1):42–6. [PubMed: 10702999]
153. Platel K, Srinivasan K. Studies on the influence of dietary spices on food transit time in experimen-talrats.

NutrRes. 2001;21:1309–14.
154. Pongrojpaw D, Chiamchanya C. The efficacy of ginger in prevention of post-operative nausea and vomiting after outpatient gynecological laparoscopy. J Med Assoc Thai. 2003;86(3):244–50. [PubMed: 12757064]
155. Pongrojpaw D, Somprasit C, Chanthasenanont A. A randomized comparison of ginger and dimen- hydrinate in the treatment of nausea and vomiting in pregnancy. J Med Assoc Thai. 2007;90(9):1703–9. [PubMed: 17957907]
156. Portnoi G, Chng L. A, Karimi-Tabesh L, Koren G, Tan M. P, Einarson A. Prospective compara-tivestudy of the safety and effectiveness of ginger for the treatment of nausea and vomiting in pregnancy. Am J Obstet Gynecol. 2003;189(5):1374–7. [PubMed: 14634571]
157. Power M. L, Holzman G. B, Schulkin J. A survey on the management of nausea and vomiting in pregnancy by obstetrician/gynecologists. Prim Care Update Ob Gyns. 2001;8:69–72. [PubMed: 11246031]
158. Pribitkin E. D, Boger G. Herbal therapy: What every facial plastic surgeon must know. Arch Facial Plast Surg. 2001;3(2):127–32. [PubMed: 11368667]
159. Qian Q. H, Yue W, Wang Y. X, Yang Z. H, Liu Z. T, Chen W. H. Gingerol inhibits cisplatin- induced vomiting by down regulating 5-hydroxytryptamine, dopamine and substance P expression in minks. Arch Pharm Res. 2009;32(4):565–73. [PubMed: 19407975]
160. Quimby E. L. The use of herbal therapies in pediatric oncology patients: Treating symptoms of cancer and side effects of standard therapies. J Pediatr Oncol Nurs. 2007;24(1):35–40. [PubMed: 17185400]
161. Reddy A. C, Lokesh B. R. Studies on spiceprinciples as antioxidants in the inhibition of lipid peroxidation of rat liver microsomes. Mol Cell Biochem. 1992;111(1-2):117–24. [PubMed: 1588934]
162. Reginster J. Y, Gillot V, Bruyere O, Henrotin Y. Evidence of nutriceutical effectiveness in the treatment of osteoarthritis. Curr Rheumatol Rep. 2000;2(6):472–7. [PubMed: 11123100]
163. Rhode J, Fogoros S, Zick S, Wahl H, Griffith K. A, Huang J, Liu J. R. Ginger inhibits cell growth and modulates angiogenic factors in ovarian cancer cells. BMC Complement Altern Med. 2007;7:44. [PMC free article: PMC2241638] [PubMed: 18096028]
164. Rong X, Peng G, Suzuki T, Yang Q, Yamahara J, Li Y. A 35-day gavage safety assessment of ginger in rats. Regul Toxicol Pharmacol. 2009;54(2):118–23. [PMC free article: PMC2785542] [PubMed: 19303040]
165. Schmid R, Schick T, Steffen R, Tschopp A, Wilk T. Comparison of seven commonly used agents for prophylaxis of seasickness. J Travel Med. 1994;1(4):203–6. [PubMed: 9815340]
166. Schulze-Osthoff K, Ferrari D, Riehemann K, Wesselborg S. Regulation of NF-kappa B activation by MAP kinase cascades. Immunobiology. 1997;198(1-3):35–49. [PubMed: 9442376]
167. Schwertner H. A, Rios D. C, Pascoe J. E. Variation in concentration and labeling of ginger root dietary supplements. Obstet Gynecol. 2006;107(6):1337–43. [PubMed: 16738161]
168. Sekiya K, Ohtani A, Kusano S. Enhancement of insulin sensitivity in adipocytes by ginger. Biofactors. 2004;22(1-4):153–6. [PubMed: 15630272]
169. Sharma S. S, Gupta Y. K. Reversal of cisplatin-induced delay in gastric emptying in rats by ginger (Zingiber officinale) J Ethnopharmacol. 1998;62(1):49–55. [PubMed: 9720611]
170. Sharma J. N, Srivastava K. C, Gan E. K. Suppressive effects of eugenol and ginger oil on arthritic rats. Pharmacology. 1994;49(5):314–8. [PubMed: 7862743]
171. Shobana S, Naidu K. A. Antioxidant activity of selected Indian spices. Prostaglandins Leukot Essent Fatty Acids. 2000;62(2):107–10. [PubMed: 10780875]
172. Shukla Y, Singh M. Cancer preventive properties of ginger: A brief review. Food Chem Toxicol. 2007;45(5):683–90. [PubMed: 17175086]
173. Smith C, Crowther C, Willson K, Hotham N, McMillian V. A randomized controlled trial of ginger to treat nausea and vomiting in pregnancy. Obstet Gynecol. 2004;103(4):639–45. [PubMed: 15051552]
174. Sripramote M, Lekhyananda N. A randomized comparison of ginger and vitamin B6 in the treatmentof

nausea and vomiting of pregnancy. J Med Assoc Thai. 2003;86(9):846–53. [PubMed: 14649969]
175. Srivastava K. C, Mustafa T. Ginger (Zingiber officinale) in rheumatismand musculoskeletal disorders. Med Hypotheses. 1992;39(4):342–8. [PubMed: 1494322]
176. Stewart J. J, Wood M. J, Wood C. D, Mims M. E. Effects of ginger on motion sickness susceptibility and gastric function. Pharmacology. 1991;42(2):111–20. [PubMed: 2062873]
177. Sung B, Jhurani S, Ahn K. S, editors. et al. Zerumbone down-regulates chemokine receptor CXCR4 expression leading to inhibition of CXCL12-induced invasion of breast and pancreatic tumor cells. Cancer Res. 2008;68(21):8938–44. [PubMed: 18974138]
178. Sung B, Murakami A, Oyajobi B. O, Aggarwal B. B. Zerumbone abolishes RANKL-induced NF-kappaB activation, inhibits osteoclastogenesis, and suppresses human breast cancer-induced bone loss in athymic nude mice. Cancer Res. 2009;69(4):1477–84. [PubMed: 19190327]
179. Surh Y. J. Molecular mechanisms of chemopreventive effects of selected dietary and medicinal phenolic substances. Mutat Res. 1999;428(1-2):305–27. [PubMed: 10518003]
180. Surh Y. J. Anti-tumor promoting potential of selected spice ingredients with antioxidative and anti-inflammatory activities: A short review. Food Chem Toxicol. 2002;40(8):1091–7. [PubMed: 12067569]
181. Surh Y. J, Lee S. S. Enzymic reduction of [6]-gingerol, a major pungent principle of ginger, in the cell-free preparation of rat liver. Life Sci. 1994;54(19):L321–6. [PubMed: 8190011]
182. Surh Y. J, Lee E, Lee J. M. Chemoprotective properties of somepungent ingredients present in red pepper and ginger. Mutat Res. 1998;402(1-2):259–67. [PubMed: 9675305]
183. Surh Y. J, Park K. K, Chun K. S, Lee L. J, Lee E, Lee S. S. Anti-tumor-promoting activities of selected pungent phenolic substances present in ginger. J Environ Pathol Toxicol Oncol. 1999;18(2):131–9. [PubMed: 15281225]
184. Takada Y, Murakami A, Aggarwal B. B. Zerumbone abolishes NF-kappaB and IkappaBalpha kinase activation leading to suppression of antiapoptotic and metastatic gene expression, upregulation of apoptosis, anddownregulation of invasion. Oncogene. 2005;24(46):6957–69. [PubMed: 16007145]
185. Talalay P, Talalay P. The importance of using scientific principles in the development of medicinal agents from plants. Acad Med. 2001;76(3):238–47. [PubMed: 11242573]
186. Tanabe M, Chen Y. D, Saito K, Kano Y. Cholesterol biosynthesis inhibitory component from Zingiber officinale Roscoe. Chem Pharm Bull (Tokyo) 1993;41(4):710–3. [PubMed: 8508473]
187. Thatte U, Bagadey S, Dahanukar S. Modulation of programmed cell death by medicinal plants. Cell Mol Biol (Noisy-le-grand) 2000;46(1):199–214. [PubMed: 10726985]
188. Thompson H. J, Potter P. J. Review: Ginger prevents 24 hour postoperative nausea and vomiting. EvidBasedNurs. 2006;9(3):80. [PubMed: 16865831]
189. Tjendraputra E, Tran V. H, Liu-Brennan D, Roufogalis B. D, Duke C. C. Effect of ginger constit-uentsand synthetic analogues on cyclooxygenase-2 enzyme in intact cells. Bioorg Chem. 2001;29(3):156–63. [PubMed: 11437391]
190. Topic B, Tani E, Tsiakitzis K, Kourounakis P. N, Dere E, Hasenohrl R. U, Hacker R, Mattern C. M, Huston J. P. Enhanced maze performance and reduced oxidative stress by combined extracts of zingiber officinale and ginkgo biloba in the aged rat. Neurobiol Aging. 2002;23(1):135–43. [PubMed: 11755028]
191. Tripathi S, Bruch D, Kittur D. S. Ginger extract inhibits LPS induced macrophage activation and function. BMC Complement Altern Med. 2008;8:1. [PMC free article: PMC2234390] [PubMed: 18173849]
192. Tripathi S, Maier K. G, Bruch D, Kittur D. S. Effect of [6]-gingerol on pro-inflammatory cytokine production and costimulatory molecule expression in murine peritoneal macrophages. J Surg Res. 2007;138(2):209–13. [PubMed: 17291534]
193. Tsui B, Dennehy C. E, Tsourounis C. A survey of dietary supplement use during pregnancy at an academic medical center. Am J Obstet Gynecol. 2001;185(2):433–7. [PubMed: 11518905]

194. Ueki S, Miyoshi M, Shido O, Hasegawa J, Watanabe T. Systemic administration of [6]-gingerol, a pungent constituent of ginger, induces hypothermia in rats via an inhibitory effect on metabolic rate. Eur J Pharmacol. 2008;584(1):87–92. [PubMed: 18295202]
195. Uz E, Karatas O. F, Mete E, Bayrak R, Bayrak O, Atmaca A. F, Atis O, Yildirim M. E, Akcay A. The effect of dietary ginger (Zingiber officinals Rosc.) on renal ischemia/reperfusion injury in rat kidneys. Ren Fail. 2009;31(4):251–60. [PubMed: 19462272]
196. Vaes L. P, Chyka P. A. Interactions of warfarin with garlic, ginger, ginkgo, or ginseng: Nature of the evidence. Ann Pharmacother. 2000;34(12):1478–82. [PubMed: 11144706]
197. Verma S. K, Bordia A. Ginger, fat and fibrinolysis. Indian J Med Sci. 2001;55(2):83–6. [PubMed: 11482162]
198. Verma S. K, Singh M, Jain P, Bordia A. Protective effect of ginger, Zingiber officinale Rosc. on experimental atherosclerosis in rabbits. Indian J Exp Biol. 2004;42(7):736–8. [PubMed: 15339040]
199. Verma S. K, Singh J, Khamesra R, Bordia A. Effect of ginger on platelet aggregation in man. Indian J Med Res. 1993;98:240–2. [PubMed: 8119760]
200. Vijaya Padma V, Arul S, Christie Diana, Ramkuma K. M. Induction of apoptosis by ginger in HEp-2 cell line is mediated by reactive oxygen species. Basic Clin Pharmacol Toxicol. 2007;100(5):302–7. [PubMed: 17448115]
201. Vimala S, Norhanom A. W, Yadav M. Anti-tumour promoter activity in Malaysian ginger rhizobia used in traditional medicine. Br J Cancer. 1999;80(1-2):110–6. [PMC free article: PMC2362999] [PubMed: 10389986]
202. Visalyaputra S, Petchpaisit N, Somcharoen K, Choavaratana R. The efficacy of ginger root in theprevention of postoperative nausea and vomiting after outpatient gynaecological laparoscopy. Anaesthesia. 1998;53(5):506–10. [PubMed: 9659029]
203. Vutyavanich T, Kraisarin T, Ruangsri R. Ginger for nausea and vomiting in pregnancy: Randomized, double-masked, placebo-controlled trial. Obstet Gynecol. 2001;97(4):577–82. [PubMed: 11275030]
204. Wang C. C, Chen L. G, Lee L. T, Yang L. L. Effects of [6]-gingerol, an antioxidant from ginger, on inducing apoptosis in human leukemic HL-60 cells. In Vivo. 2003;17(6):641–5. [PubMed: 14758732]
205. Wang W, Li C. Y, Wen X. D, Li P, Qi L. W. Plasma pharmacokinetics, tissue distribution and excretion study of [6]-gingerol in rat by liquid chromatography-electrospray ionization time-of-flight mass spectrometry. J Pharm Biomed Anal. 2009a;49(4):1070–4. [PubMed: 19217234]
206. Wang W, Li C.Y, Wen X. D, Li P, Qi L. W. Simultaneous determination of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol in rat plasma by liquid chromatography-mass spectrometry: Application to pharmacokinetics. J Chromatogr B Analyt Technol Biomed Life Sci. 2009b;877(8-9):671–9. [PubMed: 19201263]
207. Weidner M. S, Sigwart K. The safety of a ginger extract in the rat. J Ethnopharmacol. 2000;73(3):513–20. [PubMed: 11091007]
208. Weidner M. S, Sigwart K. Investigation of the teratogenic potential of a Zingiber officinale extract in the rat. Reprod Toxicol. 2001;15:75–80. [PubMed: 11137381]
209. White B. Ginger: An overview. Am Fam Physician. 2007;75(11):1689–91. [PubMed: 17575660]
210. Wilkinson J. M. Effect of ginger tea on the fetal development of Sprague-Dawley rats. Reprod Toxicol. 2000a;14(6):507–12. [PubMed: 11099876]
211. Wilkinson J. M. What do we know about herbal morning sickness treatments? A literature survey. Midwifery. 2000b;16(3):224–8. [PubMed: 10970756]
212. Willetts K. E, Ekangaki A, Eden J. A. Effect of a ginger extract on pregnancy-induced nausea: A randomised controlled trial. Aust N Z J Obstet Gynaecol. 2003;43(2):139–44. [PubMed: 14712970]
213. Wood C. D, Manno J. E, Wood M. J, Manno B. R, Mims M. E. Comparison of efficacy of ginger with

various antimotion sickness drugs. Clin Res Pr Drug Regul Aff. 1988;6(2):129–36. [PubMed: 11538042]
214. Wu K. L, Rayner C. K, Chuah S. K, editors. et al. Effects of ginger on gastric emptying and motility in healthy humans. Eur J Gastroenterol Hepatol. 2008;20(5):436–40. [PubMed: 18403946]
215. Yagihashi S, Miura Y, Yagasaki K. Inhibitory effect of gingerol on the proliferation and invasion of hepatoma cells in culture. Cytotechnology. 2008;57(2):129–36. [PMC free article: PMC2553670] [PubMed: 19003157]
216. Yoshikawa M, Hatakeyama S, Taniguchi K, Matuda H, Yamahara J. [6]-gingesulfonic acid, a new anti-ulcer principle, and gingerglycolipids A, B, and C, three new monoacyldigalactosylglycerols, from Zingiberis rhizoma originating in Taiwan. Chem Pharm Bull (Tokyo) 1992;40(8):2239–41. [PubMed: 1423791]
217. Yoshikawa M, Yamaguchi S, Kunimi K, Matsuda H, Okuno Y, Yamahara J, Murakami N. Stomachic principles in ginger. III. An anti-ulcer principle, 6-gingesulfonic acid, and three monoacyldi-galactosylglycerols, gingerglycolipids A, B, and C, from Zingiberis rhizoma originating in Taiwan. Chem Pharm Bull (Tokyo) 1994;42(6):1226–30. [PubMed: 8069973]
218. Yoshimi N, Wang A, Morishita Y, editors. et al. Modifying effects of fungal and herb metabolites on azoxymethane- induced intestinal carcinogenesis in rats. Jpn J Cancer Res. 1992;83(12):1273–8. [PubMed: 1483942]
219. Young H. Y, Liao J. C, Chang Y. S, Luo Y. L, Lu M. C, Peng W. H. Synergistic effect of ginger and nifedipine on human platelet aggregation: A study inhypertensive patients and normal volunteers. Am J Chin Med. 2006;34(4):545–51. [PubMed: 16883626]
220. Young H. Y, Luo Y. L, Cheng H. Y, Hsieh W. C, Liao J. C, Peng W. H. Analgesic and anti-inflammatory activities of [6]-gingerol. J Ethnopharmacol. 2005;96(1-2):207–10. [PubMed: 15588672]
221. Zick S. M, Djuric Z, Ruffin M. T, editors. et al. Pharmacokinetics of [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol and conjugate metabolites in healthy human subjects. Cancer Epidemiol Biomarkers Prev. 2008;17(8):1930–6. [PMC free article: PMC2676573] [PubMed: 18708382]
222. Zick S. M, Ruffin M. T, Lee J, Normolle D. P, Siden R, Alrawi S, Brenner D. E. Phase II trial of encapsulated ginger as a treatment for chemotherapy-induced nausea and vomiting. Support Care Cancer. 2009;17(5):563–72. [PMC free article: PMC4131259] [PubMed: 19005687]

## Figures

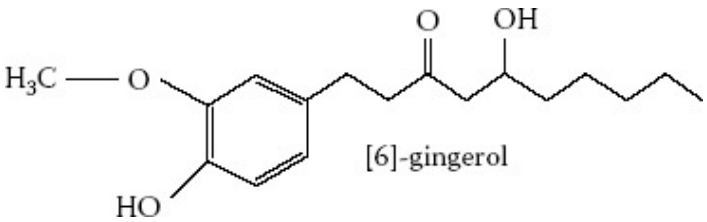


FIGURE 7.1

Structure of [6]-gingerol, believed to be the most abundant bioactive component of ginger root.

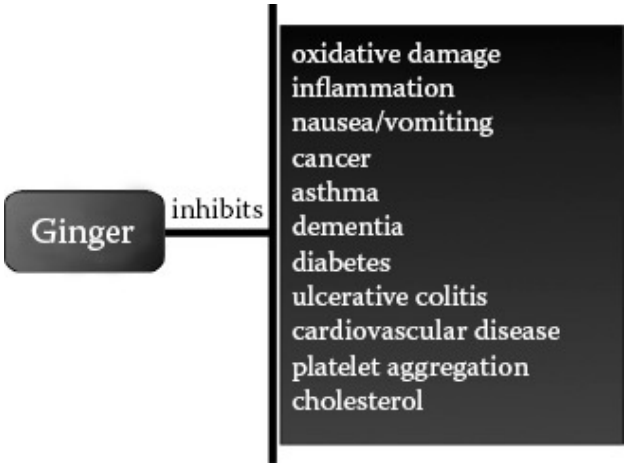


FIGURE 7.2

The variety of protective effects wielded by ginger.

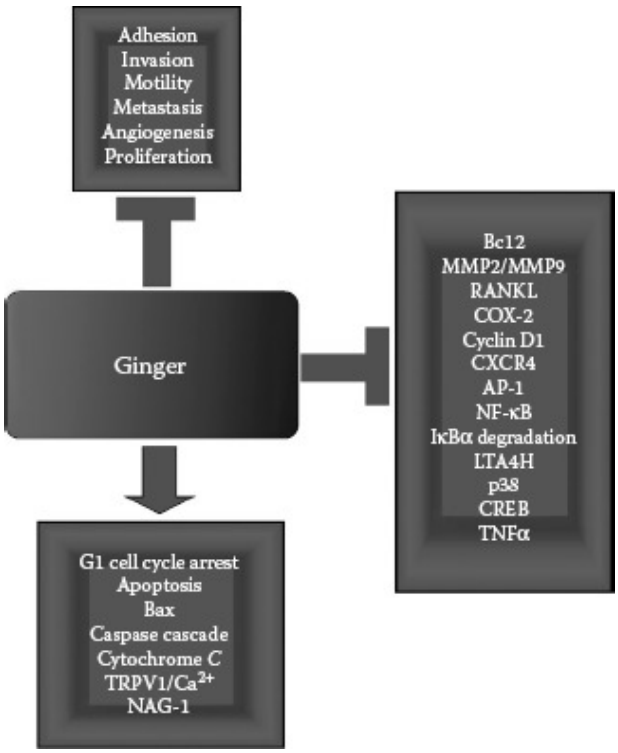


FIGURE 7.3

The anticancer activities exerted by ginger.



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