Monograph

Ginger

Zingiber officinalis

Ginger is a universal agent, almost too well known to require description. Ginger is used worldwide as a cooking spice, condiment and herbal remedy. It is one of the worlds favorite spices, and is not only known as a culinary herb but it is a domestic household remedy for many common ailments including stomach upset, fever, pain and for the common cold. It is excellent for children's colic's and cramping, and expelling gas. It is of much value in the treatment of colds and respiratory conditions relieving symptoms as well as shortening their duration. Ginger relieves chills, coughs, indigestion; counteracts nausea, dizziness, diarrhea, abdominal pain and arthritis.

Active constituents:

- Phenolic compounds (shogaols and gingerols)
- Sesquiterpenes (bisapolene, zingiberene, zingiberol, zerumbone, sesquiphellandrene, curcurmene)
- Galanolactone
- Gingesulfonic acid
- Zingerone
- Geraniol
- Neral
- Monoacyldigalactosylglycerols
- Gingerglycolipids

The active ingredients in ginger are thought to reside in its volatile oils, which comprise approximately 1-3% of its weight. The concentrations of active ingredients vary with growing conditions. Ginger's active ingredients have a variety of physiologic effects. For example, the gingerols have analgesic, sedative, antipyretic and antibacterial effects in vitro and in animals. [5-9]

New research shows that about six compounds appear to be important in ginger, especially [10]-shogao, which provides the anti-emetic activity in ginger. The activity of ginger is due to its volatile oils. Ginger contains curcumin (like turmeric) in addition to the phenolic compounds, gingerols and diarylheptanoids, which are high in antioxidants.[3]

Traditional use:

The Chinese have used ginger for at least 2500 years as a digestive aid and anti-nausea remedy and to treat bleeding disorders and rheumatism; it was also used to treat baldness, toothache, snakebite, and respiratory conditions. is a stomachic and anti-emetic. Ginger has been used historically as a carminative, to enhance digestion and reduce intestinal gas and flatulence. Its indications are for: cold excess in spleen and stomach, cold hands and feet, weak pulse; cold excess in lungs: cough with profuse clear sputum. In TCM ginger is used for ailments triggered by cold, damp weather. Ginger is used extensively in Ayurveda, the traditional medicine of India, to block excessive clotting (i.e. heart disease), reduce cholesterol and fight arthritis. In Malaysia and Indonesia, ginger soup is given to new mothers for 30 days after their delivery to help warm them and to help them sweat out impurities. In Arabian medicine, ginger is considered an aphrodisiac[1]. Some Africans believe that eating ginger regularly will help repel mosquitos. [15, 16]

It was often prescribed as a hot infusion to break up congestion and to relieve painful menstruation.[25]

Ginger, just as it is used so often in many cultures as a common condiment and flavoring agent, it was used, and still is, by herbalist as a circulatory enhancing agent, which reinforces the therapeutic activity of other herbs.

Modern science use:

Ginger, because of the ability to influence prostaglandin metabolism is a potent inhibitor of thromboxane synthesis, significantly inhibiting platelet aggregation and inflammation.[12, 13] Ginger extracts inhibited platelet cyclo-oxygenase production, thromboxane generation and platelet aggregation in a dose-dependent fashion; gingerol also inhibited thromboxane-mediated platelet aggregation.[17-20] Ginger has a slight diaphoretic and antipyretic effect making useful for reducing fever.[22] Ginger has recently been found to have a thermogenic effect, possible being useful in weight management programs.[23, 24] antioxidant effects, [31-33] and antineoplastic.[34-38] Ginger also possesses remarkable proteolytic activity making it useful for many digestive complaints. Ginger promotes the secretion of saliva and gastric juices as well as bile. Ginger's effects on circulation would be classified as a gentle diffusive stimulant, along with having a mild relaxing effect.[1]

Ginger is best known for its ability to relieve nausea. Several randomized, controlled trials support ginger's use as an anti-emetic for nausea secondary to several conditions: morning sickness, chemotherapy-associated nausea, post-operative nausea and motion sickness. In a randomized, double-blind, placebo-controlled cross-over trial of 30 women with hyperemesis gravidarum, ginger (250 mg four times daily) proved significantly more effective than placebo in preventing and reducing nausea.[26]

In shrews, dogs and rats, ginger extracts effectively reduced chemotherapy-associated vomiting.[27, 28] Ginger also proved useful in treating chemotherapy-induced nausea in a small pilot study of 11 adult patients; their nausea scores fell from an average of 2 (out of maximum of 4) to 0.7 after taking 1.5 grams of powdered ginger.[29] Another case series also supported ginger's use as an anti-emetic in patients undergoing chemotherapy. [30]

Actions:

- Cardiovascular: inhibits thromboxane-mediated platelet aggregation, lipid-regulating, anti-atherosclerotic
- Pulmonary: diaphoretic, mucolytic, expectorant
- Gastrointestinal: anti-nausea, anti-emetic, carminative and anti-ulcer, helps vertigo
- Endocrine: hypoglycemic
- Hematologic: anti-platelet – inhibits platelet aggregation
- Rheumatologic: anti-inflammatory for arthritis: down-regulates COX-2, suppresses proflammatory prostaglandins
- Anti-microbial: against Kawasaki disease and M. luteus
- Anti-neoplastic: anti-tumor, chemopreventive, induces apoptosis, inhibits AP1 and EGF, Bcl-2 inhibitor
- Anti-oxidant: free radical & superoxide scavenger, anti-beta amyloid, inhibits H2O2 in Kashin-Beck
- Anti-parasitic: against Shistosoma amd Anisakis
- Menstrual regulating: analgesic
- Other/miscellaneous: Warming/diaphoretic/thermogenic; enhances bioavailability of other herbs
- Anti-obesity

Cardiovascular:

Ginger's effects on circulation would be classified as a gentle diffusive stimulant, along with having a mild relaxing effect.[1] It is used extensively in Ayurveda to inhibit abnormal clotting, reduce cholesterol and fight arthritis. It significantly reduces serum and hepatic cholesterol levels and possesses potent cardiotonic activity,[10, 11] Ginger extracts inhibited platelet cyclo-oxygenase production, thromboxane generation and platelet aggregation in a dose-dependent fashion; gingerol also inhibites thromboxane-mediated platelet aggregation.[17-20] Ginger is a well-known synergistic herb that potentiates, harmonizes, and improves the deep circulation of other herbs.[14]

Antioxidant Effects May Attenuate Development of Atherosclerosis

Zingiber officinale (ginger) is the food of rhizoma species as well as Chinese traditional medicine and has various pharmacological effects. The last researches showed that ginger not only reduced plasma lipid levels but also the mouse atherosclerotic lesion areas. The ginger anti-oxidative effect may play an important role in attenuation of development of atherosclerosis. Anti-oxidative affect of Zingiber Officinale Rosc on hyperlipidemia rats have been studied and the changes of glutathione (GSH-Px) and plasma lipid peroxides (LPO) in their blood have been observed. Male adult Wistar rats were grouped into control, preventive and curative teams. The experimental teams were respectively fed on the test diet containing 2% ginger and 5% ginger, in order to measure the changes of (LPO) and (GSH-Px) after the experiment. The results show that ginger increased GSH-Px and reduced LPO in the rats' blood. Ginger could inhibit and/or savaging radicals of rat body in different degrees. [57]

Lowers blood pressure through blockade of voltage dependent calcium channels

The crude extract of ginger (Zo.Cr) induced a dose-dependent (0.3-3 mg/kg) fall in the arterial blood pressure of anesthetized rats. In guinea pig paired atria, Zo.Cr exhibited a cardiodepressant activity on the rate and force of spontaneous contractions. In rabbit thoracic aorta preparation, Zo.Cr relaxed the phenylephrine-induced vascular contraction at a dose 10 times higher than that required against K (80 mM)-induced contraction. Ca2+ channel-blocking (CCB) activity was confirmed when Zo.Cr shifted the Ca2+ dose-response curves to the right similar to the effect of verapamil. It also inhibited the phenylephrine (1 microM) control peaks in normal-Ca2+ and Ca2+-free solution, indicating that it acts at both the membrane-bound and the intracellular Ca2+ channels. When tested in endothelium-intact rat aorta, it again relaxed the K-induced contraction at a dose 14 times less than that required for relaxing the PE-induced contraction. The vasodilator effect of Zo.Cr was endothelium-independent because it was not blocked by L-NAME (0.1mM) or atropine (1 microM) and also was reproduced in the endothelium-denuded preparations at the same dose range. These data indicate that the blood pressure-lowering effect of ginger is mediated through blockade of voltage-dependent calcium channels.[81]

Pulmonary:

In Traditional Chinese Medicine (TCM) ginger is classified as pungent, dry, and warming. It stimulates yang energy; warms the lungs and dissolves phlegm. Its indications are for: cold excess in spleen and stomach, cold hands and feet, weak pulse; cold excess in lungs: cough with profuse clear sputum.[15, 16]
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Two hundred mothers of children under five years of age having lower respiratory tract infection were interviewed with the help of pre-tested unstructured questionnaire to know the danger signs perceived by her in a child suffering from pneumonia and the home remedies used by them before seeking medical help. 'Pasli Chalna' and refusal to feed were the most common symptoms perceived as dangerous. 'Pasli Chalna' correlated with retractions in 91.9% and fast breathing in 8.1% cases. Honey (25%) and Ginger (27%) were the most common home remedies used for relief of cough. Self advised medications were used by 24% mothers and a majority (58.4%) gained this knowledge from mass media.[44]

Gastrointestional:

In the western tradition ginger is classified as a diffusive stimulant. The Eclectics used ginger as a stimulating tonic, stomachic, carminative, and antispasmodic. It was used to treat nausea, gastrointestinal cramping, loss of appetite and cold extremities. Ginger has been used historically as a carminative, to enhance digestion and reduce intestinal gas and flatulence.[25] Ginger also possesses remarkable proteolytic activity making it useful for many digestive complaints. Ginger promotes the secretion of saliva and gastric juices as well as bile. It is excellent for children's colic and cramping, and expelling gas New research shows that about six compounds appear to be important in ginger, especially [10]-shogao, which provides the anti-emetic activity in ginger.

1. Motion Sickness

Ginger has long been used as an alternative medication to prevent motion sickness. The mechanism of its action, however, is unknown. It is hypothesized that ginger ameliorates the nausea associated with motion sickness by preventing the development of gastric dysrhythmias and the elevation of plasma vasopressin. Thirteen volunteers with a history of motion sickness underwent circular vection, during which nausea (scored 0-3, i.e., none to severe), electrogastrographic recordings, and plasma vasopressin levels were assessed with or without ginger pretreatment in a crossover-design, double-blind, randomized placebo-controlled study. Circular vection induced a maximal nausea score of 2.5 +/- 0.2 and increased tachygastric activity and plasma vasopressin. Pretreatment with ginger (1,000 and 2,000 mg) reduced the nausea, tachygastria, and plasma vasopressin. Ginger also prolonged the latency before nausea onset and shortened the recovery time after vection cessation. Intravenous vasopressin infusion at 0.1 and 0.2U/min induced nausea and increased bradygastric activity; ginger pretreatment (2,000 mg) affected neither. Ginger effectively reduces nausea, tachygastric activity, and vasopressin release induced by circular vection. In this manner, ginger may act as a novel agent in the prevention and treatment of motion sickness.[39]

2. Nausea (pregnancy):

Up to 80 per cent of pregnant women experience morning sickness during the first trimester of pregnancy. And while ginger has long been used as a remedy for nausea, research on its ability to ease morning sickness is limited. The new findings, based on a randomized, controlled trial involving 291 pregnant women, suggest the common spice could be a natural option for reducing symptoms of morning sickness. However, further evidence of its safety is still needed. Women took 1.05g of ginger or 75 mg of vitamin B6 daily in three supplements for three weeks. B6 has also been shown to improve nausea and vomiting in some pregnant women. Differences from baseline in nausea and vomiting scores were estimated for both groups at days seven, 14, and 21. Ginger was equivalent to vitamin B6 in reducing nausea, retching and vomiting. [66] A recent study examined the role of ginger in postoperative nausea and vomiting. This meta-analysis looked at numerous studies using ginger versus placebo. Researchers looked at published studies and articles, including bibliographies and contacted authors and experts in the field. After review, five randomized studies were examined that included 363 participants. The results showed that a fixed dose of at least one gram of ginger was more effective than placebo in reducing both postoperative nausea and postoperative vomiting. [70]

3. Anti-emetic in Chemotherapy:

Ginger is best known for its ability to relieve nausea. Several randomized, controlled trials support ginger's use as an anti-emetic for nausea secondary to several conditions: morning sickness, chemotherapy-associated nausea, post-operative nausea and motion sickness. In a randomized, double-blind, placebo-controlled cross-over trial of 30 women with hyperemesis gravidarum, ginger (250 mg four times daily) proved significantly more effective than placebo in preventing and reducing nausea.[26]

In shrews, dogs and rats, ginger extracts effectively reduced chemotherapy-associated vomiting. [27, 28] Ginger also proved useful in treating chemotherapy-induced nausea in a small pilot study of 11 adult patients; their nausea scores fell from an average of 2 (out of maximum of 4) to 0.7 after taking 1.5 grams of powdered ginger.[29] Another case series also supported ginger's use as an anti-emetic in patients undergoing chemotherapy. [30]

4. Vertigo

The effect of powdered ginger root upon vertigo and nystagmus following caloric stimulation of the vestibular system was studied in 8 healthy volunteers in a double-blind crossover placebo trial. The results reported are based upon 48 vertigo scores and 48 electronystagmograms. Ginger root reduced the induced vertigo significantly better than did placebo. There was no statistically significant action upon the duration or the maximum slow phase velocity of nystagmus.[45]

5. Anti-Ulcer

By monitoring the effects on HCl/ethanol-induced gastric lesions in rats, a new anti-ulcer principle named 6-gingesulfonic acid was isolated from Zingiberis Rhizoma, the dried rhizome of Zingiber officinale Roscoe (cultivated and processed in Taiwan) together with three new monoacyldigalactosylglycerols named gingerglycolipids A, B and C. Their chemical structures were elucidated on the basis of chemical and physicochemical evidence. 6-Gingesulfonic acid showed more potent anti-ulcer activity than 6-gingerol and 6-shogaol.[46]

Endocrine: Hypoglycemic

An Indian homeopathic journal reported in the late 1970's that freshly squeezed ginger juice had hypoglycemic effects in both diabetic and non-diabetic rats.[55]

Hematologic:

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Rheumatologic:

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1. Osteoarthritis

Ginger extract has been found to be as effective as Ibuprofen in treating osteoarthritis. [21] Alternative medicine is used extensively by patients with chronic pain due to e.g., osteoarthritis. Only few of these drugs have been tested in a controlled setting and the present study was undertaken to examine the effect of ginger extract, one of the most popular herbal medications. Design: Ginger extract was compared to placebo and Ibuprofen in patients with osteoarthritis of the hip or knee in a controlled, double blind, double dummy, cross-over study with a wash-out period of one week followed by three treatment periods in a randomized sequence, each of three weeks duration. Acetaminophen was used as rescue medication throughout the study. The study was conducted in accordance with Good Clinical Practice (European Guideline for GCP). Results: A ranking of efficacy of the three treatment periods: Ibuprofen>ginger extract>placebo was found for visual analogue scale of pain. In the cross-over study, no significant difference between placebo and ginger extract could be demonstrated, while explorative tests of differences in the first treatment period showed a better effect of both Ibuprofen and ginger extract than placebo .[40]

2. Useful for Inflammation and Rheumatic Disorders

One of the features of inflammation is increased oxygenation of arachidonic acid that is metabolized by two enzymic pathways--the cyclooxygenase (COX) and the 5-lipoxygenase (5-LOX)--leading to the production of prostaglandins and leukotrienes respectively. Amongst the COX products, PGE2 and amongst the 5-LOX products, LTB4 are considered important mediators of inflammation. More than 200 potential drugs ranging from non-steroidal anti-inflammatory drugs, corticosteroids, gold salts, disease modifying anti-rheumatic drugs, methotrexate, cyclosporine are being tested. None of the drugs has been found safe; all are known to produce from mild to serious side-effects. Ginger is described in Ayurvedic and Tibb systems of medicine to be useful in inflammation and rheumatism. In all 56 patients (28 with rheumatoid arthritis, 18 with osteoarthritis and 10 with muscular discomfort) used powdered ginger against their afflictions. Amongst the arthritis patients more than three-quarters experienced, to varying degrees, relief in pain and swelling. All the patients with muscular discomfort experienced relief in pain. None of the patients reported adverse effects during the period of ginger consumption that ranged from 3 months to 2.5 years. It is suggested that at least one of the mechanisms by which ginger shows its ameliorative effects could be related to inhibition of prostaglandin and leukotriene biosynthesis, i.e. it works as a dual inhibitor of eicosanoid biosynthesis.[47, 48]

Antimicrobial:

For example, the gingerols have analgesic, sedative, antipyretic and antibacterial effects in vitro and in animals.[5-9]

Treatment of Kawasaki Disease

Kawasaki disease, a mucocutaneous lymph node syndrome predominantly prevalent in children, presents with coronary artery aneurysms and thrombocytosis, and investigators have suggested use of anticoagulants in addition to platelet inhibiting drugs. In Kawasaki disease, hypersensitivity reactions due to antigen/antibody complexes (Arthus type III) may damage the vessel wall and induce arthritis, and antigens may be of microbial or viral origin. Since thromboxane has been implicated in the pathogenesis of Kawasaki disease, I suggest use of ginger and carbon dioxide, novel thromboxane synthetase inhibitors. Thromboxane synthetase inhibitors may act as anticoagulants, platelet inhibitors, anti-inflammatory agents, and agents with both antimicrobial and antiviral activity.[49]

2. Inibits Micrococcus luteus

This study was carried out to understand the antibacterial properties of some spice plants before and after heat treatment in boiling water. The samples included the core and the outer layers of onion, the white and the green parts of green onion, garlic bulb, ginger, ginger root, sweet pepper, chili pepper, brown pepper, and mustard. The test microorganisms included Escherichia coli, Salmonella typhimurium, Vibrio parahaemolyticus, Pseudomonas aeruginosa, Proteus vulgaris, Staphylococcus aureus, Mycobacterium phlei, Streptococcus faecalis, Bacillus cereus, and Micrococcus luteus. Raw garlic bulb could inhibit all of the test strains. The antibacterial activities of green onion are slightly weak than that of onion. However, green onion could inhibit P. aeruginosa and M. luteus, but onion could inhibit E. coli, P. vulgaris, S. faecalis, and B. cereus. Ginger and ginger root could only inhibit M. luteus. Chili pepper could inhibit V. parahaemolyticus and P. vulgaris. Brown pepper could also inhibit P. vulgaris. Sweet pepper and mustard showed no antibacterial activity to all of the test strains. In general, antibacterial components in the spice plants were heat labile. All the spices tested lost their antibacterial activities within 20 min at 100 degrees C.[50]

Antineoplastic:

Ginger, the key ingredient in Asia's culinary triangle could contain a powerful component to combat the growth of human colorectal cancer cells. Some pungent constituents present in ginger and other zingiberaceous plants have potent antioxidant and anti-inflammatory activities, and some of them exhibit cancer preventive activity in experimental carcinogenesis. The anticancer properties of ginger are attributed to the presence of certain pungent vallinoids, viz. [6]-gingerol and [6]-paradol, as well as some other constituents like shogaols, zingerone etc. A number of mechanisms that may be involved in the chemopreventive effects of ginger and its components have been reported from the laboratory studies in a wide range of experimental models. [74]

Molecular anti-cancer targets for [6]-gingerol: 1) antioxidant, 2) anti-inflammation, 3) antitumor promoting properties:

- decrease inducible nitric oxide synthase (iNOS),
- decreases tumor necrosis factor alpha (TNF-alpha) expression through suppression of I-kappaB alpha (IkappaBalpha) phosphorylation,
- decreases nuclear factor kappa B (NF-kappaB) nuclear translocation.
- Other antiproliferative mechanisms of [6]-gingerol include the release of Cytochrome c, Caspases activation, and increase in apoptotic protease-activating factor-1 (Apaf-1) as mechanism of apoptosis induction.[80]

Presenting their findings at the American Association for Cancer Research researchers from the University of Minnesota report how they found slower rates of cancer growth in mice given thrice-weekly feedings of [6]-gingerol - the main active component of ginger and the one that gives ginger its distinctive flavor.

Researchers tested [6]-gingerol's powers by feeding a half milligram to 20 mice three times a week before and after injecting human colorectal tumor cells into their flanks. Control mice were treated the same, except their food contained no [6]-gingerol. Tumors were allowed to grow until they reached a size of one cubic centimeter (0.06 cubic inch), after which the mice were euthanised. The first tumors appeared 15 days after the cells were injected. At that time, 13 tumors of measurable size had appeared among the control mice, four among the [6]-gingerol-treated mice. Mice consuming [6]-gingerol lagged in both the number of animals with measurable tumors and the average size of tumors within the group. These results strongly suggest that ginger compounds may be effective chemopreventive and/or chemotherapeutic agents for colorectal carcinomas. Because mice were not allowed to live with tumors bigger than one cubic centimetre, it's difficult to know if the ginger-treated mice would

have lived longer if left to die of their tumors, but it looks that these results strongly suggest that ginger compounds may be effective chemopreventive and/or chemotherapeutic agents. [37]

Researchers reported that Minnesota University has applied for a patent on the use of [6]-gingerol as an anti-cancer agent, and the technology has been licensed to Pediatric Pharmaceuticals

1. Inhibits EBV Activation at the Tumor Promoting Stage

Zingiberaceae rhizomes commonly used in the Malaysian traditional medicine were screened for anti-tumour promoter activity using the short-term assay of inhibition of 12-O-tetradecanoyl phorbol-13-acetate (TPA)-induced Epstein-Barr virus early antigen (EBV-EA) in Raji cells. The inhibition of TPA-induced EBV-EA was detected using the indirect immunofluorescence assay (IFA) and Western blot technique. The indirect IFA detected the expression/inhibition of EBV-EA-D (diffused EA antigen), whereas the Western blot technique detected the expression/inhibition of both EBV-EA-D and EA-R (restricted EA antigen). Seven rhizomes were found to possess inhibitory activity towards EBV activation, induced by TPA; they are: Curcuma domestica, C. xanthorrhiza, Kaempferia galanga, Zingiber cassumunar, Z. officinale, Z. officinale (red variety), and Z. zerumbet. A cytotoxicity assay was carried out to determine the toxicity of the Zingiberaceae rhizome extracts. The rhizome extracts that exhibited EBV activation inhibitory activity had no cytotoxicity effect in Raji cells. Therefore, the present study shows that several Zingiberaceae species used in Malaysian traditional medicine contain naturally occurring non-toxic compounds that inhibit the EBV activation, which, if further investigated, could contribute in the development of cancer prevention methods at the tumor-promoting stage. [56]

2. Chemopreventive for colon and stomach cancer

Ginger root has been used traditionally for the treatment of gastrointestinal ailments such as motion sickness, dyspepsia and hyperemesis gravidarum, and is also reported to have chemopreventive activity in animal models. The gingerols are a group of structurally related polyphenolic compounds isolated from ginger and known to be the active constituents. Since Helicobacter pylori (HP) is the primary etiological agent associated with dyspepsia, peptic ulcer disease and the development of gastric and colon cancer, the anti-HP effects of ginger and its constituents were tested in vitro. MATERIALS AND METHODS: A methanol extract of the dried powdered ginger rhizome, fractions of the extract and the isolated constituents, 6-,8-,10-gingerol and 6-shogoal, were tested against 19 strains of HP, including 5 CagA+ strains. RESULTS: The methanol extract of ginger rhizome inhibited the growth of all 19 strains in vitro with a minimum inhibitory concentration range of 6.25-50 micrograms/ml. One fraction of the crude extract, containing the gingerols, was active and inhibited the growth of all HP strains with an MIC range of 0.78 to 12.5 micrograms/ml and with significant activity against the CagA+ strains. CONCLUSION: These data demonstrate that ginger root extracts containing the gingerols inhibit the growth of H. pylori CagA+ strains in vitro and this activity may contribute to its chemopreventative effects. [58]

3. Ginger and Turmeric together Show Strong Anti-cancer Activity

In the present study the anti-oxidant, anti-cancer, and anti-mycobacterial activities of extracts from ginger rosemary (*Rosmarinus officinalis*), and turmeric (*Curcuma longa*) were evaluated. The extracts were obtained using supercritical CO(2) with and without ethanol and/or isopropyl alcohol as a co-solvent. The extracts' anti-oxidant power was assessed using the reaction between beta-carotene and linolenic acid, the anti-mycobacterial activity against M. tuberculosis was measured by the MABA test, and their anti-cancer action was tested against nine human cancer ancestries: lung, breast, breast resistant, melanoma, colon, prostate, leukemia, and kidney. The rosemary extracts exhibited the strongest antioxidant and the lowest anti-mycobacterial activities. Turmeric extracts showed the greatest anti-mycobacterial activity. Ginger and turmeric extracts showed selective anticancer activities. [59]

4. Counters Side Effects of Cisplatin Chemotherapy

Cisplatin is one of the chemotherapy drugs associated with nausea, vomiting, and delayed emptying of the stomach. Researchers from India found that extracts from ginger helped to speed up this process in dogs and rats that were given cisplatin chemotherapy. However, extracted chemicals or substances are different from the raw plant. Thus, study results of extracts will not necessarily be consistent with studies using the raw plant. While ginger may be an effective herb in treating nausea and vomiting associated with some cancer therapies, it may also interfere with blood clotting, which could be life threatening to some patients receiving chemotherapy.[60]

5. Suppresses Tumor Promoter TPA-induced EBV Activation

Zerumbone (ZER), a sesquiterpene fromginger root, has recently been found to suppress tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced Epstein-Barr virus activation in a potent manner. In the present study, we evaluated the anti-inflammatory and chemopreventive potentials of ZER in a variety of cell culture experiments. ZER effectively suppressed TPA-induced superoxide anion generation from both NADPH oxidase in dimethylsulfoxide-differentiated HL-60 human acute promyelocytic leukemia cells and xanthine oxidase in AS52 Chinese hamster ovary cells. The combined lipopolysaccharide- and interferon-gamma-stimulated protein expressions of inducible nitric oxide synthase and cyclooxygenase (COX)-2, together with the release of tumor

necrosis factor-alpha, in RAW 264.7 mouse macrophages were also markedly diminished. These suppressive events were accompanied with a combined decrease in the medium concentrations of nitrite and prostaglandin E(2), while the expression level of COX-1 was unchanged. ZER inhibited the proliferation of human colonic adenocarcinoma cell lines in a dose-dependent manner, while the growth of normal human dermal (2F0-C25) and colon (CCD-18 Co) fibroblasts was less affected. It also induced apoptosis in COLO205 cells, as detected by dysfunction of the mitochondria transmembrane, Annexin V-detected translocation of phosphatidylserine, and chromatin condensation. Intriguingly, alpha-humulene, a structural analog lacking only the carbonyl group in ZER, was virtually inactive in all experiments conducted, indicating that the alpha,beta-unsaturated carbonyl group in ZER may play some pivotal roles in interactions with unidentified target molecule(s). Taken together, our results indicate that ZER is a food phytochemical that has distinct potentials for use in anti-inflammation, chemoprevention, and chemotherapy strategies. [61]

6. Induces Apoptosis in Promyelocytic Leukemia

[6]-Gingerol has been reported to possess a strong anti-inflammatory activity, which is considered to be closely associated with its cancer chemopreventive potential. [6]-Paradol, another pungent phenolic substance found in ginger and other Zingiberaceae plants, also has a vanilloid structure found in other chemopreventive phytochemicals including curcumin. In the present study, [6]-gingerol and [6]-paradol were found to exert inhibitory effects on the viability and DNA synthesis of human promyelocytic leukemia (HL-60) cells. The cytotoxic and anti-proliferative effects of both compounds were associated with apoptotic cell death. The above results suggest that [6]-gingerol and [6]-paradol possess potential cytotoxic/cytostatic activities. [62]

7. Ginger inhibits AP-1 and EGF

Many spices, including plants of the ginger family, possess anti-carcinogenic activity. However, the molecular mechanisms by which they exert their anti-tumorigenic effects are unknown. Activator Protein 1 (AP-1) has a critical role in tumor promotion, and blocking of tumor promoter-induced activation of AP-1 inhibits neoplastic transformation. Epidermal growth factor induces cell transformation and AP-1 activity. The purpose of this study was to investigate 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. Our results provide the first evidence that both block EGF-induced cell transformation but act by different mechanisms. [63]

8. Suppresses Formation of DNA Adducts

Essential oils from common spices such as nutmeg, ginger, cardamom, celery, xanthoxylum, black pepper, cumin, and coriander were tested for their ability to suppress the formation of DNA adducts by aflatoxin B1 in vitro in a microsomal enzyme-mediated reaction. All oils were found to inhibit adduct formation very significantly and in a dose-dependent manner. The adduct formation appeared to be modulated through the action on microsomal enzymes, because an effective inhibition on the formation of activated metabolite was observed with each oil. The enzymatic modulation is perhaps due to the chemical constituents of the oils, and this could form a basis for their potential anti-carcinogenic roles. [38]

9. Bcl-2 Inhibition

6-Gingerol is one of the major components of fresh ginger. In this paper, the anti-oxidative effects of 6-gingerol were detected by DPPH and DCFH assays and, as predicted, 6-gingerol as an antioxidant was shown to protect HL-60 cells from oxidative stress. Moreover, it induced cell death in promyelocytic leukemia HL-60 cells, caused DNA fragmentation and inhibited Bcl-2 expression in HL-60 cells. These results suggested that the inhibition of Bcl-2 expression in HL-60 cells might account for the mechanism of 6-gingerol-induced apoptosis. In the inhibitory assay, the cytotoxic effect of 6-gingerol could be prevented by catalase. We suggest that 6-gingerol induced cell death by mediating reactive oxygen species such as hydrogen peroxide and the superoxide anion. Therefore, the results showed that 6-gingerol induced apoptosis in HL-60 cells, not due to its anti-oxidative activity. [65]

10. Anti-angiogenic: Inhibits VEGF and bFGF

6-gingerol possesses novel anti-angiogenic activity in vitro and in vivo. In vitro, [6]-gingerol inhibited both the VEGF- and bFGF-induced proliferation of human endothelial cells and caused cell cycle arrest in the G1 phase. It also blocked capillary-like tube formation by endothelial cells in response to VEGF, and strongly inhibited sprouting of endothelial cells in the rat aorta and formation of new blood vessel in the mouse cornea in response to VEGF. Moreover, i.p. administration, without reaching tumor cytotoxic blood levels, to mice receiving i.v. injection of B16F10 melanoma cells, reduced the number of lung metastasis, with preservation of apparently healthy behavior. Taken together, these results demonstrate that **6-gingerol** inhibits angiogenesis and may be useful in the treatment of tumors and other angiogenesis-dependent diseases. [67]

11. Inhibits COX-2, NF-kappa beta

Cyclooxygenase-2 (COX-2), a key enzyme in the prostaglandin biosynthesis, has been recognized as a molecular target for many anti-inflammatory as well as chemopreventive agents. [6]-Gingerol possesses anti-tumor effects in

which mechanisms of action include inhibition of cyclooxygenase-2 (COX-2). In our present study, topical application of [6]-gingerol inhibited COX-2 expression in mouse skin stimulated with a prototype tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA). Since the transcription factor nuclear factor-kappaB (NF-kappaB) is known to regulate COX-2 induction, we attempted to determine the effect of [6]-gingerol on TPA-induced activation of NF-kappaB. Pretreatment with [6]-gingerol resulted in a decrease in both TPA-induced DNA binding and transcriptional activities of NF-kappaB through suppression of IkappaBalpha degradation and p65 nuclear translocation. Phosphorylation of both IkappaBalpha and p65 was substantially blocked by [6]-gingerol. In addition, [6]-gingerol inhibited TPA-stimulated interaction of phospho-p65-(Ser-536) with cAMP response element binding protein-binding protein, a transcriptional coactivator of NF-kappaB. Moreover, [6]-gingerol prevented TPA-induced phosphorylation and catalytic activity of p38 mitogen-activated protein (MAP) kinase that regulates COX-2 expression in mouse skin. The p38 MAP kinase inhibitor SB203580 attenuated NF-kappaB activation and subsequent COX-2 induction in TPA-treated mouse skin. Taken together, our data suggest that [6]-gingerol inhibits TPA-induced COX-2 expression in mouse skin in vivo by blocking the p38 MAP kinase-NF-kappaB signaling pathway. [68]

11. Inhibits COX-2, NF-kappa beta II

Previous studies have demonstrated that 6-gingerol inhibits mouse skin tumor promotion and anchorage-independent growth of cultured mouse epidermal cells stimulated with epidermal growth factor. Topical application of [6]-gingerol inhibited phorbol 12-myristate 13-acetate -induced COX-2 expression. One of the essential transcription factors responsible for COX-2 induction is NF-kappaB. 6-Gingerol suppressed NF-kappaB DNA binding activity in mouse skin. In addition, 6-gingerol inhibited the phoshorylation of p38 mitogen-activated protein kinase which may account for its inactivation of NF-kappaB and suppression of COX-2 expression. [69]

12. Radiation protective: gastroprotective, antiemetic action comparable to drugs – free radical scavenging mechanism.

A study was conducted that looked at the gastroprotective action of a hydroalcoholic extract of ginger against radiation-induced conditioned taste aversion (CTA) in both male and female species of animals, for testing its potential as a behavioral radioprotector. Administration of ginger extract 1 h before 2-Gy gamma-radiation was significantly effective in blocking the saccharin avoidance response, with 200 and 250 mg/kg b.wt. i.p., being the most effective doses for male and female rats, respectively. A comparison of the efficacy of ginger extract with two antiemetic drugs, ondansteron and dexamethasone, revealed that the extract rendered comparable protection against radiation-induced CTA. To correlate the mechanism of action, the free-radical-scavenging potential of ginger extract to scavenge hydroxyl ion and nitric oxide was also tested, in cell-free system and a concentration of 1000 microg/ml, was found to be the most potent, which has been proposed as one the many activities assisting in its overall ability to modulate radiation-induced taste aversion. The results demonstrate that ginger possesses antioxidant, radioprotective and neuromodulatory properties that can be effectively utilized for behavioral radioprotection and for efficiently mitigating radiation-induced CTA. [71]

The radioprotective effect of hydroalcoholic extract of ginger was studied in mice administered 250 mg/kg ZOE orally using oral gavage once daily for 5 consecutive days before exposure to 6, 7, 8, 9, 10, or 11 Gy of gamma-radiation. The animals were monitored daily up to 30 days post-irradiation for the development of symptoms of radiation sickness and mortality. Pretreatment of mice with ZOE reduced the severity of symptoms of radiation sickness and mortality at all the exposure doses and also increased the number of survivors in a ZOE + irradiation group compared to the concurrent double-distilled water + irradiation group. The ZOE treatment protected mice against gastrointestinal-related deaths as well as bone-marrow-related deaths. The dose-reduction factor was found to be 1.2.. Treatment of mice with ZOE before irradiation caused a significant depletion in lipid peroxidation followed by a significant elevation in GSH concentration in the livers of mice at 31 days post-irradiation. The mechanism of action of ZOE was determined by evaluating its free-radical scavenging capability. Ginger was found to scavenge *OH, O2*- and ABTS*+ radicals in a dose-dependent manner in vitro. The drug was nontoxic up to a dose of 1500 mg/kg body weight, the highest drug dose that could be tested for acute toxicity. [72]

The radioprotective effect of the hydroalcoholic extract of ginger, was studied. Mice were given 10 mg/kg ZOE intraperitoneally once daily for five consecutive days before exposure to 6-12 Gy of gamma radiation and were monitored daily up to 30 days postirradiation for the development of symptoms of radiation sickness and mortality. Pretreatment of mice with ZOE reduced the severity of radiation sickness and the mortality at all doses. The ZOE treatment protected mice from GI syndrome as well as bone marrow syndrome. The dose reduction factor for ZOE was found to be 1.15. The optimum protective dose of 10 mg/kg ZOE was 1/50 of the LD50 (500 mg/kg). Irradiation of the animals resulted in a dose-dependent elevation in the lipid peroxidation and depletion of GSH on day 31 postirradiation; both effects were lessened by pretreatment with ZOE. ZOE also had a dose-dependent

antimicrobial activity against Pseudomonas aeruginosa, Salmonella typhimurium, Escherichia coli and Candida albicans. [73]

13: Circumvent the resistance of mutant p53- expressing cells

[6]-gingerol on two human pancreatic cancer cell lines, HPAC expressing wild- type (wt) p53 and BxPC-3 expressing mutated p53. We found that [6]-gingerol inhibited the cell growth through cell cycle arrest at G1 phase in both cell lines. Western blot analyses indicated that [6]-gingerol decreased both Cyclin A and Cyclin-dependent kinase (Cdk) expression. These events led to reduction in Rb phosphorylation followed by blocking of S phase entry. p53 expression was decreased by [6]-gingerol treatment in both cell lines suggesting that the induction of Cyclin-dependent kinase inhibitor, p21cip1, was p53-independent. [6]-Gingerol induced mostly apoptotic death in the mutant p53-expressing cells, while no signs of early apoptosis were detected in wild type p53-expressing cells and this was related to the increased phosphorylation of AKT. These results suggest that [6]-gingerol can circumvent the resistance of mutant p53- expressing cells towards chemotherapy by inducing apoptotic cell death while it exerts cytostatic effect on wild type p53- expressing cells by inducing temporal growth arrest. [75]

14: Chemotherapy: Kidney protective against cisplatin induced oxidative damage

The nephroprotective effects of ethanol extract of Zingiber officinale alone and in combination with vitamin E (alpha-tocopherol) were evaluated using cisplatin (single dose of 10 mg/kg body wt, i.p) induced acute renal damage in mice. The results of the study indicated that Z. officinale significantly and dose dependently protected the nephrotoxicity induced by cisplatin. The serum urea and creatinine levels in the cisplatin alone treated group were significantly elevated ($P<0.01$) with respect to normal group of animals. The levels were reduced in the Z. officinale (250 and 500 mg/kg, p.o) plus cisplatin, vitamin E (250 mg/kg) plus cisplatin, and Z. officinale (250 mg/kg) with vitamin E plus vitamin E treated groups. The renal antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) activities and level of reduced glutathione (GSH) were declined; level of malondialdehyde (MDA) was elevated in the cisplatin alone treated group. The activities of SOD, CAT GPx and level of GSH were elevated and level of MDA declined significantly ($P<0.05$) in the Z. officinale (250 and 500 mg/kg) plus cisplatin and Z. officinale (250 mg/kg) with vitamin E plus cisplatin treated groups. The protective effect of Z. officinale (250 mg/kg body wt) was found to be better than that of vitamin E (250 mg/kg body wt). The results also demonstrated that combination of Z. officinale (250 mg/kg) with vitamin E (250 mg/kg) showed a better protection compared to their 250 mg/kg alone treated groups. This study concluded that ethanol extract of Z. officinale alone and in combination with vitamin E partially ameliorated cisplatin-induced nephrotoxicity. This protection is mediated either by preventing the cisplatin-induced decline of renal antioxidant defense system or by their direct free radical scavenging activity. [76]

15: [6]-Gingerol Suppresses Colon Cancer Growth by Targeting Leukotriene A4 Hydrolase.

[6]-Gingerol, a natural component of ginger, exhibits anti-inflammatory and antitumorigenic activities. Despite its potential efficacy in cancer, the mechanism by which [6]-gingerol exerts its chemopreventive effects remains elusive. The leukotriene A4 hydrolase (LTA4H) protein is regarded as a relevant target for cancer therapy. Our in silico prediction using a reverse-docking approach revealed that LTA4H might be a potential target of [6]-gingerol. We supported our prediction by showing that [6]-gingerol suppresses anchorage-independent cancer cell growth by inhibiting LTA4H activity in HCT116 colorectal cancer cells. We showed that [6]-gingerol effectively suppressed tumor growth in vivo in nude mice, an effect that was mediated by 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. [78]

16: Anti-cancer/anti-inflammatory – suppression of NF-kB & TNF-a

To evaluate the effect of ginger extract on the expression of NFkappaB and TNF-alpha in liver cancer-induced rats. METHODS: Male Wistar rats were randomly divided into 5 groups based on diet: i) control (given normal rat chow), ii) olive oil, iii) ginger extract (100mg/kg body weight), iv) choline-deficient diet + 0.1% ethionine to induce liver cancer and v) choline-deficient diet + ginger extract (100mg/kg body weight). Tissue samples obtained at eight weeks were fixed with formalin and embedded in paraffin wax, followed by immunohistochemistry staining for NFkappaB and TNF-alpha. RESULTS: The expression of NFkappaB was detected in the choline-deficient diet group, with 88.3 +/- 1.83% of samples showing positive staining, while in the choline-deficient diet supplemented with ginger group, the expression of NFkappaB was significantly reduced, to 32.35 +/- 1.34% ($p<0.05$). In the choline-deficient diet group, 83.3 +/- 4.52% of samples showed positive staining of TNF-alpha, which was significantly reduced to 7.94 +/- 1.32% ($p<0.05$) when treated with ginger. There was a significant correlation demonstrated between NFkappaB and TNF-alpha in the choline-deficient diet group but not in the choline-deficient diet treated with ginger extract group. CONCLUSION: In conclusion, ginger extract significantly reduced the elevated expression of NFkappaB and TNF-alpha in rats with liver cancer. Ginger may act as an anti-cancer and anti-inflammatory agent by inactivating NFkappaB through the suppression of the pro-inflammatory TNF-alpha. [79]

17: Anti-emetic effect of ginger powder versus placebo as an add-on therapy in children and young adults receiving high emetogenic chemotherapy.

PATIENTS AND METHODS: Sixty chemotherapy cycles of cisplatin/doxorubicin in bone sarcoma patients were randomized to ginger root powder capsules or placebo capsules as an additional antiemetic to ondensetron and dexamethasone in a double-blind design. Acute CINV was defined as nausea and vomiting occurring within 24 hr of start of chemotherapy (days 1-4) and delayed CINV as that occurring after 24 hr of completion of chemotherapy (days 5-10). CINV was evaluated as per Edmonton's Symptom Assessment Scale and National Cancer Institute criteria respectively.

RESULTS: Acute moderate to severe nausea was observed in 28/30 (93.3%) cycles in control group as compared to 15/27 (55.6%) cycles in experimental group (P = 0.003). Acute moderate to severe vomiting was significantly more in the control group compared to the experimental group [23/30 (76.7%) vs. 9/27 (33.33%) respectively (P = 0.002)]. Delayed moderate to severe nausea was observed in 22/30 (73.3%) cycles in the control group as compared to 7/27 (25.9%) in the experimental group (P < 0.001). Delayed moderate to severe vomiting was significantly more in the control group compared to the experimental group [14/30 (46.67%) vs. 4/27 (14.81%) (P = 0.022)].

CONCLUSION: Ginger root powder was effective in reducing severity of acute and delayed CINV as additional therapy to ondensetron and dexamethasone in patients receiving high emetogenic chemotherapy.[82]

Antioxidant:

Ginger contains curcumin (like turmeric) in addition to the phenolic compounds, gingerols and diarylheptanoids, which are high in antioxidants.[3]

1. Protects Against Free Radical and ROS Lipid Peroxidation

Ayurveda identified a large number of plant components to be used in the diet for the prevention or the delayed development of degenerative disorders. They include some of the commonly used spices, namely pepper and ginger. Health promoting herbs and spices which are classified pharmacologically as rejuvenating, nourishing, invigorating, cleansing, wound-healing, etc., are used as food additives. Amrita Bindu is a salt-spice-herbal mixture based on these principles and was tested for its effect in maintaining anti-oxidant defense systems in blood and liver when exposed to a carcinogenic nitrosamine, N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). Amrita Bindu supplementation prevented MNNG induced depletion of the anti-oxidant enzymes and the scavenger anti-oxidants glutathione and vitamins A, C and E. Amrita Bindu provides protection against free radical and reactive oxygen species induced tissue lipid peroxidation and the resultant tissue degeneration.[51]

2. Superoxide Scavanger

Ginger can significantly scavenge O2-. in hypo-xanthinexanthine oxidase system and .OH in ultraviolet exposure of H2O2 system. The scavenging effects of ginger on O2-. and .OH may contribute to explaining some of the pharmacological mechanisms of this drug.[52]

3. Protection from Beta Amyloid (an oxidative inflammatory contributing process to dementia)

From the rhizome of Zingiber officinale L. (Zingiberaceae), four shogaols that protect IMR32 human neuroblastoma and normal human umbilical vein endothelial cells from beta-amyloid (25 - 35) insult at EC50 = 4.5 - 81 microM were isolated. The efficacy of cell protection from beta-amyloid (25 - 35) insult by these shogaols was shown to improve as the length of the side chain increases. [64]

4. Inhibits Production of H2O2 on Kashin-Beck Disease

In order to investigate the effect of ginger on Kashin-Beck disease (KBD), an endemic polyarthritis limited to certain areas of Asia., the ginger volatile oil was taken as a scavenger and proved effective in inhibiting the production of hydrogen peroxide in chondrocytes induced by fulvic acid from KBD area. KBD is be-lieved to be a form of mycotoxicosis caused by eating grain contaminated with Fusarium sporotrichiella. [33]

Antiparasitic:

1. Lethal to Anisakis Larvae

Zingiber officinale, traditionally eaten along with raw fish and used in traditional Chinese medicine, effectively destroyed Anisakis larvae in vitro. In this study, we analyzed whether the effective components of ginger rhizomes Authentic [6]-shogaol and [6]-gingerol could kill Anisakis larvae at a minimal effective dose of 62.5 and 250 micrograms/ml, respectively. However, the concentration of [6]-gingerol in fraction 1 was greater than 20 times that of [6]-shogaol, making the former the most active component in the fraction. Furthermore, synergistic effects between [6]-gingerol and a small amount of [6]-shogaol were observed. Pyrantel pamoate, an available antinematodal drug, had no lethal effect, even at a concentration of 1 mg/ml. In saline solution containing [6]-shogaol (62.5 micrograms/ml), greater than 90% of larvae lost spontaneous movement within 4 h and were destroyed completely within 16 h. Microscopical examinations showed destruction of the digestive tract and disturbances of culticulae. [43]

2. Effective Against Schistosoma

Experiments were conducted to study the major constituents of Zingiber officinale responsible for its molluscicidal activity and the effect of the active component on different stages of Schistosoma mansoni. Gingerol and shogaol exhibited potent molluscicidal activity on Biomphalaria glabrata. Gingerol (5.0 ppm) completely abolished the infectivity of Schistosoma mansoni miracidia and cercariae in B. glabrata and mice, respectively, indicating that the molluscicide is capable of interrupting schistosome transmission at a concentration lower than its molluscicidal concentrations. [53]

Menstrual Regulating:

Analgesic

Clonidine substantially reduces the pain and cramping of dysmenorrhea. The mechanisms for this effect may lie in increased release of analgesic opioids. It is suggested that perhaps a thromboxane synthetase inhibitor such as ginger which activates endorphin receptors may also be an effective treatment.

Ginger is often prescribed as a hot infusion to break up congestion and to relieve painful menstruation. [25]

Anti-obesity

Ginger prevents obesity in mice fed a high-fat diet. In this experiment, the effects of zingerone, the major pungent component of ginger on fat storage in ovariectomized (Ovx) rats was studied. Oral administration of 170 mg/kg zingerone significantly reduced body weight and the final parametrail adipose tissue weight in ovariectomized rats. Blood glucose levels after oral administration of glucose were lower in zingerone-treated Ovx-rats than in the Ovx-rats (control). Basal lipolysis in zingerone-treated Ovx-rats was increased compared with that in the Ovx-rats. Zingerone significantly increased norepinephrine-induced lipolysis associated with the translocation of hormone-sensitive lipase (HSL) from the cytosol to lipid droplets in adipocytes. These results indicate that zingerone may prevent the fat storage through increasing norepinephrine-induced lipolysis in adipocytes. [77]

Other/Miscellaneous: Warming/diaphoretic/thermogenic

Ginger is a well-known synergistic herb that potentiates, harmonizes, and improves the deep circulation of other herbs.[14] It has recently been found to have a thermogenic effect, possible being useful in weight management programs.[23, 24]

Safety:

1. Does Not Interact with Warfarin

In three different studies on rats, the effects of a patented standardized ginger extract, EV.EXT 33, on blood glucose, blood coagulation, blood pressure and heart rate were investigated. This extract had no significant effect on blood glucose levels at the doses used. It also had no significant effects on coagulation parameters or on Warfarin-induced changes in blood coagulation, indicating that it did not interact with Warfarin. EV.EXT 33 neither decreases systolic blood pressure nor increases heart rate in the rat. As also seen from the literature, ginger is thus pharmacologically safe regarding the investigated aspects.[41]

2. Prenatal Use:

The teratogenicity of EV.EXT 33, a patented Zingiber officinale extract, was examined in Wistar SPF rats according to GLP Guidelines. Ginger was administered by oral gavage in concentrations of 100, 333, and 1000 mg/kg, to three groups of 22 pregnant female rats from days 6 to 15 of gestation. For comparison, a fourth group received the vehicle, sesame oil. Body weight and food and water intake were recorded during the treatment period. The rats were killed on day 21 of gestation and examined for standard parameters of reproductive performance. The fetuses were examined for signs of teratogenic and toxic effects. The extract was well tolerated. No deaths or treatment-related adverse effects were observed. Weight gain and food consumption were similar in all groups during gestation. Reproductive performance was not affected. The examination of fetuses for external, visceral, and skeletal changes showed no embryotoxic or teratogenic effects. Based on these results, it was concluded that Ginger extract, when administered to pregnant rats during the period of organogenesis, caused neither maternal nor developmental toxicity at daily doses of up to 1000 mg/kg body weight.[42]

Summary of Ginger effects:

Ginger is a well-known synergistic herb that potentiates, harmonizes, and improves the deep circulation and bioavailablity of other herbs, reinforcing the therapeutic activity of the herb formulation. Ginger, because of its diverse therapeutic applications, long historic use by several cultures, and the confirmation of modern science is classified as a Companion Adaptogen. Ginger influences prostaglandin metabolism is a potent inhibitor of thromboxane synthesis, significantly inhibiting platelet aggregation and inflammation.[12, 13,17-20] Ginger has a slight diaphoretic and antipyretic effect making useful for reducing fever.[22] Ginger has recently been found to have a thermogenic effect, possible being useful in weight management programs.[23, 24] Ginger significantly reduces serum and hepatic cholesterol levels and possesses potent cardiotonic [10, 11] activity, anti-oxidant effects,[31-33] and

anti-neoplastic.[34-38] Ginger also possesses remarkable proteolytic activity making it useful for many digestive complaints. Ginger promotes the secretion of saliva and gastric juices as well as bile. Ginger extract has been found to be as effective as Ibuprofen in treating osteoarthritis.[21] Ginger is best known for its ability to relieve nausea.

References

1. Duke JA, Ayensu ES. Medicinal Plants of China. Medicinal Plants of the World. Vol. 1. Algonac, MI:Reference Publications, Inc, 1985:362.
2. Qureshi S, Shah AH, Tariq M, Ageel AM. Studies on herbal aphrodisiacs used in Arab system of medicine. *Am J Chin Med* 1989; 17:57-63.
3. *Vegetables, Fruits, and Herbs in Health Promotion*, Ronald R. Watson, CRC Press 2001, Chapter 12, pg. 180.
4. Newall CA, Anderson LA, Phillipson JD. Herbal medicines: a guide for health-care professionals. London: Pharmaceutical Press, 1996:ix, 296.
5. Connell D, Sutherland M. A re-examination of gingerol, shogaol and zingerone, the pungent principles of Ginger (Zingiber officinale Roscoe). *Aust J Chem* 1969; 22:1033-43.
6. Yoshikawa M, Hatakeyama S, Chatani N, Nishino Y, Yamahara J. Qualitative and quantitative analysis of bioactive principles in Zingiberis Rhizoma by means of high performance liquid chromatography and gas liquid chromatography. On the evaluation of Zingiberis Rhizoma and chemical change of constituents during Zingiberis Rhizoma processing. *Yakugaku Zasshi* 1993; 113:307-15.
7. Mascolo N, Jain R, Jain SC, Capasso F. Ethnopharmacologic investigation of ginger (Zingiber officinale). *J Ethnopharmacol* 1989; 27:129-40.
8. Connell D. The chemistry of the essential oil and oleoresin of ginger (Zingiber officinale Roscoe). *Flavour Industry* 1970; 1:677-93.
9. Ding GH, Naora K, Hayashibara M, Katagiri Y, Kano Y, Iwamoto K. Pharmacokinetics of [6]-gingerol after intravenous administration in rats. *Chem Pharm Bull* (Tokyo) 1991; 39:1612-4.
10. Kobayashi M, Ishida Y, Shoji N, Ohizumi Y. Cardiotonic action of [8]-gingerol, an activator of the Ca++-pumping adenosine triphosphatase of sarcoplasmic reticulum, in guinea pig atrial muscle. J *Pharmacol Exp Ther* 1988; 246:667-73.
11. Shoji N, Iwasa A, Takemoto T, Ishida Y, Ohizumi Y. Cardiotonic principles of ginger (Zingiber officinale Roscoe). *J Pharm Sci* 1982; 71:1174-5.
12. Kiuchi F, Shibuya M, Sankawa U. Inhibitors of prostaglandin biosynthesis from ginger. *Chem Pharm Bull* (Tokyo) 1982; 30:754-7.
13. Flynn D, Rafferty M, Boctor A. Inhibition of human neutrophil 5-liopxygenase activity by gingerdione, shogaol, capsaicin and related pungent compounds. *Prostaglandins Leukotrienes Med* 1986; 24:195-8.
14. Duke JA, Ayensu ES. Medicinal Plants of China. Medicinal Plants of the World. Vol. 1. Algonac, MI: Reference Publications, Inc, 1985:362.
15. Kapil U, Sood AK, Gaur DR. Maternal beliefs regarding diet during common childhood illnesses. *IndianPediatr* 1990; 27:595-9.
16. Johri RK, Zutshi U. An Ayurvedic formulation 'Trikatu' and its constituents. *J Ethnopharmacol* 1992; 37:85-91.
17. Srivastava KC. Aqueous extracts of onion, garlic and ginger inhibit platelet aggregation and alter arachidonic acid metabolism. *Biomed Biochim Acta* 1984; 43:S335-46.
18. Backon J. Ginger: inhibition of thromboxane synthetase and stimulation of prostacyclin: relevance for medicine and psychiatry. *Med Hypotheses* 1986; 20:271-8.
19. Srivastava KC. Isolation and effects of some ginger components of platelet aggregation and eicosanoid biosynthesis. Prostaglandins Leukot Med 1986; 25:187-98.
20. Guh J-H, Ko F-N, Jong T-T, Ting C-M. Antiplatelet effect of gingerol isolated from Zingiber officinale. *J Pharmacy Pharmacology* 1995; 47:329-32.
21. Bliddal H. Rosetzsky A. Schlichting P. Weidner MS. Andersen LA. Ibfelt H-H. Christensen K. Jensen ON. Barslev J. Dr. H. Bliddal, Parker Institute, Frederiksberg Hospital, DK-2000, Copenhagen F; Denmark. A randomized, placebo-controlled, cross-over study of ginger extracts and Ibuprofen in osteoarthritis. *Osteoarthritis & Cartilage*. Vol 8(1) (pp 9-12), 2000.
22. Mascolo N, Jain R, Jain SC et al. *J Ethnopharmacol* 1989; 27 (1-2): 129-140.
23. Yamahara J, Miki K, Chisaka T et al *J Ethnopharmacol* 1985; 13 (2): 217-225.
24. Eldershaw TP, Colquhoun EQDora KA et al. *Ent J Obesity Relat Metab Discord* 1992; 16 (10): 755-63.
25. Lyle TJ. Physio-medical therapeutics, materia medica and pharmacy, 1897, pg. 343.
26. Kawai T, Kinoshita K, Koyama K, Takahashi K. Anti-emetic principles of Magnolia obovata bark and Zingiber officinale rhizome. *Planta Med* 1994; 60:17-20.

27. Yamahara J, Rong HQ, Naitoh Y, Kitani T, Fujimura H. Inhibition of cytotoxic drug-induced vomiting in suncus by a ginger constituent. *J Ethnopharmacol* 1989; 27:353-5.
28. Sharma SS, Kochupillai V, Gupta SK, Seth SD, Gupta YK. Antiemetic efficacy of ginger (Zingiber officinale) against cisplatin- induced emesis in dogs. *J Ethnopharmacol* 1997; 57:93-6.
29. Meyer K, Schwartz J, Crater D, Keyes B. Zingiber officinale (ginger) used to prevent 8-Mop associated nausea. *Dermatol Nurs* 1995; 7:242-4.
30. Pecoraro A, Patel J, Guthrie T, Ndubisi B. Efficacy of ginger as an adjunctive anti-emetic in acute chemotherapy-induced nausea and vomiting. ASHP Midyear Clinical Meeting 1998; 33:P-429E.
31. Zhou Y, Xu R. Antioxidative effect of Chinese drugs. *Chung Kuo Chung Yao Tsa Chih* 1992; 17:368-9, 373 inside backcover.
32. Sujatha R, Srinivas L. Modulation of lipid peroxidation by dietary componenets. *Toxicology in vitro* 1995; 9:231-36.
33. Guo P, Xu J, Xu S, Wang K. Inhibition of hydrogen peroxide production in chondrocytes induced by fulvic acid by ginger volatile oil. *China J Chinese Materia Medica* 1997; 22:559-61.
34. Vimala S, Norhanom AW, Yadav M. Anti-tumour promoter activity in Malaysian ginger rhizobia used in traditional medicine. *Br J Cancer* 1999; 80:110-6.
35. Murakami A, Morita H, Safitri R, Ramlan A, Koshimizu K, Ohigashi H. Screening for in vitro anti-tumor promoting activities of edible plants from Indonesia. *Cancer Detect Prev* 1998; 22:516-25.
36. Lee E, Surh Y. Induction of apoptosis in HL-60 cells by pungent vanilloids, 6-gingerol and 6-paradol. *Cancer Letters* 1998; 134:163-8.
37. Surh YJ, Lee E, Lee JM. Chemoprotective properties of some pungent ingredients present in red pepper and ginger. *Mutat Res* 1998; 402:259-67.
38. Hashim S, Aboobaker V, Madhubala R, Bhattacharya R, Rao A. Modulatory effects of essential oils from spices on the formation of DNA adduct by an aflatoxin B1 in vitro. *Nutr Cancer* 1994; 21:169-75.
39. Lien HC. Sun WM. Chen YH. Kim H. Hasler W. Owyang C. Department of Internal Medicine Division of Gastroenterology Taichung Veterans General Hospital, National Yang-Ming University, Taipei, Taiwan. Effects of ginger on motion sickness and gastric slow-wave dysrhythmias induced by circular vection. *American Journal of Physiology - Gastrointestinal & Liver Physiology*. 284(3):G481-9, 2003 Mar.
40. Bliddal H. Rosetzsky A. Schlichting P. Weidner MS. Andersen LA. Ibfelt H-H. Christensen K. Jensen ON. Barslev J. Dr. H. Bliddal, Parker Institute, Frederiksberg Hospital, DK-2000 Copenhagen F; Denmark. A randomized, placebo-controlled, cross-over study of ginger extracts and Ibuprofen in osteoarthritis. *Osteoarthritis & Cartilage*. Vol 8(1) (pp 9-12), 2000.
41. Weidner MS. Sigwart K. Institute of Drug Analysis A/S, Symbion Science Park, Fruebjergvej 3, DK-2100, Copenhagen, Denmark. The safety of a ginger extract in the rat. *Journal of Ethnopharmacology* 73(3):513-20, 2000 Dec.
42. Weidner MS. Sigwart K.Investigation of the teratogenic potential of a zingiber officinale extract in the rat. *Reprod Toxicol*. 15(1):75-80, 2001 Jan-Feb.
43. Goto C, Kasuya S, Koga K, Ohtomo H, Kagei N. Lethal efficacy of extract from Zingiber officinale (traditional Chinese medicine) or [6]-shogaol and [6]-gingerol in Anisakis larvae in vitro.
44. Mishra S, Kumar H, Sharma D. How do mothers recognize and treat pneumonia at home? *Indian Pediatr*. 1994 Jan;31(1):15-8.
45. Grontved A, Hentzer E. Vertigo-reducing effect of ginger root. A controlled clinical study. *ORL J Otorhinolaryngol Relat Spec*. 1986;48(5):282-6.
46. 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 Aug;40(8):2239-41.
47. Srivastava KC, Mustafa T. Ginger (Zingiber officinale) in rheumatism and musculoskeletal disorders. *Med Hypotheses*. 1992 Dec;39(4):342-8.
48. Srivastava KC, Mustafa T. Ginger (Zingiber officinale) and rheumatic disorders. Med Hypotheses. 1989 May;29(1):25-8.
49. Backon J. Implication of thromboxane in the pathogenesis of Kawasaki disease and a suggestion for using novel thromboxane synthetase inhibitors in its treatment. *Med Hypotheses*. 1991 Mar;34(3):230-50. Chen HC, Chang MD, Chang TJ. Antibacterial properties of some spice plants before and after heat treatment *Zhonghua Min Guo Wei Sheng Wu Ji Mian Yi Xue Za Zhi*. 1985 Aug;18(3):190-5.

51. Shanmugasundaram KR, Ramanujam S, Shanmugasundaram ER. Amrita Bindu--a salt-spice-herbal health food supplement for the prevention of nitrosamine induced depletion of antioxidants. *J Ethnopharmacol.* 1994 Apr;42(2):83-93.
52. Cao ZF, Chen ZG, Guo P, Zhang SM, Lian LX, Luo L, Hu WM Scavenging effects of ginger on superoxide anion and hydroxyl radical *Zhongguo Zhong Yao Za Zhi*. 1993 Dec;18(12):750-1, 764.
53. Adewunmi CO, Oguntimein BO, Furu P. Molluscicidal and antischistosomal activities of Zingiber officinale. *Planta Med*. 1990 Aug;56(4):374-6.
54. Backon J. Mechanism of analgesic effect of clonidine in the treatment of dysmenorrhea. *Med Hypotheses.* 1991 Nov;36(3):223-4.
55. Sharma M, Shukla S. Hypoglycemic effect of ginger. *J Res Ind Med Yoga Homeopath* 1977; 12:127-
56. Vimala S, Norhanom AW, Yadav M. Anti-tumour promoter activity in Malaysian ginger rhizobia used in traditional medicine. *Br J Cancer*. 1999 Apr;80(1-2):110-6. Medicinal Plant Division, Forest Research Institute Malaysia, Kuala Lumpur.
57. Liu N, Huo G, Zhang L, Zhang X. [Effect of Zingiber Officinale Rosc on lipid peroxidation in hyperlipidemia rats] *Wei Sheng Yan Jiu*. 2003 Jan;32(1):22-3. Chinese.
58. Mahady GB, Pendland SL, Yun GS, Lu ZZ, Stoia A., Ginger (Zingiber officinale Roscoe) and the gingerols inhibit the growth of Cag A+ strains of Helicobacter pylori. *Anticancer Res*. 2003 Sep-Oct;23(5A):3699-702.
59. Leal PF, Braga ME, Sato DN, Carvalho JE, Marques MO, Meireles MA., Functional properties of spice extracts obtained via supercritical fluid extraction. *J Agric Food Chem*. 2003 Apr 23;51(9):2520-5.
60. Sharma SS, Gupta YK. Reversal of cisplatin-induced delay in gastric emptying in rats by ginger (Zingiber officinale). *J Ethnopharmacol*. 1998;62:49-55.
61. Murakami A, Takahashi D, Kinoshita T, Koshimizu K, Kim HW, Yoshihiro A, Nakamura Y, Jiwajinda S, Terao J, Ohigashi H. Zerumbone, a Southeast Asian ginger sesquiterpene, markedly suppresses free radical generation, proinflammatory protein production, and cancer cell proliferation accompanied by apoptosis: the alpha,beta-unsaturated carbonyl group is a prerequisite. *Carcinogenesis*. 2002 Nov;23(11):1961; author reply 1963.
62. Lee E, Surh YJ., Induction of apoptosis in HL-60 cells by pungent vanilloids, [6]-gingerol and [6]-paradol. *Cancer Lett*. 1998 Dec 25;134(2):163-8.
63. Bode AM, Ma WY, Surh YJ, Dong Z., Inhibition of epidermal growth factor-induced cell transformation and activator protein 1 activation by [6]-gingerol. *Cancer Res*. 2001 Feb 1;61(3):850-3.
64. Kim DS, Kim DS, Oppel MN. Shogaols from Zingiber officinale protect IMR32 human neuroblastoma and normal human umbilical vein endothelial cells from beta-amyloid(25-35) insult. Planta Med. 2002 Apr;68(4):375-6.
65. Wang CC, Chen LG, Lee LT, Yang LL. Effects of 6-gingerol, an antioxidant from ginger, on inducing apoptosis in human leukemic HL-60 cells. *In Vivo*. 2003 Nov-Dec;17(6):641-5.
66. Smith, Dr Caroline, Ginger could relieve the nausea and vomiting experienced by pregnant women to a similar extent as vitamin B6, April issue of *Obstetrics and Gynecology* (103:639-645)
67. Kim EC, Min JK, Kim TY, Lee SJ, Yang HO, Han S, Kim YM, Kwon YG. [6]-Gingerol, a pungent ingredient of ginger, inhibits angiogenesis in vitro and in vivo. Biochem Biophys Res Commun. 2005 Sep 23;335(2):300-8.
68. Kim SO, Kundu JK, Shin YK, Park JH, Cho MH, Kim TY, Surh YJ. [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 Apr 7;24(15):2558-67.
69. Kim SO, Chun KS, Kundu JK, Surh YJ. Inhibitory effects of [6]-gingerol on PMA-induced COX-2 expression and activation of NF-kappaB and p38 MAPK in mouse skin. Biofactors. 2004;21(1-4):27-31.
70. Chaiyakunapruk N, et al. The efficacy of ginger for the prevention of postoperative nausea and vomiting: A meta-analysis. American Journal of Obstetrics and Gynecology. Jan 2006;194(1):95-9.
71. Haksar A, Sharma A, Chawla R, Kumar R, Arora R, Singh S, Prasad J, Gupta M, Tripathi RP, Arora MP, Islam F, Sharma RK. Zingiber officinale exhibits behavioral radioprotection against radiation-induced CTA in a gender-specific manner. Pharmacol Biochem Behav. 2006 Jun;84(2):179-88. Epub 2006 Jun 21.
72. 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 Aug;19(4):422-35.
73. Jagetia GC, Baliga MS, Venkatesh P, Ulloor JN. 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 Nov;160(5):584-92.
74. Shukla Y, Singh M. Cancer preventive properties of ginger: A brief review. Food Chem Toxicol. 2006 Nov 12.

75.Park YJ, Wen J, Bang S, Park SW, Song SY. [6]-Gingerol induces cell cycle arrest and cell death of mutant p53-expressing pancreatic cancer cells. Yonsei Med J. 2006 Oct 31;47(5):688-97.
76. Ajith TA, Nivitha V, Usha S. Zingiber officinale Roscoe alone and in combination with alpha-tocopherol protect the kidney against cisplatin-induced acute renal failure. Food Chem Toxicol. 2007 Jun;45(6):921-7. Epub 2006 Nov 29.
77.Han LK, Morimoto C, Zheng YN, Li W, Asami E, Okuda H, Saito M. Effects of zingerone on fat storage in ovariectomized rats. Yakugaku Zasshi. 2008 Aug;128(8):1195-201.
78. Jeong CH, Bode AM, Pugliese A, Cho YY, Kim HG, Shim JH, Jeon YJ, Li H, Jiang H, Dong Z. [6]-Gingerol Suppresses Colon Cancer Growth by Targeting Leukotriene A4 Hydrolase. Cancer Res. 2009 Jun 1
79. Habib SH, Makpol S, Abdul Hamid NA, Das S, Ngah WZ, Yusof YA. Ginger extract (Zingiber officinale) has anti-cancer and anti-inflammatory effects on ethionine-induced hepatoma rats. Clinics (Sao Paulo). 2008 Dec;63(6):807-13.
80. Biofactors. 2010 Mar 15, Molecular targets of [6]-gingerol: Its potential roles in cancer chemoprevention. Oyagbemi AA, Saba AB, Azeez OI.
81. Ghayur MN, Gilani AH., Ginger lowers blood pressure through blockade of voltagedependent calcium channels. J Cardiovasc Pharmacol. 2005 Jan;45(1):74-80.
82.Pillai AK, Sharma KK, Gupta YK, Bakhshi S. Anti-emetic effect of ginger powder versus placebo as an add-on therapy in children and young adults receiving high emetogenic chemotherapy. Pediatr Blood Cancer. 2010 Sep 14.