# GINGER: AN ETHNOMEDICAL, CHEMICAL AND PHARMACOLOGICAL REVIEW

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**SUMMARY**

Powerful medicinal properties have been recorded for *Zingiber officinale,* commonly known as ginger. All of these medicinal activities have been compiled with 99 references to the present status of the plant in the literature. Volatile components and the presence of trace metals are included. In addition, details of individual medicinal activities are given and the molecular structures of identified organic metabolites and their synthesis are described.

**KEY WORDS**

ginger, volatile oils, trace metals, gingerol, shogaol, cassumunins, curcumin

## 1. INTRODUCTION

Ginger, *Zingiber officinale* Roscoe (Zingiberaceae), is classified as a perennial plant, and its rhizome is consumed. Its generic name Zingiber is actually derived from the Greek word *zingiberis*. This, however, came from *sringavera*, the Sanskrit name for ginger /1/.

Ginger's therapeutic effects have been recognized for thousands of years. It plays a vital role in the treatment of many ailments and is indigenous in traditional folk medicine in various parts of the world. This plant has also been mentioned in certain religious scriptures. Dating back to around 2000 BC, the Vedic literature of India mentions many spices including cinnamon, coriander, sandalwood and ginger and their therapeutic uses. This traditional form of Indian medicine, named Ayurvedic medicine, is still systematically and faithfully practiced today in India /2/. An example of an Ayurvedic 'recipe' amongst many used to treat various disorders is the one named 'Trikatu' which contains black pepper, long pepper and ginger. Hundreds of years after its formulation, Trikatu, alongside numerous other Ayurvedic preparations, has been investigated to scientifically establish its therapeutic use /3/. At present, ginger is commonly used in home remedies to treat several childhood health problems including problematic coughs /4,5/.

Ginger is a valued and highly regarded plant in China where its uses are diverse. It is extensively used in Chinese cooking and is known to have been used in religious ceremonies such as the Li-Ki and Tcheou-Li /6/. In China and Japan, ginger is the most widely used ingredient in treating gastrointestinal and hepatic disorders. It is also popular for the treatment of hypertension /7/.

The Arab world has long recognized the advantageous uses of ginger. Thus Arabs use ginger to give warmth to the body. In Yemen, ginger mixed with other plants is commonly used for gastrointestinal disorders and treatment for colds. Ginger is commonly used by the Arabs as a remedy for constipation, catarrh, acidity of the stomach, bronchitis and cataracts. The juice of ginger extract is sometimes even used as eye-drops. Ginger tea is very popular and is used as a general tonic. It is even thought to be an aphrodisiac /6/. African folk medicine also has high value for ginger, using it as a carminative, diuretic and antiemetic /7/.

It was not until the first century AD that traders introduced this spice to the Mediterranean region, and it had reached well into England by the 11$^{th}$ century. Soon after the Spanish conquest, ginger was introduced to the West Indies and Mexico by the Spaniards. From that time onwards, it has been traded and consumed worldwide /8/. Today, aside from its reputed and popular use in homeopathy, ginger is used in bread-making, confectionery, drinks and pickles /1/.

## 2. CHEMISTRY AND COMPOSITION OF GINGER

The oleoresin of ginger (gingerin) is responsible for the pungency of this spice. This fraction extracted from ginger is a mixture of volatile oils which accounts for ginger's distinct aroma and pungent compounds. The oleoresin can be extracted with organic solvents

### 2.1 Volatile oils

The main constituents of these oils are sesquiterpene hydrocarbons: the most abundant being zingeberene (35%) and farnesene (10%). Bisabolene and β-sesquiphellandrene make only a minor part of these constituents. Monoterpene hydrocarbons, although found in smaller quantities, exist in many forms. 1,8-Cineole, linalool, borneol, neral and geraniol predominantly make up the monoterpenes. Zingeberol, a sesquiterpene alcohol, is found in ginger and has been successfully isolated /9,10/ (Fig. 1).

### 2.2 Pungent compounds

Being nonvolatile in nature, these compounds account for ginger's biological effects. The major components found among these are different types of gingerols /10/, which are a family of homologous compounds differentiated by the number of carbon atoms in their side-chain: 10, 12, and 14 carbon atoms give rise to [6]-, [8]- and [10]-gingerols, respectively, [6]-gingerol being the most common. With prolonged storage of ginger, large amounts of [6]-, [8]- and [10]-shogaols are also found /10/, which are the dehydrated form of the gingerols. Zingerone co-occurs with shogaols in stored ginger. Shogaols may undergo reduction to form paradols which are also

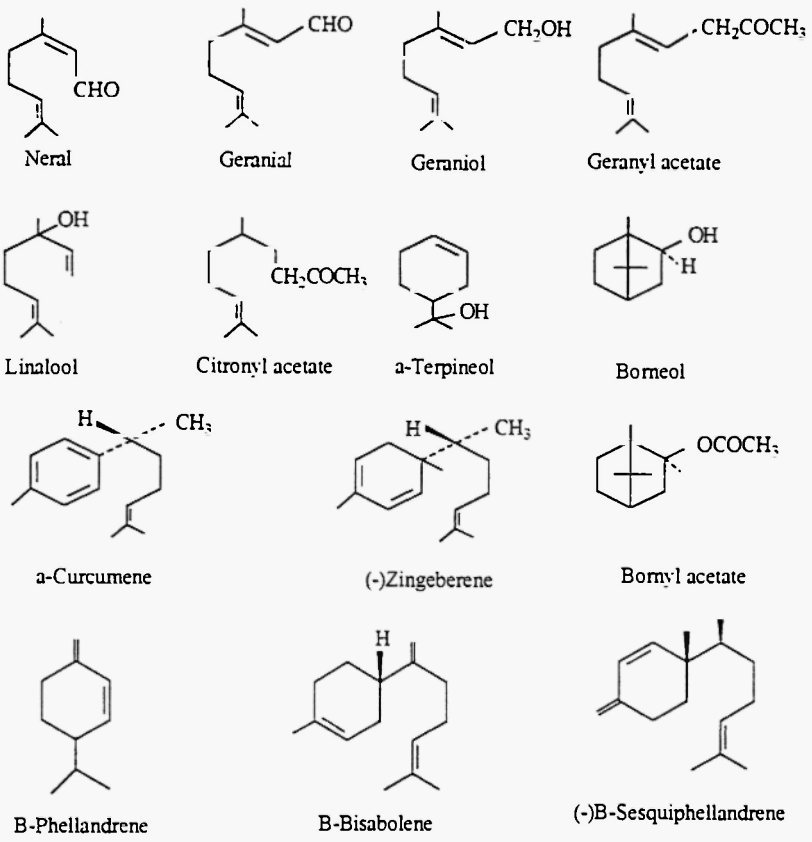


**Fig. 1:** Volatile oil components of ginger.

present in ginger. These transformations are shown in Figure 2. Other minor components identified in ginger are outlined in Figure 3.

### 2.3 Other components of ginger

Apart from the compounds found in the oleoresin fraction and pungent compounds of ginger, the remaining composition includes fats (~7%), fiber (~2-4%), carbohydrates, waxes, vitamins and minerals.

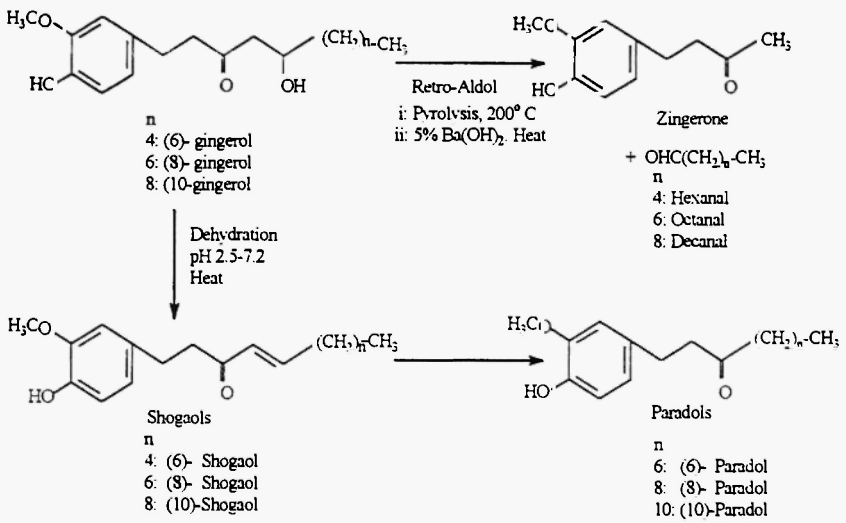


**Fig. 2:** Chemical conversion of gingerols (adapted from /25/).

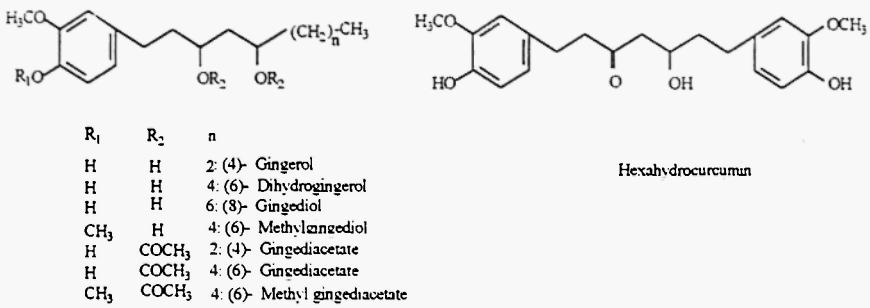


**Fig. 3:** Minor components found in ginger (adapted from /25/).

## 3. ANALYTICAL TECHNIQUES FOR ANALYSIS OF GINGER

Various methods have been established in order to analyze ginger's pungent compounds. However, it is still an area of ongoing research whereby more precise and time saving techniques are sought after and aimed for. The essential oil of ginger is extracted using supercritical

carbon dioxide and analyzed by methods including gas-liquid chromatography (GLC) combined with mass spectroscopy.

Extracting essential oils from herbs and spices by supercritical $CO_2$ has been practiced for over a decade. The high pressure and low temperature process utilizes energy efficiently and the source of $CO_2$ is exclusively a fermentation by-product /11/. Being an environmentally friendly process, this method is used extensively. Recently, a new method employing the $CO_2$ extraction technique has been established for the determination of pungent compounds in ginger in which extraction was carried out using 0.85 g/ml supercritical $CO_2$ followed by direct electrospray-mass spectrometric identification. Gingerols and shogaols have been identified and their concentrations measured. Low shogaol concentrations have been reported due to the mildness of the extraction technique. Collective results could be obtained rapidly using this technique /12/.

Chromatography has been the most popular form of analysis for ginger. It has proven to be very effective in combination with mass spectroscopy (GC-MS). High-resolution gas chromatography and GC-MS have been successfully utilized in the analysis of Nigerian ginger /13/. Fractionation of gingerols by high performance liquid chromatography (HPLC) preceded by isolation of these components by thin-layer chromatography (TLC) has been responsible for the identification of the isomeric derivatives of shogaols and their methylated products /14/.

Ginger has also been analyzed by means of packed-column GC to produce standard fingerprint chromatograms using two different stationary phases: polyethylene glycol 20 M and methyl polysiloxane /15/ (Table 1).

Two relatively new techniques of column chromatography have been employed to separate ginger's pungent compounds: vacuum and flash chromatography (using toluene:methanol [16:10] as the mobile phase). Of the two methods, vacuum chromatography has succeeded in being rapid and effective in the separation of the pungent components of ginger, whereas flash chromatography has not been very successful for separation of these compounds /16/. Atomic-emission spectroscopy methods have also been shown to be effective and accurate in determining the components of food spices and essential oils.

**TABLE 1**

Gas chromatographic fingerprint of ginger

| Peak indentity | Essential oil of ginger (Nigeria) | | | |
|---|---|---|---|---|
| | Polyethylene glycol 20 M (polar) stationary phase | | Methyl polysiloxane (nonpolar) stationary phase | |
| | RRI | RPA% | RRI | RPA% |
| Tricyclene | 1014 | 0.2 | 911 | 0.2 |
| α-Pinene | 1028 | 3.3 | 926 | 3.0 |
| Camphene | 1072 | 8.8 | 944 | 8.3 |
| Methyl heptenone | | | 951 | 0.4 |
| β-Pinene | 1117 | 0.5 | 963} | 0.7 |
| β-Myceren | 1116 | 1.5 | 963} | |
| Sabinene | 1124 | 0.8 | | |
| α-Phellandrene | 1176 | 0.5 | | |
| β-Phellandrene | 1224 | 8.2 | 1021 | 9.6 |
| Limonene} | 1213 | 1.7 | | |
| 1,8-Cineole | 1213 | | | |
| γ-Terpene | 1255 | 0.1 | | |
| p-Cymene | 1278 | 0.1 | | |
| Terpenolene | 1291 | 0.3 | | |
| α-Copaene | 1506 | 0.7 | 1362 | 0.4 |
| Linalol | 1541 | 0.4 | 1088 | 0.8 |
| Bornyl acetate | 1600 | 0.8 | | |
| α-Terpineol | | | 1176 | 0.3 |
| Nerol | | | 1210 | 0.2 |
| Neral | 1886 | 1.3 | 1216 | 1.4 |
| Borneol | 1704 | 1.1 | 1152 | 0.8 |
| α-Zingiberene} | 1741 | 29 | 1498 | 29 |
| Geranial} | 1741 | | 1244 | 1.4 |
| β-Bisabolene | 1741 | 5.8 | 1509} | 14 |
| α-Farnesene} | 1755 | 7.3 | 1509} | |
| Geranyl acetate | 1755 | | 1360 | 0.9 |
| Sesqui-β-phellandrene | 1784 | 14 | 1525 | 9.9 |
| Geraniol | 1848 | 0.4 | 1233 | 0.5 |
| β-Elemene | | | 1393 | 0.7 |

RRI = relative retention indices; RPA% = relative peak area percentages.
Reproduced from /15/ with permission from The Royal Society of Chemistry.

Apart from the analysis of the pungent substances in ginger, other aspects have also been analyzed. Eighteen trace elements (essential, toxic and non-toxic) have been studied and measured in ginger /17/ (Table 2).

**TABLE 2**

Trace element concentrations in ginger

| **Element** | **Concentration** μg/g on dry wt. basis |
|---|---|
| Cr | 0.89 (± 0.02) |
| Mn | 358 (± 10) |
| Fe | 145 (± 9) |
| Co* | 18 (± 2) |
| Zn | 28.2 (± 2) |
| Na | 443 (±13) |
| K | 12900 (± 1100) |
| As* | 12 (± 10) |
| Se | 0.31 (± 0.02) |
| Hg* | 6.0 (± 1) |
| Sb* | 39 (± 3) |
| Cl | 579 (± 23) |
| Br | 2.1 (± 0.2) |
| Hf | 0.07 (± 0.003) |
| Rb | 2.7 (± 0.6) |
| Cs* | 24 (± 2) |
| Sc* | 42 (± 4) |
| Eu* | 44 (± 3) |

* Concentration in $ng.g^{-1}$.
Adapted from Zaidi *et al.* /17/.

## 4. PHYSIOLOGICAL EFFECTS

### 4.1 Gastrointestinal effects

Ginger exhibits its most prominent effects on the gastrointestinal system where it appears to stimulate gastric motility. Oral doses of organic ginger extract administered to mice (75 mg/kg; 2.5 mg of (6)-shogaol/kg; or 5 mg of (6)-, (8)- or (10)-gingerol/kg) have been shown to stimulate the transport of a charcoal meal. Studies have suggested that the route of administration of ginger extracts may govern the resulting gastric effect. Thus intravenous (6)-gingerol and (6)-shogaol, administered at a dose of 3.5 mg/kg to rats after a charcoal meal, inhibits gastric motility. However, when administered orally, (6)-shogaol increases gastric motility at a dose of 35 mg/kg /18,19/. Other factors, including dose and type of meal, may be the reason for different results. Some studies have indicated the ineffectiveness of ginger in gastric emptying /20/.

Anti-ulcer effects and prevention of mucosal damage have been exhibited by ginger. Gastric lesions induced by HCl and ethanol in rats have been shown to be inhibited by orally administered acetone extracts of ginger (1 g/kg) as well as isolated zingeberene and (6)-gingerol (100 mg/kg) by 97.5%, 53.6% and 54.5%, respectively /21/. Gastric mucosal lesions and damage brought about by drugs, such as indomethacin and aspirin, have been shown to be inhibited by pretreatment with ginger. It has been observed, however, that ginger exhibits no inhibitory effect against ulcers resulting from reserpine. Moreover, pretreatment with ginger has been found to significantly reduce ulceration (38%) and gastric secretion (18%) in pylorus-ligated rats. Such results show a certain cytoprotective activity of ginger against ulcers and intraluminal bleeding. Another study has reported that dry ginger, when administered orally to experimental gastric ulcer models, protects against stomach damage in all models except the indomethacin-induced model /94/. Furthermore, a new compound isolated from ginger, (6)-gingesulfonic acid, reportedly has shown more potent anti-ulcer activity and weaker pungency than (6)-gingerol and (6)-shogaol in an experimental rat model /23/.

Recently, ginger has been found to markedly enhance intestinal lipase as well as disaccharidase, such as sucrase and maltase, activities

/24/, which makes this plant even more interesting for further investigation.

### 4.2 Cardiovascular effects

#### *4.2a Eicosanoid formation and effects on platelet formation*

The eicosanoids (collectively consisting of prostaglandins, thromboxanes, prostacyclins, hydroperoxy- and hydoxy-acids, leukotrienes and lipoxins) are formed from commonly occurring C20 polyunsaturated fatty acids, such as arachidonic acid (AA). The oxygenation of AA is induced by tissue damage, thereby stimulating the production of the eicosanoids (Fig. 4).

In inflamed tissues, the amounts of prostaglandins and leukotrienes are increased by the enhanced activity of cyclooxygenase and 5-lipoxygenase, respectively, which are key reactions in the process of inflammation /25/. It has been observed that several compounds in ginger have inhibitory action toward the synthesis of prostaglandins and leukotrienes by direct inhibition of prostaglandin synthetase and

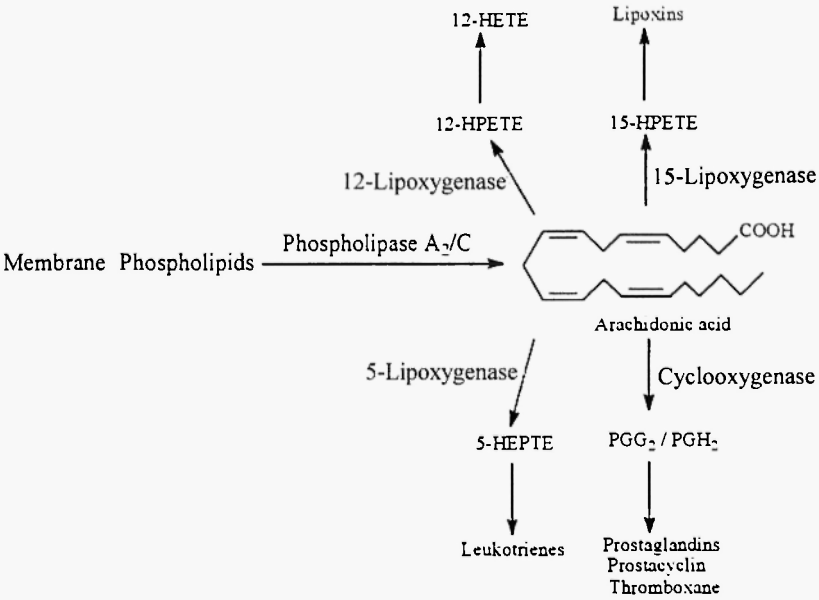


**Fig. 4:** Arachidonic acid cascade (adapted from /25/).

5-lipoxygenase. Gingerols, shogaols and several gingerdiones are particularly active /26/. Thromboxane levels contributing to platelet aggregation are also reduced by ginger consumption /27/. Platelet aggregation has long been associated with atherosclerosis, and ginger's inhibitory effects on thromboxane production could become instrumental in future clinical use provided further work is carried out on this plant. Thromboxane $A_2$, a pro-aggregatory thromboxane moiety, which is a robust platelet aggregatory agent, has been found to be strongly inhibited by a small volume of aqueous ginger extract. This has been found to be accompanied by reduced synthesis of PG-endoperoxides and prostaglandins in a dose-dependent response /28/. This reflects exceedingly positively on the medicinal potential of ginger.

More recently, in an all-male subjects study, who had enhanced platelet aggregation due to daily intake of butter, platelet aggregation was shown to be significantly inhibited with serum lipids unchanged after consuming 5 g of dried ginger twice daily /29/. However, in a double-blind experiment, it was shown that eight healthy males experienced no difference in bleeding time or platelet aggregation between the ginger-treated group (2 g of dried ginger daily) and the placebo group /30/. Similarly, 60 patients suffering from coronary artery disease receiving a daily dose of 4 g powdered ginger for 3 months exhibited no decrease in platelet aggregation induced by ADP and epinephrine. On the other hand, platelet aggregation was found to be strikingly lower 4 hours after receiving a single 10 g dose of powdered ginger /31/. This suggests that large doses may be required to induce the desired effect of reduction of platelet aggregation.

The use of ginger has also been suggested for the treatment of Kawasaki's disease. This is a mucocutaneous lymph node syndrome with high incidence in children. It is argued that since thromboxane is involved in the development of Kawasaki disease and ginger potently inhibits thromboxane biosynthesis, therefore ginger seems a suitable choice for treatment /32/. However, in a recent study involving humans, the anti-thrombotic effect of ginger could not be confirmed /33/.

Ginger has reportedly shown significant effects on blood coagulation time. Interestingly, administration of roasted ginger led to a marked decrease in blood coagulation in mice, whereas fresh and dry ginger did not show the same effect /34/.

### *4.2b Effects on blood pressure*

In other areas related to blood, ginger has been found to directly affect blood pressure and hence heart rate. In a study carried out to measure these effects, ginger extract was observed to decrease blood pressure when injected into the femoral vein of rats, due to (6)-shogaol (1-100 μg/kg) and (6)-gingerol (0.1-100 μg/kg) dose-dependently. At higher concentrations, (6)-shogaol and (6)-gingerol have been shown to cause an immediate decrease in blood pressure followed by a significant rise which is followed by a subsequent depression of pressure /18/.

Over a decade ago, ginger was found to stimulate $Ca^{2+}$-pumping activity of fragmented sarcoplasmic reticulum (SR) prepared from rabbit skeletal and dog cardiac muscles /35/. Although established as a potent cardiotonic at that time, ginger shows a direct effect on SR $Ca^{2+}$-adenosine triphosphatase (ATPase) activity. More specifically, gingerol (3-30 μM) enhances the $Ca^{2+}$-pumping rate of skeletal and cardiac SR dose-dependently /35/. SR $Ca^{2+}$-ATPase is necessary in the process of muscle relaxation to transport $Ca^{2+}$ from the cytoplasm into the SR lumen. Cardiac SR $Ca^{2+}$-ATPase is believed to be regulated by cAMP or $Ca^{2+}$ phosphorylation dependent upon calmodulin. Relaxation of muscles is suggested to result from an increased amount of $Ca^{2+}$ storage which is released upon subsequent contraction and hence enhanced muscle relaxation /35/. Thus, the activity of gingerol on the $Ca^{2+}$ pumping rate is, in effect, dependent upon its activation of $Ca^{2+}$-ATPase. Details of this regulatory mechanism of SR $Ca^{2+}$ pumps and muscle contractibility are still under study, therefore this study involving gingerol may be useful in investigations aimed at deciphering these uncertainties /35/.

In another study, involving guinea-pig isolated atrial muscle, (8)-gingerol has been reported to exhibit dose-dependent positive inotropic effects on the left atria at concentrations of $1x10^{-6}$ to $3x10^{-5}$. Furthermore, (8)-gingerol has been found to show positive inotropic and chronotropic effects on guinea-pig atria /36/. The postulated mode of action is similar to that previously mentioned.

Studies utilizing isolated mouse mesenteric veins and arteries have concluded that (6)- and (8)-gingerols enhance contractions caused by various protaglandins (PGF2, PGE2 and PG12). Contraction activated by thromboxane $A_2$ and leukotrienes has been shown to be inhibited

/37/. Moreover, it is observed that both (6)-gingerol and (6)-shogaol inhibit contraction induced by norepinephrine, and stimulate contraction induced by $PGF_2$-α /38/.

### *4.2c Cholesterolemic effects*

Results concerning the cholesterolemic effects of ginger are controversial /39/. Some studies have confirmed that oral or intragastric intake of ginger extract reduces serum and liver cholesterol levels strikingly whilst increasing fecal cholesterol levels. These results suggest that ginger could enhance malabsorption of cholesterol. Furthermore, a newly isolated compound from ginger, [E]-8β,17-epoxylabd-12-ene-15,16-dial (Fig. 5) has been found to reduce plasma cholesterol concentrations in hypercholesterolemia-induced mice /40/.

More recently, a study investigating the effect of ginger and garlic on cholesterol and blood glucose has been reported /41/. In an experiment involving adult male Wistar rats, it was found that all of the rats exhibited an increase in body weight except those that were fed ginger and garlic in combination. Moreover, a significant reduction in blood glucose, serum cholesterol and serum alkaline phosphatase was noted in all groups. High-density lipoprotein (HDL)-cholesterol was increased in rats fed on ginger exclusively and in combination with garlic. In addition, combinations of ginger and garlic are shown to have the most dramatic effect on cholesterol levels and atherogenic indices /41/.

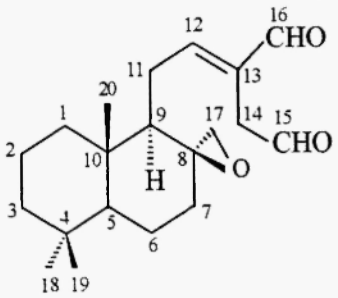


**Fig. 5:** (E)-8β,17-Epoxylabd-12-ene-15,16-dial.

However, experimental findings reveal that whilst being fed with normal and hypercholesterolemic diets, ginger, when administered at five times the average human intake to rats, showed no significant hypocholesterolemic effect /42/. A recent investigation involving human subjects has shown that in patients suffering from coronary artery disease, the daily consumption of 4 g powdered ginger for three months had no effect on plasma cholesterol levels /31/.

### *4.2d Hepatic cholesterolemic effects*

Apart from affecting cholesterol levels directly, ginger has been also tested for the hepatic mixed function oxygenase system (MFOS). This complex of enzymes is involved in the hydroxylation of steroids and metabolism of xenobiotics in the body. *In vivo*, experiments done on adult female albino rats have shown that ginger (10 and 40 mg%) generally enhances liver microsomal cytochrome P450 and cytochrome $b_5$ levels. NADPH-cytochrome *c* reductase and glucuronyl transferase activities are not altered by spices including ginger /43/.

Similar results have been reported in two animal studies. Thus cholesterol-7-hydroxylase (a hepatic rate-limiting enzyme needed for the biosynthesis of bile acids from cholesterol) activity is significantly elevated in rats fed with ginger /37/. Ginger may not affect cholesterol concentrations directly, but it does affect enzymes involved in the conversion of cholesterol to bile acids in the liver, which might ultimately decrease plasma cholesterol levels.

### *4.2e Antioxidant properties*

Lipid peroxidation is a process occurring due to reactive oxygen species (ROS) randomly attacking lipids (particularly polyunsaturated fatty acids), resulting in lipid peroxides. These are potentially damaging to the cell and the DNA. Low-density lipoproteins, if oxidized, may be a key factor in forming atherosclerotic plaque, thus posing a high risk for heart disease. Recently it has been shown that peroxidation in living organisms is closely related to the initiation of some human diseases such as cancer, coronary heart disease and Alzheimer's disease /44/.

Extensive research is being undertaken in order to find substances that inhibit lipid peroxidation. Ginger extract has been shown to

possess such antioxidant properties. In fact, zingerone has been found to function as a scavenger of superoxide anions (ROS) measured by nitrobluetetrazolium reduction in a xanthine-xanthine oxidase system /45/. In another study, zingerone has been found to inhibit lipid peroxidation at high concentrations, in contrast to other samples under study /46/.

Other workers /47/ have reported that ginger exhibits antioxidant properties in human erythrocyte membranes when lipid peroxidation is induced by the $FeSO_4$-ascorbate system. Ginger inhibited lipid peroxidation by 72% and, in addition, it inhibited the formation of diene, triene and tetraene conjugates in human erythrocyte membranes.

A commonly consumed health food in India called Amitra Bindu contains ginger as one of its main ingredients. This mixture has been investigated and results show that it acts as a scavenger for free radicals, thus inhibiting lipid peroxidation. This mixture is reported to exhibit anticarcinogenic effects as well /48/. It is to be noted that tropical ginger (*Zingiber cassumunar*) has been found to be a powerful antioxidant which contains cassumunins A and B (Fig. 6) and

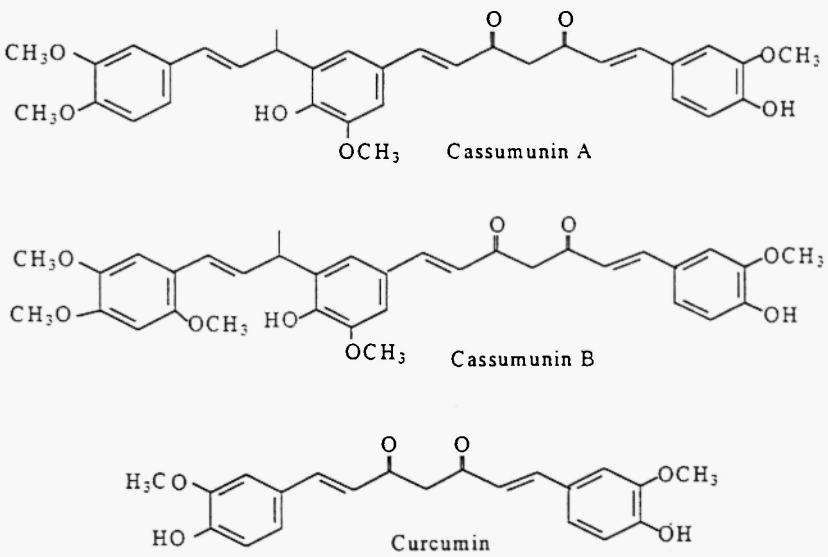


**Fig. 6:** Curcuminoids.

cassumunarins, which are newly isolated curcuminoids exhibiting antioxidative properties in $H_2O_2$-induced oxidative stress in rats. These effects of cassumunins A and B are comparable with curcumin, which is a natural antioxidant and precursor to the curcuminiods /49/. Curcumin (Fig. 6), a component of turmeric, has been selected as a possible chemopreventive agents for cancer /44/.

## 5. NEUROPHYSIOLOGY: SEROTONIN ANTAGONISTIC EFFECT

Ginger extract has yielded a diterpenoid called galanolactone. This compound exhibits an antagonistic effect against serotonin (5-hydroxytryptamine [5-HT]) receptors /50/. Serotonin is a neurotransmitter which is released by platelets during aggregation. 5-HT is also involved in the neural network that regulates intestinal motility.

Galanolactone has been shown to inhibit contractile responses to 5-HT in guinea-pig ileum, which has mainly 5-$HT_3$ receptors, to a greater extent than in rat fundus strips, which contain 5-$HT_1$ receptors, and rabbit aorta strips, which mainly possess 5-$HT_2$ receptors. It is concluded that the anti-5HT action of galanolactone is targeted at 5-$HT_3$ receptor antagonism /50/. It may turn out that the effect of ginger on gastrointestinal motility (discussed previously) might be due to this 5-HT antagonistic action. Ginger has been found to markedly inhibit serotonin-induced hypothermia and diarrhea /51/.

## 6. EFFECTS ON OTHER AILMENTS

### 6.1 Anti-arthritic and antirheumatic effects

Many studies have shown an anti-inflammatory effect of ginger in arthritis and related diseases. Arthritis is characterized as a chronic inflammatory condition whereby inflammation is due to mediation by the eicosanoids: prostaglandin $E_2$ and leukotriene $B_4$. Treatment of arthritis has been tackled with synthetic drugs which show side effects. It is known that daily ingestion of ginger (5 g fresh or 0.5-1 g powdered form) relieves pain, enhances joint movement and depresses swelling and stiffness in patients with rheumatoid arthritis /52/. In a recent animal study, ginger oils (33 mg/kg) administered to rats, suffering from induced arthritis in the right knee and paw, have shown significant inhibition of joint and paw swelling /53/.

A human study has provided further evidence for an anti-arthritic effect of ginger. Twenty-eight patients with rheumatoid arthritis and 18 patients with osteoarthritis experienced varying degrees of decreased joint swelling and pain relief. These ameliorative effects are considered to be due to the inhibitory action of ginger toward prostaglandin and leukotriene biosynthesis. After a long administration of ginger to two patients with osteoarthritis, it was shown to significantly decrease pain /54/.

Pain associated with muscular discomfort has been shown to be alleviated due to ginger consumption. In a recent study all ten patients suffering from muscular discomfort experienced pain relief after receiving ginger extracts (ranging from 3 months to 2.5 years) /25/.

### 6.2 Antimigraine effect

Migraine is described as a neurological disorder with doubtful findings assuming vascular involvement. Unlike arthritis, various drugs have been developed for the treatment of migraine, e.g. imigran, ergotamine and dihydroergotamine, etc. However, all such drugs seem to exhibit side effects. Ginger, on the other hand, when administered before or after a migraine attack, may exhibit inhibitory effects toward attacks with no side effects /25/. The effect of ginger on the inhibition of serotonin in bovine platelets and its relation to migraine have also been investigated /56/. Although the inhibitory mechanism involved is presently undefined, the efficacy of ginger administration for migraine treatment may involve the following factors as suggested by Mustafa /25/:

- As an antioxidant, the ability to prevent free radical formation, enables ginger to inhibit histamine release.
- Upon inhibition of thromboxane synthesis, opiate receptors can be activated. Since opiates are effective in the treatment of migraine, the inhibitory effect of ginger on thromboxane synthesis may cause the cessation of such attacks.
- The anti-aggregatory action of ginger may also contribute to migraine treatment. It is found that prostaglandin inhibitors and inhibitors of platelet aggregation provide effective results on acute migraine, thus making ginger a good candidate.

### 6.3 Antinausea effect

Many studies regarding the effects of ginger upon nausea have been carried out. Motion sickness, post-operative nausea, hyperemesis gravidarum (nausea of pregnancy) collectively result in a feeling of discomfort, usually accompanied by distaste for food and an urge to vomit (emesis). Results involving the effect of ginger on nausea are controversial.

#### *6.3a Antimotion sickness*

Today, motion sickness can be treated with various drugs, including antihistamines, parasympathetics and sympathomimetics. However, as with many drugs, side effects limit their use /57/. The inhibitory action of ginger against motion sickness has been found to be caused by its action on the CNS and/or gastrointestinal system /57,58/.

In animal studies, ginger juice has been found to produce anti-motion sickness effects, possibly by central and peripheral anti-cholinergic and antihistamine effects /59/. In a contradictory human study, it was shown that ginger exhibits neither anti-motion sickness activity nor does it alter gastric function during motion sickness /60/. Many factors affect the measurement of the anti-motion sickness action of ginger. Therefore, more studies need to be conducted to confirm these findings.

#### *6.3b Postoperative nausea*

Ginger is shown to significantly reduce this type of nausea, experienced as a side effect of anesthesia. Ginger has been found to significantly reduce incidences of nausea in some patients recovering from major gynecological surgery. Some studies, however, do not show any effect of ginger in post-operative nausea.

There are reports to show that ginger has the same effect as metaclopramide in treating post-operative nausea /61/. One hundred and twenty women undergoing laporascopic gynecological surgery have reinforced previous findings by showing that ginger lessens nausea and vomiting almost as much as metoclopramide. Furthermore, a reduced requirement for post-operative antiemetics has been reported, after ingesting ginger. Ginger has been found to be an

effective prophylactic antiemetic /62/. However, ginger has been shown to be ineffective, in certain doses, in reducing nausea and vomiting in other postoperative patients /63/. Certain factors, including the type of anesthesia used and method and amount of ginger administration, may account for such differences in results. Ginger is also used in preventing nausea resulting from certain drugs, such as 8-Mop, which is a drug administered to patients undergoing photopheresis /64/.

### *6.3c Antiemetic effect*

Although emesis is a common symptom of motion sickness and post-operative nausea, investigations pertaining to only the antiemetic effects of ginger are extensive. Experiments measuring sickness have shown that ginger significantly reduces vomiting and sweating, although nausea and vertigo persist /65/. An acetone extract of ginger and (6)-gingerol, administered to an experimental animal model (*Suncus murinus* Soricidae), 1 hour before cyclophosphamide, has been found to prevent emesis completely /66/. Ginger has also shown antiemetic effects in other experiments /67/ and the antiemetic action of ginger and its possible side effects due to its action on thromboxane synthesis have been investigated /68/. Antiemetic activity due to ginger seems to be more effective against cisplatin-induced emesis when administered as acetone and ethanolic extracts as opposed to an aqueous extract. More specifically, acetone extracts are most effective. However, neither organic extract showed any effect against apomorphine-induced emesis. These results verify ginger as a potent cheap antiemetic that could be utilized in cancer chemotherapy /69/.

Hyperemesis gravidarum, commonly known as morning sickness, is characterized by nausea and frequent vomiting in early pregnancy. Drugs are sometimes prescribed to treat this unpleasant condition, yet many are reluctant to consume synthetic drugs due to the possible side effects on the fetus. Alternative therapies, such as natural products and vitamin consumption, have been shown to be effective in ameliorating this condition. Ginger, for example, has been shown to significantly diminish or eliminate the symptoms of nausea associated with pregnancy /70/. In a study involving 27 women, 19 women experienced fewer symptoms of nausea and vomiting after taking daily doses of powdered ginger /70/. Ginger consumption, therefore, has been found

to be a beneficial alternative treatment for hyperemesis gravidarum /71,72/.

However, with the consumption of ginger in early pregnancy, care must be taken. Since ginger is a potent inhibitor of thromboxane biosynthesis (by direct inhibition of thromboxane synthetase), it may affect testosterone receptor binding in the fetus /73/. Therefore, it is still unknown whether ginger may or may not affect the development of the fetus, and hence more studies should be directed to explore the effects of ginger on the fetus.

### 6.4 Antipyretic and analgesic effects

Ginger has effective antipyretic activity. More specifically, [6]-shogaol has shown this effect at an i.v. dose of 1.75-3.5 mg/kg /54/. More recently, the action of (6)-shogaol on substance P-containing primary afferents of rats has also been suspected to be responsible for the analgesic effect of ginger /74/.

## 7. OTHER BIOLOGICAL ACTIONS

### 7.1 Antitumorigenic activity

Studies have shown that ginger, along with some other naturally occurring plants, may in fact possess anticarcinogenic activity. One study suggests that ginger, treated with sodium borohydride, can inhibit the formation of the carcinogenic N-nitrosodimethylamine /75/. Furthermore, ginger has been reported to significantly elevate the activity of aryl hydrocarbon hydroxylase activity. This enzyme is one of the hepatic carcinogen-metabolizing enzymes. These enzymes are responsible for the detoxification of xenobiotic compounds - carcinogens and mutagens /68/.

Ginger provides protection against skin tumor formation and multiplicity when applied topically to SENCAR mice /76/. Such results may be just the first stepping stone to discovering a multitude of anticarcinogenic properties of ginger.

### 7.2 Antiparasitic and antiviral activity

Ginger has been shown to reduce *Dirofilaria immitus* microfilarial concentrations in infected dogs by 98% /77/. Sesquiterpenes isolated

from ginger have been found to substantially reduce rhinoviral activity /78/.

Synergetic effects of (6)-gingerol and (6)-shogaol have been observed in the destruction of *Anisakis* larvae. These components of ginger exhibit a dose-dependent lethal effect on the parasite /79/. This parasite causes a common infection due to the frequent consumption of raw seafood in Japan. However, ginger is less effective than some other essential oils in altering microbial action /80/.

### 7.3 Mutagenicity

Ginger extract, in the presence of *Salmonella* strains and S9 mix, exhibits weak mutagenicity. It is suggested that since zingerone shows no mutagenicity and gingerol and shogaol (which resemble the chemical structure of zingerone) do in a dose-dependent manner, then the side-chains of the two latter components of ginger may account for the actual mutagenic effect. The opposing effects of zingerone and gingerol and shogaol may in effect, be responsible for the weak mutagenic action of ginger extract /81/.

In a recent study, safrole (Fig. 7), a natural mutagenic component found in ginger (500 mg/g) and other spices, is destroyed by drying or cooking the substance investigated. Safrole has been found to undergo degradation by heat (70°C) or by high irradiation doses (20 kGy) /82/. However, a study has concluded that ginger is not mutagenic when compared with a variety of other South Indian food items /83/.

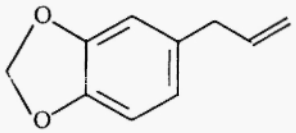

**Fig. 7:** Safrole.

### 7.4 Thermogenic action

Ginger extracts induce the rat hind limb to consume more oxygen, and (6)-gingerol shows potent thermogenic activity. Removal of high doses of ginger results in an increased oxygen uptake rate. Therefore, it is suggested that ginger may cause disruption of mitochondrial function /84/. Another study has reported only slight thermogenic activity in rats due to ginger intake /85/.

## 8. OTHER FINDINGS

Further miscellaneous studies involving ginger have been carried out and the results are interesting. Thus, treatment of buffalo meat with 2% lactic acid or ginger extract with 20% sodium chloride has been shown to extend the shelf-life of the meat by significantly inhibiting microbial growth whilst maintaining taste, color and aroma of the treated meat samples /86/. These results imply the possibility of using ginger in the preservation of meats.

Ginger has been tested as an ovipositional deterrent of *Delia antiqua* (onion fly) and has shown 99% deterrence. Theoretically, ginger may be a useful insecticide. However, since gingerol is relatively expensive and is found only in small amounts in ginger extracts, commercial field use of ginger as a major deterrent may be questionable /87/. Efforts aimed at chemically synthesizing gingerols may provide the means to adopt ginger as a commercial insecticide whilst being cost-effective.

In a recent study, the psychophysical properties of zingerone were tested. Analysis of zingerone oral irritation has shown that the sensations produced are mostly those of burning and warmth, resembling that of capsaicin (Fig. 8), found in red pepper. Other studies also have shown that repeated oral zingerone irritation causes slight desensitization to capsaicin following a stimulatory hiatus. Zingerone is even capable of self-desensitization /88/.

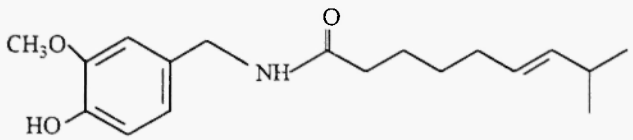


**Fig. 8:** Capsaicin.

Other findings have shown zingicomb (a commercial product made of a combination of *Ginkgo biloba* and ginger extracts) has anxiolytic effects which resemble those of diazepam (a known anxiolytic compound), but in high doses may exhibit anxiogenic effects. The anxiolytic effects of zingicomb are suggested to be associated with the anti-seratonergic action of ginger and *Ginko biloba* /89/.

In psychiatric tests, different odors, including ginger, have been included to investigate the relationship between odor and depression in Japanese elderly /90/. A study carried out in China suggests that ginger paste applied at the 'Zhihying' acupoint to pregnant women with breech position might be responsible for correcting the fetal presentation - a significant difference in correction rate was observed between the treated and control groups /91/.

Ginger has been found to contain proteases, all of which have a molecular mass of 29 kDa as measured by SDS-polyacrylamide gel electrophoresis and by TSK G2000SW XL gel /62/. In addition, an inhibitory effect of ginger on adenosine 3′,5′-cyclic monophosphate phosphodiesterase has been reported /92/.

## 9. METABOLISM OF GINGEROL AND SHOGAOL

Recently, *in vitro* experiments have been performed in order to investigate the metabolic pathway of (6)-gingerol using rat hepatic postmitochondrial fraction. It was concluded that *S*-(6)-gingerol is reduced enzymatically to (6)-gingerdiol. Based on the results collected and theoretical assumptions, it is likely that *S*-(6)-gingerol is reduced to a mixture with more of the *S,S*-isomer than the *R,S*-isomer. It is of great importance to determine the pharmacological activity of each stereoisomer since each component of the enantiomeric pair could vary in its biological activity. Apparently (6)-gingerdiol retains some of the original activity possessed by gingerol, but further studies should be carried out in order to determine which stereoisomer of (6)-gingerdiol exhibits more pharmacological activity /93/.

The reductive metabolic pathway of shogaol has been monitored *in vitro* and the metabolites involved have been followed. Two major metabolites, paradol and reduced paradol, have been found to be the metabolic intermediates of shogaol (Fig. 2). It has been reported that paradol is found as an intermediate in the reductive metabolism of the αβ-unsaturated ketone moiety of shogaol to its saturated alcohol counterpart /94/.

Another study has identified a new metabolite in the reduction of shogaol: an allyl alcohol, 1-(4′-hydroxy-3′-methoxyphenyl)-dec-4-en-3-ol. Dehydroparadol has also been shown to be reduced to its corresponding allyl alcohol by the post-mitochondrial fraction of rat kidney in the presence of an NADPH-generating system /95/.

## 10. CHEMICAL SYNTHESIS OF ZINGERONE AND SHOGAOL

Successful chemical syntheses of two of the pungent principles and cassumanins in ginger extract have been accomplished /96/. A general schematic outline of the procedures undertaken is shown (Fig. 9).

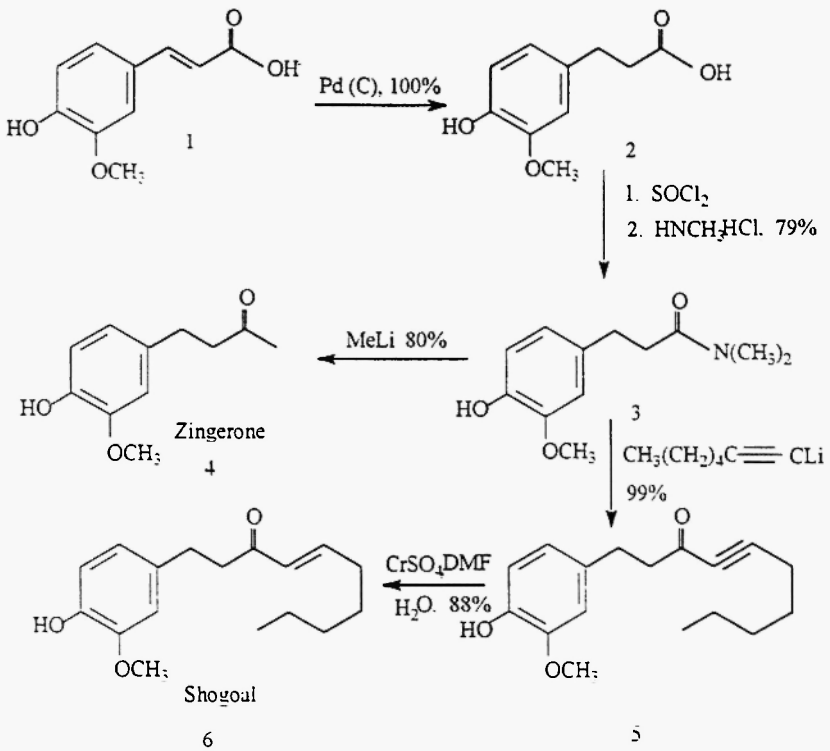


**Fig. 9:** Scheme for the chemical synthesis of zingerone and shogaol (adapted from /38/).

1. 3-(4-hydroxy-3-methoxy)-2-propenoic acid;
2. 3-(4-hydroxy-3-methoxyphenyl)-2-propanoic acid;
3. 3-(4-hydroxy-3-methoxyphenyl)-*N*,*N*-dimethyl-propanamide;
4. 3-(4-hydroxy-3-methoxyphenyl)-2-butanone (zingerone);
5. 3-(4-hydroxy-3-methoxyphenyl)-dec.4-yn-3-one;
6. 3-(4-hydroxy-3-methoxyphenyl)-dec-4-ene-3-one (shogaol).

## 11. TOXICITY AND DOSAGE

Ginger has been recognized by the US Food and Drug Administration (FDA) and is listed as a food additive that is 'Generally Recognized as Safe' (GRAS) and a "natural flavor and natural flavor additive" (Regulatory Status of Direct Food Additives). However, independent studies have shown that ginger and other spices may produce allergic reactions in some individuals. Allergic dermatitis has been associated with contact with ginger /97/. Although rare, incidences of such allergies have been correlated with occupation. Upon the investigation of 1,000 individuals working in places associated with foods containing ginger, only five were found to suffer from hand or finger dermatitis /98/.

Interestingly enough, two cases involving osteoarthritic individuals have shown that prolonged consumption of ginger exhibits no adverse effects. In fact, marked pain relief was experienced in both cases /54/.

On the other hand, since ginger appears to inhibit platelet aggregation and prostaglandin, leukotriene and thromboxane biosynthesis, its use for post-operative nausea and vomiting may result in complications in wound healing /99/. In addition, the use of ginger during pregnancy in treating nausea has unknown effects pertaining to the fetus and its development, therefore ginger must be consumed with caution in such situations.

There is also a report that ginger taken in large doses for long periods can cause inflammation and weakness. As with every drug, even natural compounds that have been consumed by humans over the centuries must be taken in moderation.

## 12. FUTURE OF GINGER

As we enter the new millennium, thousands of years after its discovery, ginger has now been scientifically proven to possess highly significant pharmacological properties. Knowledge of the other biological effects of ginger is sketchy and remains to be elucidated. Since there is a renascence in herbal medicine, extensive research efforts are required to uncover more about ginger for its potential use in the treatment of many chronic diseases.

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