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# Ginger Protects the Liver against the Toxic Effects of Xenobiotic Compounds: Preclinical Observations

**Raghavendra Haniadka[1], Arpit Saxena[2], Arnadi R Shivashankara[2], Raja Fayad[2], Princy L Palatty[3], Nithin Nazreth[1], Athul Francis[1], Rajesh Arora[3] and Manjeshwar Shrinath Baliga[1*]**

*[1]Department of Research and Development, Father Muller Medical College, Kankanady, Mangalore, Karnataka, India*
*[2]Center for Colon Cancer Research, University of South Carolina, Columbia, SC, 29208, USA*
*[3]Radiation Biosciences Division and Division of CBRN Defence, Institute of Nuclear Medicine and Allied Sciences, Brig SK Mazumdar Marg, Delhi, India*

## Abstract

According to the World Health Organization, chronic liver disease is a major ailment and causes significant morbidity and mortality in both western and developing countries. However, till date no ideal hepatoprotective agents are available in the modern system of medicine to effective prevent and cure liver ailments. This has necessitated the need to depend on complementary and alternative systems of medicine for liver ailments and diseases. *Zingiber officinale* Roscoe commonly known as ginger is arguably one of the most commonly used spice, and is an integral part of our diet. In addition to its dietary use, ginger is also reported to possess myriad health benefits, and has been used in the various traditional and folk systems of medicine to treat various ailments and illnesses. Preclinical studies carried out in the past decade have shown that ginger possesses hepatoprotective effects, and to protect against diverse xenobiotic compounds like alcohol, acetaminophen, fungicides, tetracycline, heavy metals and organophosphorus compounds. Mechanistic studies have shown that the protective actions are mediated through free radical scavenging, antioxidant, cytoprotective, and to modulate the levels of the detoxifying enzymes. This review for the first time summarizes the results related to the beneficial properties of ginger in ameliorating the toxic effects of hepatotoxins, and also emphasizes the aspects that warrant future research to establish its activity and utility as a broad spectrum hepatoprotective agent.

**Keywords:** Hepatoprotection; *Zingiber officinale* Roscoe; Ginger; Antioxidant; Liver

**Abbreviations:** ADH=Alcohol dehydrogenase; ALDH=Aldehyde dehydrogenase; ALP= Alkaline phosphatase; ALT=Alanine transaminase; AST=Aspartate Aminotransferase; CAT=Catalase; $CCl_4$=Carbon Tetra Chloride; COX-2=Cyclooxygenase 2; DEN=Diethylnitrosoamine; ERK=Extracellular Signal-Regulated Kinase; GGT= Gamma-Glutamyltransferase; GLDH=Glutamate Dehydrogenases; GPx=Glutathione Peroxidase; GR=Glutathione Reductase; GSH=Glutathione; GST=Glutathione S transferase; HDL=High density lipoprotein; IFN-γ=Interferon gamma; IL-1β=Interleukin 1 beta; IL-6=Interleukin 6; IL-8=Interleukin 8; i-NOS=Inducible nitric oxide synthase; IκBα=Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; LC50=Lethal Concentration 50; LDH=Lactate Dehydrogenase; LDL=Low-Density Lipoprotein; LPS=Lipopolysaccharide; LPx=Lipid Peroxidation; MAPK=Mitogen-Activated Protein Kinase; NFκB=Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; SAPK/JNK=Stress-Activated Protein Kinases/Jun Amino-Terminal Kinases; SDH= Succinate dehydrogenase; SOD=Super oxide dismutase; TNF-α=Tumor Necrosis Factor Alpha; UDPGT=Uridine Diphosphate Glucuronyl Transferase

## Introduction

Ginger, the rhizomes of the plant *Zingiber officinale* Roscoe (Family Zingiberaceae), is arguably one of the most widely used culinary agent and spice in the world [1,2]. In addition to its culinary use, ginger also possess medicinal properties, and has been used since antiquity to treat ailments like cold, headaches, nausea, stomach upset, diarrhea, digestive, gastrointestinal disturbances, rheumatic complaints, diarrhea, nausea, asthma and parasitic infections, arthritis and muscular discomfort in the various alternative and folk systems of medicine in the world [1-7]. Phytochemical studies have shown that the unique culinary and medicinal properties of ginger are due to the presence of phytochemicals like zingerone (Figure 1), shogaols (Figure 1), gingerols (Figure 1), pardols (Figure 1), β-phellandrene, curcumene, cineole, geranyl acetate, terphineol, terpenes, borneol, geraniol, limonene, β-elemene, zingiberol, linalool, α-zingiberene, β-sesquiphellandrene, β-bisabolene, zingiberenol and α-farmesene [1-7]. Scientific studies carried out in accordance to the principles of modern system of medicine have convincingly shown that ginger possesses numerous health benefits like antimicrobial, antiviral, gastroprotective, antidiabetic, anti-hypertensive, cardioprotective, anticancer, chemopreventive and immunomodulatory effects [1,4]. Additionally, preclinical studies carried out with laboratory animals have also shown that ginger to possess hepatoprotective effects, and to protect the liver against the toxic effects of diverse class of xenobiotic agents like alcohol [8,9], country liquor [10], acetaminophen [11], heavy metals [12,13], $CCl_4$ [14], paraben [15] and bromobenzene [16]. In the following section, the observations from these studies will be addressed in detail.

## Ginger Protects Against the Alcohol-Induced Hepatotoxicity

Innumerable studies have proved that the chronic consumption of

***Corresponding author:** Manjeshwar Shrinath Baliga, Research and Development, Father Muller Medical College, Kankanady, Mangalore, Karnataka-575003, India, Tel: 91-824-2238331; Fax: +91-824-2437402; +91-824-2436352; E-mail: msbaliga@gmail.com

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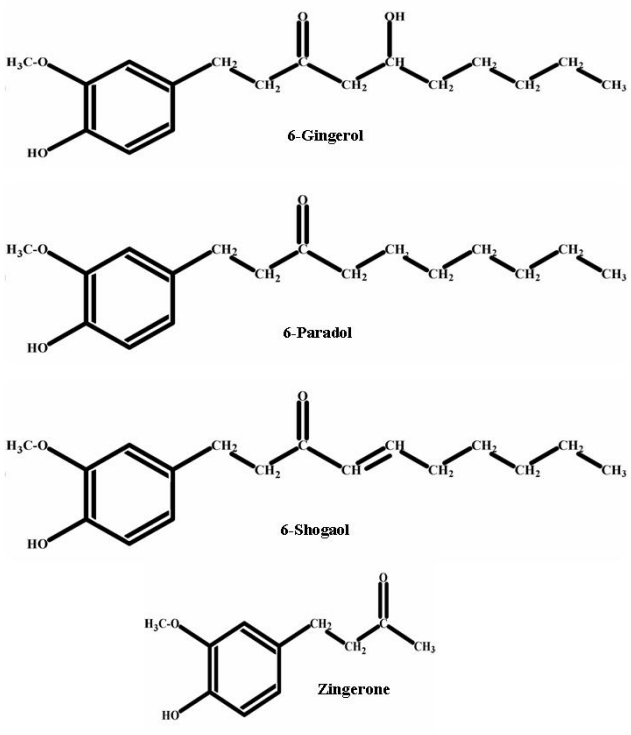


**Figure 1:** Important phytochemicslspresent in ginger

high doses of ethanol is a major cause for liver cirrhosis and cancer [17]. In the liver, the consumed ethanol is mainly oxidized by ADH to acetaldehyde, and is further detoxified to acetate by ALDH [17]. Variations in the genes for these enzymes have been found to influence alcohol consumption, alcohol-related tissue damage and alcohol dependence [17]. Preclinical studies have shown that feeding rats a diet containing ginger (1%) for four consecutive weeks was effective in ameliorating the ethanol-induced hepatotoxic effects [8]. When compared to the rats feeding only on the laboratory diet (without ginger) the cohorts feeding on the ginger containing diet had increased levels of SOD, GPx, GR, CAT and GSH and a concomitant decrease in the levels of LPx [8].

Subsequent studies with laboratory mice have also shown that administering aqueous extract of ginger (500 mg/kg b.wt.) for two consecutive weeks was effective in decreasing the levels of ethanol induced increase in nitric oxide and LPx, to increase the total antioxidant capacity, GPx activity, and to reduce the levels of alcohol induced increase in the levels of the liver function enzymes the L-gamma-glutamyl transpeptidase and butyryl cholinesterase in the serum [9]. Additionally, studies have also shown that the oral administration of ethanolic extract of ginger (200 mg/kg) was effective in reducing the serum levels of AST, ALT, ALP, GGT and the levels of tissue LPx [10]. The authors also observed that the beneficial effects of ginger were comparable to that of a clinically used hepatoprotective drug silymarin (25 mg/kg) [10]. Together all these observations clearly indicate that ginger was effective irrespective of whether it was administered through diet or orally, and also in two species of animals (rats and mice).

## Ginger Protects against the Acetaminophen (Paracetamol)-Induced Hepatotoxicity

Acetaminophen or paracetamol is arguably one of the most commonly used analgesic and antipyretic agent in the modern system of medicine [11,18]. However, long term usage and at high concentration of acetaminophen is proved to cause hepatotoxicity and more when along with ethanol [18]. Seminal studies by Ajith et al. [11] have shown that administration of single dose of aqueous extract of ginger (200, 400 mg/kg prior to acetaminophen) was effective in preventing the acetaminophen-induced hepatotoxicity. The cohorts administered with ginger had decreased levels of ALT, AST and ALP in serum and increased activities of SOD, GST, CAT and GSH levels in the liver [11]. Additionally, studies have also shown that administering rats with graded doses of ginger (100, 200 and 400 mg/kg) at 12 hour interval for 48 hours, prior to single dose (640 mg/kg) of paracetamol was effective in causing a concentration dependent hepatoprotective effects [18]. When compared to the paracetamol only treated cohorts, pretreatment with ginger affording significant reduction in paracetamol-induced increase in the serum levels of ALT, AST, ALP and total bilirubin and the histopathological observations supported the biochemical observations. Studies with primary culture of rat hepatocytes have also shown that the extract was protective at a non toxic concentration of 15 µg/ml (the LC50 was 750 µg/ml), indicating it to be safe and non toxic [18].

Very recently, Abdel-Azeem et al. [19] have also reported that ginger (100 mg/kg) was effective in reducing the acetaminophen-induced hepatotoxicity. Pretreatment with ginger decreased the acetaminophen-induced increase in the biochemical levels of the hepatic marker enzymes (AST, ALT, ALP and arginase) and total bilirubin, ameliorated the levels of LPx and restored the altered levels of plasma triacylglycerols in plasma [19]. The histopathological examination showed that when compared to the acetaminophen alone cohorts, the animals co treated with ginger had reduced levels in the necrosis and vacuolization of cells, indicating its beneficial effects. Together all these observations clearly indicate ginger to be beneficial in preventing the acetaminophen-induced hepatotoxicity, and to mediate these effects at non toxic concentrations.

## Ginger Protects against Carbon Tetrachloride-Induced Hepatotoxicity

$CCl_4$ is a very toxic agent and depending on the dose and route of exposure causes damage to many organs [14]. Studies with laboratory rats have shown that the oral administration of ethanolic extract of ginger reduces the $CCl_4$-induced increase in levels of ALT, AST, LDH, ALP, SDH and GLDH, and to mitigate the histological damage [14]. The ethanolic extract of ginger is also shown to be effective in ameliorating $CCl_4$-induced increased levels of ALT, AST and ALP in serum, decrease the liver fibrosis, and to concomitantly increase the levels of serum albumin [20]. Administering ginger mitigated the oxidative stress by increasing the activity of SOD and decreasing the levels of LPx in the rat liver [20]. In addition to the extract, studies have also shown that feeding rats a diet containing ginger was also effective in preventing against the $CCl_4$-induced liver damage [21]. Studies have shown that feeding rats on ginger decreased the $CCl_4$-induced increase in the levels of serum AST, ALT, ALP and lipid peroxidation [21]. Additionally, the histopathological observations corroborated with the biochemical results and together these observations clearly indicate the usefulness of ginger as a protective agent against the $CCl_4$-induced hepatotoxic effects [21].

## Ginger Protects against Lindane-Induced Hepatotoxicity

Lindane, an anti-lice and anti-scabies agent, is a potent toxin and

damages the nervous system, liver and kidneys [22]. Studies have shown that ginger provided in diet (1% w/w) was effective in reducing the lindane (30 mg/kg b.wt)-induced hepatotoxicity by enhancing the levels of ROS-scavenging enzymes (GPx, GR, GST), and GSH and concomitantly decreasing the levels of the lindane-induced lipid peroxidation [22].

## Ginger Protects against Mancozeb-Induced Hepatotoxicity

Mancozeb (ethylene-bis-dithiocarbamate) is a very useful fungicide, and is widely used to protect fruits, nuts and field crops from a wide spectrum of plant fungal diseases [23]. Mancozeb is a cholinesterase inhibitor, and also affects the nervous system [23]. Studies have shown that ginger (24 mg/ml) three times a week for 6 weeks was beneficial in protecting against the mancozeb-induced liver toxicity. When compared to the mancozeb treated cohorts, the co administration of ginger reduced the mancozeb-induced increase in the levels of ALT, AST, LPx and a concomitant increase in the level of the antioxidant enzyme SOD [24]. The investigators also observed that the histopathological observations corroborated with the biochemical results, and together these observations clearly indicate the usefulness of ginger in preventing the mancozeb-induced hepatotoxicity [24].

## Ginger Protects against Bromobenzene-Induced Hepatotoxicity

Bromobenzene, an aryl halide formed by electrophilic aromatic substitution of benzene using bromine, is a very useful industrial solvent, and is widely used as an additive to motor oils [16]. Unfortunately, the exposure to bromobenzene causes neuro and hepatoxicity, and this limits its industrial use [16]. Studies by El-Sharaky [16] have shown that the administration of the ethanolic extract of ginger (100, 200, 300 mg/kg b.wt) two weeks prior to one week of bromobenzene (460 mg/kg b.wt) was effective in reducing the hepatoxic effects of the toxicant. Ginger mediated the beneficial effects by increasing the levels of the antioxidant enzymes, reducing the toxicant-induced production of nitric oxide metabolites, the cyclooxygenase-2 and the caspase-3 [16].

## Ginger Protects against Paraben-Induced Hepatotoxicity

Parabens (p-hydroxybenzoic acid) are an important class of preservatives, and are widely used in cosmetic and pharmaceutical industries for preparing shampoos, commercial moisturizers, shaving gels, personal lubricants, topical/parenteral pharmaceuticals, spray tanning solution and toothpaste. The most commonly used parabens like methylparaben, ethylparaben, propylparaben, butylparaben and heptylparaben are shown to induce allergic reactions, hepatotoxicity, and to increase the chances of breast cancer and skin cancer [15]. Studies with laboratory mice have shown that when compared to the paraben only cohorts, the co administration of the aqueous extract of ginger (3 mg/animal/day), along with paraben for 30 days ameliorated the toxin-induced lipid peroxidation [15]. Administering ginger increased the activities of SOD, GPx, CAT and the non enzymatic antioxidants (GSH and ascorbic acid) in the mouse liver, and thereby, reduces the hepatotoxic effects of parabens [15].

## Ginger Protects against Heavy Metal-Induced Hepatotoxicity

Trace metals like lead, cadmium, zinc, mercury and arsenic are an important environmental pollutants and affect a range of animals [12,13]. Experiments carried out in the recent past indicate that ginger is effective in preventing the hepatotoxic effects of lead [13], cadmium [25] and mercury [12]. With respect to ginger's protective effect in ameliorating the lead-induced toxicity, studies by Vitalis et al. [12] have shown that feeding ginger containing diet (10%) to rats was effective in ameliorating the hepatotoxicity of mercury, and to reduce the toxicant induced increase in serum enzymes AST, ALT, ALP [12]. Subsequent studies have also shown that ginger was effective in reversing lead-induced reduction in the liver weight, to increase plasma SOD and CAT activity, and decrease LPx [13]. The investigators observed that administering ginger caused a reduction in the number of apoptotic cells, indicating that the prevention of lead-induced apoptosis contributed towards the hepatoprotective effects at least in part [13]. Additionally, recent studies by Eteng et al. [25] have also shown that ginger was effective in reducing the cadmium induced hepatotoxicity. The authors observed that feeding ginger containing diet (10%) decreased the elevated levels of ALP, acid phosphatase in serum, and to normalize blood hemoglobin, PCV, RBC count and serum testosterone in rats [25].

## Ginger Prevents Oxytetracycline-Induced Fatty Liver

Tetracycline, an antibiotic with broad spectrum of effect against many clinically important bacteria, possess inherent hepatotoxic effects and induces micro vesicular steatosis by increasing the of accumulation triglyceride, inhibiting β-oxidation of free fatty acids, secretion of lipoprotein from the liver and mitochondrial lipid metabolism [26]. Recent studies by Helal et al. [26] with laboratory rats have shown that when compared to the cohorts receiving only tetracycline, the group also receiving aqueous extract of ginger had reduced levels of blood glucose, total lipids, triglycerides, cholesterol, LDL cholesterol, ALT, AST, GGT, LDH, urea and creatinine [26]. Additionally, the co treatment with ginger increased the levels of total protein, albumin, globulin and HDL cholesterol, indicating its beneficial effects. The histopathological observations clearly showed that the rats fed with ginger extract had reduced levels of fatty liver tissue when compared to the parallel tetracycline only cohorts, indicating ginger to be effective in ameliorating the undue effects of the useful antibiotic.

## Ginger Prevents Chemical-Induced Liver Cancer

Liver cancer, scientifically known as hepatocellular carcinoma, is one of the five most common cancers in the world, and is caused by chronic consumption of hepatotoxins and infection by the hepatitis B viruses [27]. Scientific studies carried out in the recent past have shown that ginger possess chemopreventive properties, and was effective in preventing ethionine-induced [28,29], and DEN-initiated and $CCl_4$-promoted hepatocarcinogenesis in rats [30]. Seminal studies by Poli [31] showed for the first time that when compared to the carcinogen, only cohorts, co administering ginger oleoresin (100 mg/kg body wt.) to the rats feeding on choline deficient diet and accessing 0.1% ethionine containing drinking water for eight weeks reduced the number of liver nodules. Additionally, co administering ginger decreased the LPx levels [32]. Molecular studies have also shown that ginger reduces the elevated expression of NFκB and TNF-α in rats with liver cancer, suggesting that the observed chemopreventive effects may be mediated through the inhibitory effects on NFκB, possibly through the suppression of the pro-inflammatory TNF-α [27]. Ginger extract decreased LPx level in the blood of rats being subjected to hepatocarcinogenesis, by administering a choline deficient diet and carcinogen ethionine in drinking water [28].

Studies have also shown that ginger was effective in preventing hepatocarcinogenesis initiated by DEN and promoted by $CCl_4$. Providing animals with ginger (50 mg/kg/day) in drinking water

for 8 weeks was observed to be effective in inhibiting the chemical hepatocarcinogenesis [30]. When compared to the DEN-induced and $CCl_4$ promoted cohorts, the animals receiving ginger (along with the carcinogens and promoters), had reduced levels of neoplastic changes, levels of serum hepatic tumor markers, decreased levels of hepatic tissue growth factors (vascular endothelial growth factor, basic fibroblast growth factor), and increased levels of hepatic metallothionein and endostatin [30].

## Mechanism/s of Action

### Ginger is a scavenger of free radicals

Innumerable studies have proved that increased generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) are implicated in various liver diseases, and in the toxic manifestations of various hepatotoxins [31]. Innumerable studies have shown that ginger extracts, oleoresins and the volatile oils possess free radical scavenging effects, and to be effective in scavenge, superoxide, hydroxyl, nitric oxide *in vitro* [32-34]. The phytochemical zingerone is also reported to be an effective scavenger of the free radicals like superoxide [35], peroxyl [36] and peroxynitrite [37], and to also inhibit the formation of peroxynitrite-mediated tyrosine nitration [37]. Another important phytochemical of the ginger [6]-Gingerol is also shown to scavenge peroxyl radicals [36], to inhibit the production of nitric oxide and reduce generation of iNOS in LPS-stimulated J774.1 cells [38].

### Ginger inhibits /breaks the chain of lipid peroxidation

The ROS and RNS cause oxidation of lipids, proteins and DNA [39]. The polyunsaturated fatty acids in the membranes are the target of free radicals which produce lipid peroxides and hydroperoxides [39]. Lipid peroxides have destructive effects on cell membrane structure, properties and functions [39]. Cell free assays have shown ginger and its phytochemicals [6]-gingerol and zingerone to be effective in preventing/inhibiting lipid peroxidation, and this would have contributed to the observed hepatoprotective effects [36,40-42].

### Ginger enhances antioxidant defense systems *in vivo*

Eukaryotic cells are equipped with enzymatic and non enzymatic antioxidant defense mechanisms to protect against the deleterious effects of free radicals, and based on their mode of action are categorized as preventive and chain breaking. The biochemical enzymes, SOD, CAT and GPx, are the preventive antioxidants, while uric acid, vitamin C, GSH, albumin, vitamin E are the major chain breaking antioxidants [39,43,44]. Scientific studies have shown that ginger reduces the oxidative stress induced by various hepatotoxins by increasing the activity/levels of the antioxidant enzymes [8,45,46], and this mechanism would have played a cardinal role in the observed hepatoprotective effects of ginger against diverse class of toxicants.

### Ginger possesses anti-inflammatory effects

The anti-inflammatory properties of ginger have been known and valued for centuries, and numerous scientific studies have validated this beneficial effect of ginger and its phytochemicals in various study models [47]. Mechanistically, the pathogenesis of inflammatory diseases is proposed to be mediated by the enhanced expressions of TNF-α, NF-κb, i-NOS and COX-2, and increased generation of proinflammatory eisonaoids and nitric oxide [1,48]. Ginger is shown to inhibit the enzymes required for synthesis of prostaglandins and leukotrienes, namely, cyclooxygenase and lipooxygenase respectively [47,49].

The extract of ginger is shown to reduce the activity of COX-2, NF-κB, and to inhibit the release of IL-1β, IL-6, IL-8, and TNF-α from LPS-stimulated human peripheral blood mononuclear cells [50]. *In vitro* studies have also shown that the phytochemicals of ginger, namely 8-paradol and 8-shogaol, also possess strong inhibitory effects on the enzymatic activity of COX-2 [51]. Ginger and its phytochemicals are also shown to decrease the levels of pro-inflammatory cytokines (TNF-α, IL 1β, IL- 6 and IFN-γ), and to reduce the elevated expression of NF-κB [52].

Seminal studies by Choi et al. [53] have shown that ginger inhibits the LPS-induced inflammation in ICR mouse. The investigators observed that the oral administration of the aqueous extract of dried ginger (100 or 1000 mg/kg) for three consecutive days was effective in reducing the LPS-induced pathological changes in the liver, and to decrease the levels of proinflammatory cytokines like IFN-γ and IL-6 in the serum [53]. In addition, ginger inhibited LPS-induced activation of NF-κB by preventing the degradation of the IκBα, as well as the phosphorylation of ERK1/2, SAPK/JNK and p38 MAPKs [53]. A strong decrease in the expression of iNOS and COX-2 were also observed [53]. Together all these observations clearly indicate that ginger modulating myriad pathways, and thereby, affords the anti-inflammatory effects.

### Ginger modulates detoxifying enzymes

In mammals, the liver is the major organ responsible for the metabolism and detoxification of xenobiotic compounds, and is performed by the specific phases I and II enzymes [16,54,55]. The phase I reactions increase polarity of the xenobiotic compounds by adding new functional groups to xenobiotic molecules, and is principally catalyzed by cytochrome P-450 monooxygenase system [16,54,55]. During phase II reaction, conjugation to endogenous hydrophilic molecules (like GSH by GST), and the resulting reaction increases the polarity and water solubility to eliminate the xenobiotic metabolite out of the body [54,55].

Studies have shown that the extracts of ginger and some of its phytochemicals modulate the activity of both phase I and II enzymes, and to mediate their hepatoprotective affects, at least in part, through this mechanism. With respect to the phase I enzymes, studies have shown that feeding ginger causes an increase in the levels of microsomal cytochrome P 450-dependent aryl hydroxylase, cytochrome P 450 and cytochrome b5, and this effect would have increased the polarity of non polar xenobiotic compounds [16,56]. Additionally, studies have also shown that the oral feeding of ginger oil increases the activity of aryl hydrocarbon hydroxylase and GST in mice [57]. Additionally, studies have also shown that ginger increases the activities of GST, UDPGT, aryl hydrocarbon and quinone reductase, and to fasten the elimination of the partially metabolized hepatotoxins from the liver [54,55,57].

## Conclusion

Ginger has been shown to be a hepatoprotective agent, and studies with various hepatotoxins like ethanol, paracetamol, $CCl_4$, lead, cadmium, tetracycline, organophosphorus compounds validate the property. However, although considerable work has been done to exploit the hepatoprotective effects, countless possibilities for investigation still remain. There are hardly any reports of toxic effects of ginger. Studies should be conducted to assess for the possible adverse effects of ginger, especially at higher concentrations and when consumed over longer periods. Additionally, further in-depth mechanistic *in vitro* studies, relevant animal studies and rationally designed clinical trials are required. By virtue of its free radical scavenging, antioxidant enhancing, anti-inflammatory and modulation of the detoxifying enzymes, it

is safe to suggest that ginger merits clinical studies, especially in the high risk group like chronic alcoholics and people with compromised liver functions. The outcomes of such studies may be useful for further clinical applications of ginger in humans, and may open up a new therapeutic avenue.

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