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REVIEW

Dietary agents in the prevention of alcohol-induced hepatotoxicity: preclinical observations†

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Long term alcohol consumption is one of the important causes for liver failure and death. To complicate the existing problem there are no dependable hepatoprotective drugs and a large number of patients prefer using complementary and alternative medicines for treating and managing hepatic complications. Almost 25 centuries ago, Hippocrates, the father of medicine, proclaimed “Let food be thy medicine and medicine be thy food.” Exploring the association between diet and health continues even today. Preclinical studies carried out in the recent past have shown that the commonly used dietary agents like *Allium sativum* (garlic), *Camellia sinensis* (tea), *Curcuma longa* (turmeric), *Emblia officinalis* (Indian gooseberry), *Ferula asafoetida* (asafoetida), *Garcinia cambogia* (Malabar tamarind), *Glycine max* (soyabean), *Murraya koenigii* (curry leaves), *Piper betle* (beetle leaf), *Prunus armeniaca* (apricot), *Ocimum gratissimum* (wild basil), *Theobroma cacao* (cocoa), *Trigonella foenum-graecum* (fenugreek) and *Vitis vinifera* (grapes) protect against ethanol-induced hepatotoxicity. Mechanistic studies have shown that the beneficial effects of these phytochemicals in preventing the ethanol-induced hepatotoxicity are mediated by the antioxidant, free radical scavenging, anti-inflammatory and anti-fibrotic effects. The present review for the first time collates the hepatoprotective effects of these agents and also emphasizes on aspects that need future research to establish their utility in humans.

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Introduction

According to the World Health Organization, in the year 2000, alcohol-related death and disability accounted for nearly 4.0% of the total global burden of disease.¹ Alcohol, when consumed chronically and at high concentrations, affects the liver, heart, brain, immune system, pancreas and kidneys. Of these, the liver is the most affected organ and accounts for a significant number of deaths from liver cirrhosis and cancer.² Classically the alcoholic liver injury and the sequential pathological features comprise of fatty liver (steatosis), followed by liver fibrosis, hepatitis and cirrhosis. The fatty liver is present in more than 90% of chronic alcoholics, while about 10–20% of heavy drinkers progress to alcoholic hepatitis and cirrhosis. These observations indicate that other factors like genetic background, nutrition;

viral infection (HBV); chronic intake/exposure to paracetamol, aflatoxins, heavy metals and xenobiotic compounds interact to influence the progression of the alcohol-induced liver damage and disease.³

Metabolism of ethanol

Studies indicate that over 90% of the absorbed alcohol is metabolized in the body, while the remainder is excreted unchanged in the urine, expired in air and sweat.^{2,4} Ethanol absorbed from the gut is metabolized mainly by the liver. The brain, pancreas and stomach are also involved in the metabolism of ethanol but to a lesser amount than the liver. Alcohol is principally metabolized in the cytosol of the liver by the enzymes ADH and ALDH. In the first step, ADH metabolizes alcohol to



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acetaldehyde, which in the second step is converted to acetate by ALDH. The acetate formed may be converted to acetyl-CoA by Acetyl-CoA synthetase. Acetaldehyde is a highly toxic substance and if not converted quickly by ALDH can cause mutagenesis and cytotoxicity.⁴ Acetaldehyde can also be converted to acetoin and hydroxyketohexanoic acid, which are also known to be cytotoxic.⁴

Another metabolic pathway which plays a significant role in alcohol toxicity and detoxification, but only after a person has consumed large amounts of alcohol, is through the cytochrome P450 system (CYP2E1) present in the liver microsomes.² Minuscule amounts of alcohol interact with fatty acids to form fatty acid ethyl esters and these compounds are known to damage both liver and pancreas.² Chronic exposure to ethanol promotes free radical generation, oxidative stress, depletes antioxidants and elicits inflammatory response, which subsequently cause fibrosis, necrosis and apoptosis of the liver cells. Together all these processes are implicated in the pathogenesis of alcohol-induced liver damage.⁴

In spite of all the advances in medical sciences, no drugs are available in modern medicine that can effectively protect the liver against ethanol-induced hepatotoxicity. Because of this a large number of patients prefer using complementary and alternative medicines for treating and managing the hepatic complications.⁵ Plants have been used in the various traditional and folk systems of medicine to treat liver ailments, and scientific studies performed indicate that the dietary agents like *Allium sativum* (garlic), *Trigonella foenum-graecum* (fenugreek), *Emblica officinalis* (Indian gooseberry), *Ferula asafoetida* (asafoetida), *Vitis vinifera* (grapes), *Piper betle* (betel leaf), *Murraya koenigii* (curry leaves), *Prunus armeniaca* (apricot) and *Camellia sinensis* (tea) offer protection against the hepatotoxic effects of alcohol. In the following sections the validated observations and mechanisms responsible for the prevention/amelioration of alcohol-induced hepatotoxicity are addressed.

***Allium sativum* L (Family Amaryllidaceae; common name garlic)**

Allium sativum, commonly known as garlic, is an important kitchen spice with a myriad of health benefits. Preclinical studies have shown that garlic ameliorates alcohol-induced oxidative stress,^{6,7} inhibits induction of CYP,⁸ and prevents fatty liver and liver cirrhosis.⁷ Administration of fresh garlic juice to mice co-treated with alcohol caused reduction in the hepatic activity of ALDH and concomitantly decreased the level of acetaldehyde in serum. It also decreased the induction of certain CYP enzymes while concomitantly increased the activity of CYP 2E1 and CYP 1A2.⁸ Garlic (bulb/leaves homogenate) is also shown to reduce the ethanol-induced increase in the lipid peroxidation and to increase the levels of antioxidants (GSH, ascorbic acid, CAT and GR) in the rat liver.⁶ Garlic oil when administered after acute ethanol intoxication is also reported to mitigate the ensuing oxidative stress in liver by reducing lipid peroxidation and increasing the antioxidant enzymes GST, GR, GSH-Px and SOD.⁷ Together all these observations indicate the usefulness of garlic in the prevention of ethanol-induced hepatotoxicity.

***Camellia sinensis* (L.) Kuntze (Family Theaceae; common name green tea)**

Tea is one of the most widely consumed beverages in the world today, second only to water, and its medicinal properties have been widely explored. The tea plant, *Camellia sinensis*, is a member of the Theaceae family, and black, oolong, and green tea are produced from its leaves. Of the total commercial tea production worldwide, about 78% is consumed in the form of black tea, 18% in the form of green tea (Japan, China, Korea, parts of India and a few countries in North Africa and the Middle East) and 2% is oolong tea (Southeastern China).⁹ Green tea is a medicinal herb of repute and has been used by the Asian population for centuries. The aqueous soluble polysaccharides and polyphenols are scientifically shown to be responsible for the antioxidant action of green tea.^{9,10} Green tea is rich in polyphenols like epicatechin, epicatechin-3-gallate, epigallocatechin, epigallocatechin-3-gallate, theanine and caffeine. These polyphenols are potent antioxidants and are far more effective than vitamin C and vitamin E.⁹

Black tea has been shown to be effective in preventing the ethanol-induced hepatotoxicity.^{11–13} Das *et al.*,¹² have observed that co-administration of black tea extract was effective in reducing the ethanol-induced increased levels of AST, ALT, ALP, GGT, malondialdehyde and nitric oxide, and concomitantly to increase the levels of antioxidant enzymes SOD and CAT.¹² Studies have also shown that black tea prevented ethanol-induced changes in the antioxidant parameters (GPx, GR, CAT, GSH, β -carotene, vitamin C, A and E) in the liver¹¹ and protected proteins and lipids against oxidative modification, and preserved the redox and proteolytic homeostasis.¹³

With regard to the hepatoprotective properties of green tea, preclinical studies have shown that green tea ameliorated ethanol-induced oxidative stress,^{14–17} prevented liver cell damage and release of enzymes into circulation,^{14,18,19} and prevented/reduced fatty liver.¹⁹ Supplementation of green tea to rats chronically fed on ethanol has also been shown to decrease lipid peroxidation and protein oxidation, and to attenuate the antioxidants SOD, CAT, GR, GSH-Px, vitamin C, vitamin E and β carotene in liver.^{14–17} When compared to the cohorts feeding on ethanol, co-administration of green tea decreased the elevated serum levels of ALT and AST, the liver marker enzymes and normalized the liver histology.^{14,18,19} Green tea prevented fatty liver by inhibiting expression of TNF α ;¹⁸ by reversing the ethanol-induced reduction in activities of hepatic fat-mobilizing enzymes p-ACC and CPT-1¹⁹ and by preventing steatosis.^{18,20}

With regard to the protective effect of epigallocatechin gallate (EGCG), the most abundant phytochemical in green tea, studies have shown it to be effective in preventing ethanol-induced hepatotoxicity.^{22,23} EGCG prevented liver cell injury and release of enzymes to blood;^{21,22} mitigates oxidative stress;^{22,23} promotes mobilization of fat from liver and reduces expression of pro-inflammatory molecules.¹⁹ Administration of EGCG effectively prevented/reversed the histological changes and increased serum levels of aminotransferases in the ethanol-fed mice with overload of iron.²¹

Dietary EGCG prevented fatty liver by enhancing the activities of enzymes CPT1 and phospho-acetyl CoA carboxylase and thus, promoting β oxidation of fatty acids.¹⁹ EGCG

supplementation reduced the elevated expressions of CD14, TNF- α , COX-2 and iNOS in the liver of rats subjected to ethanol toxicity.²² *In vitro* studies with Chang liver cells (normal hepatocyte cell line) have also demonstrated that EGCG ameliorated the ethanol-induced reduction in the growth of liver cells, leakage of LDH from cells, reduction in GSH, increase in lipid peroxidation and apoptosis.²³

***Curcuma longa* L (Family Zingiberaceae; common name turmeric)**

The perennial herb *Curcuma longa*, whose rhizome is commonly referred to as turmeric, is an important spice for Asians. It is one of the primary ingredients in the Indian curry and is used in most Indian dishes. Curcuma is an important medicinal plant for over 4000 years. It has been used in various folk and traditional Asian and African systems of medicine to treat a wide variety of ailments. The rhizome and its active principle, a group of curcuminoids, are widely used as: culinary spices, preservatives, food additives, cosmetics, and as oleoresin in food and pharmaceutical industries. In the last two decades, there has been considerable interest among biomedical scientists to explore the possible therapeutic benefits of turmeric and its active principle curcumin and innumerable studies have validated the ethnomedicinal uses.^{24,25}

Scientific studies have shown that curcumin (Fig. 1) was effective in preventing alcohol-induced hepatotoxicity.^{24,26,27} Curcumin is also shown to be effective in preventing cigarette smoke and ethanol-induced lipid alterations in rat liver.²⁸ *In vitro* studies with the liver slice culture have shown that curcumin decreased lipid peroxidation, reduced the release of LDH and attenuated the antioxidant enzymes SOD, CAT and GSH-Px.²⁶ Studies with rat hepatocytes have also shown that curcumin decreased the ethanol-induced increase in malondialdehyde, decreased the levels of LDH and AST, increased the GSH levels and induced heme oxygenase.²⁷ Animal studies have also shown that curcumin exerts its protective effect against ethanol-induced hepatotoxicity by decreasing the lipid peroxidation and improving antioxidant status (vitamin C, vitamin E, GSH, SOD, CAT and GPx) indicating that the *in vitro* observations extends to *in vivo* models of study.^{24,25}

Curcumin decreased serum levels of AST and ALP in rats subjected to ethanol-induced hepatotoxicity,^{29,30} prevented ethanol induced alteration in the fatty acid composition (palmitic acid, stearic acid, oleic acid, palmitoleic and arachidonic acid) of liver²⁹ and reduced the inflammatory response of ethanol by reducing the level of prostaglandins²⁹ specifically the prostaglandins (E1), E(2), F(2 α) and D(2) in the liver.³⁰ Curcumin also decreased the ethanol induced increase in matrix metalloproteinase expressions.²⁵ Administration of curcumin to rats feeding on alcohol, prevented NF-kB activation^{31,32} and reduced expression of cytokines, chemokines, COX-2 and iNOS in the Kupffer cells.³¹ Together all these observations indicate the usefulness of turmeric and its principle phytochemical curcumin the prevention of ethanol-induced hepatotoxicity.

***Emblica officinalis* L (Family Phyllanthaceae; common name Indian gooseberry)**

Emblica officinalis Gaertn. or *Phyllanthus emblica* Linn commonly known as the Indian gooseberry or amla is arguably

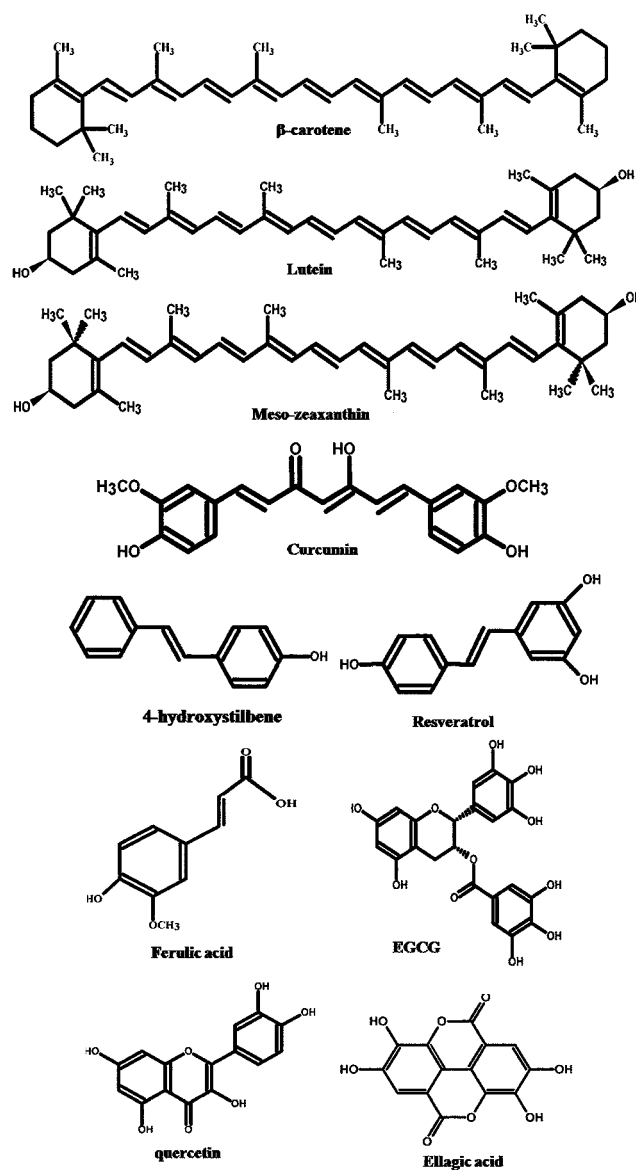


Fig. 1 Phytochemicals shown to be effective in preventing ethanol-induced hepatotoxicity.

the most important medicinal plant in the Indian traditional system of medicine, the Ayurveda. The fruits are the most important plant part and also of dietary use. Amla fruits are regularly used to make pickle, chutneys and as a vegetable in various dishes. The ripe fruits are also used to prepare a sweet delicacy named murabbah. The fruits are soaked in concentrated sugar syrup for extended period till the aroma of the fruits exudates in to the sugar syrup. The ripe fruits are also used to prepare fresh juice and are recently marketed as concentrates.^{33,34}

Amla and some of its phytochemicals like gallic acid, ellagic acid, quercetin and corillagin possess hepatoprotective effects against various xenobiotic compounds.^{33,34} Preclinical studies have shown that amla is very effective in ameliorating ethanol-induced hepatotoxicity.^{33,34} Amla reduced the alcohol-induced elevated serum levels of ALT, AST, ALP and GGT, and concomitantly decreased the levels of carbonyl content, lipid peroxidation and nitric oxide in the liver mitochondria. When

compared with the alcohol alone cohorts, administering amla restored the levels of the mitochondrial enzymes SDH, NADH dehydrogenase, and cytochrome C oxidase suggesting its usefulness in preventing the alcohol-induced hepatic damage.³³ Amla normalized the ethanol-induced altered levels of total protein, A/G ratio, uric acid, creatinine, total bilirubin and plasma nitrate in rats subjected to ethanol intoxication.³⁴

With regard to phytochemicals, studies with rats have also shown that when compared to the ethanol alone cohorts, co-treatment with ellagic acid (Fig. 1) decreased the levels of aminotransferases, lipid peroxides and hydroperoxides and concomitantly reduced the elevated hepatic contents of cholesterol, free fatty acids, triglycerides and phospholipids.³⁵ Ellagic acid mitigated the alcohol-induced toxicity in rats by improving the body weight, restoring antioxidant status, modulating micronutrients and attenuating the lipid levels in blood.³⁶ Ellagic acid decreased ethanol-induced hepatotoxicity by modulating the ethanol induced alterations in the expression of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases³⁷ and possesses anti-fibrotic effects.^{37,38}

Quercetin (Fig. 1), a flavonoid present in the amla possesses hepatoprotective effects against the ethanol-induced damage. Studies with cultured liver cells have shown that quercetin ameliorated ethanol-induced liver cell injury, lipid peroxidation, depletion of GSH, release of LDH and AST and upregulated heme oxygenase-1 through the MAPK/Nrf2 pathways.^{39,40} *In vivo* studies with rats have also shown that quercetin prevented and reversed the ethanol-induced hepatotoxicity by reducing the elevated serum levels of AST, ALT, ADH, GGT, TG, IL-1 β , IL-1, IL-6, IL-8 and TNF- α ; reducing the levels of malondialdehyde and increasing the levels of GSH in the liver and increasing IL-10 in plasma. Treatment with quercetin following ethanol intoxication to rats decreased the levels of serum amino transferases, lipid peroxides in the liver and restored GSH, SOD, GSH-Px and GR.⁴¹

***Ferula asafoetida* L (Family: Apiaceae; common names Asafoetida, devil's dung, stinking gum, Hing)**

Asafoetida is an important culinary spice with immense medicinal benefits. Asafoetida is used to treat various diseases, including asthma, gastrointestinal disorders and intestinal parasites in the various traditional systems of medicine. The oleo-gum-resin has been known to possess antifungal, anti-diabetic, anti-inflammatory, anti-mutagenic, antineoplastic and antiviral activities. Ferulic acid (4-hydroxy-3-methoxy cinnamic acid), the principal compound is a potent free radical scavenger and antioxidant. With regard to its hepatoprotective effect, ferulic acid is shown to decrease the elevated serum levels of AST, ALT, ALP and GGT in rats subjected to ethanol-induced hepatotoxicity.²⁵ Ferulic acid also ameliorated ethanol-induced oxidative stress and improved the antioxidant status.⁴²

***Garcinia cambogia* (Gaertn.) Desr. (Family Clusiaceae; common name Malabar tamarind)**

Garcinia cambogia commonly known as the Malabar tamarind is an indigenous tree of Southeast Asia and India. The rinds of the fruits which are astringent are an important culinary agent. They

are added as a souring agent in the Indian curries and to tenderize meat. The rinds are of medicinal use and are used in the various folk medicines to treat ulcers, haemorrhoids, diarrhoea and dysentery. Studies have shown that treatment of rats with the extract of the rinds of *Garcinia cambogia* decreased ethanol-induced increase in serum AST, ALT, ALP, peroxidative damage and improved the antioxidant status indicating its usefulness as a hepatoprotective agent.⁴³

***Glycine max* (L.) Merr. (Family Fabaceae; commonly known as soybean)**

Soybean, a traditional dietary agent of the Asians is today one of the most popular agents. Products like soymilk, tofu, tempeh, miso, soy sauce, fermented bean paste, natto, tempeh, soy meats and soy cheeses are commonly used in Europe and America. The beans contain significant amounts of phytic acid, α -linolenic acid, and the isoflavones genistein and daidzein. Several studies have shown soya beans to possess hypocholesterolaemic and anticarcinogenic effects.⁴⁴ Preclinical studies have shown that administration of soyasaponins-rich extract isolated from the soybean was effective in preventing the acute alcohol-induced hepatotoxicity in mice.⁴⁴ The authors observed that administration of soya saponins-rich extract prior to alcohol significantly prevented the increases in serum AST, ALT, ALP and LDH caused by alcohol, as well as hepatic triglyceride, total cholesterol, and malondialdehyde levels. When compared with the ethanol treated cohorts, pretreatment with soya saponin-rich extract before the administration of ethanol increased the levels of SOD, GST, GPx and GSH. Histopathological observations also showed that administering soya saponins-rich extract prevented alcohol-induced hepatic steatosis, necrosis, inflammation, and swelling, thereby confirming the biochemical observations.⁴⁴

***Theobroma cacao* L. (Family Malvaceae or Sterculiaceae; common name cocoa tree)**

Theobroma cacao commonly known as the cocoa tree is a small evergreen tree originally native to South America. Its seeds are used to make cocoa powder and chocolate. It is an economically important tree as the cocoa butter extracted from the seeds are used in the confectionery industry. In addition to the butter the seeds also contain polyphenols and flavonoids that possess myriad health benefits. McKim *et al.*,⁴⁵ have observed that co-administration of the cocoa flavonoid extract composed mostly of epicatechin and epicatechin oligomers, protects rats against early alcohol-induced liver injury. The investigators observed that when compared to the ethanol alone cohorts, co-administering cocoa flavonoid extract decreased levels of serum ALT, liver TNF α protein and protein adducts of 4-hydroxynonenal. The extract also reduced steatosis, inflammation and necrosis in the liver indicating that the flavanols of cocoa were effective in preventing alcohol-induced liver injury.⁴⁵

***Trigonella foenum-graecum* L (Family Fabaceae; common name fenugreek)**

In the various Asian systems of medicine, fenugreek is an important medicinal plant. The seeds and leaves are of use in the

management of diabetes, in allergies, gastric disorders, lung infections, anemia, asthma, boils, bronchitis, cancer, fevers, gallbladder problems, heartburn and inflammation. The seeds of fenugreek contain folic acid, disogenin, gitogenin, neogitogenin, homorientin saponaretin, neogigogenin, trigonelline, trigogenin, fibers, flavonoids, polysaccharides, saponins and fixed oils.^{46,47} Studies have shown that the polyphenol-rich extract of fenugreek seed ameliorated oxidative stress, reduced the levels of lipid peroxides and protein carbonyls, and attenuated the antioxidant enzymes in the liver of rats subjected to chronic ethanol intoxication.⁴⁷

The extract was also observed to prevent liver cell damage and to reduce the ethanol-induced increase in the levels of ALT, AST, LDH, bilirubin and ALP in the serum. Fenugreek also increased the content of liver glycogen, inhibited the induction of CYP and cytochrome reductase, and concomitantly increased the activity of GST in the liver of rats chronically exposed to ethanol.⁴⁶ Mechanistic studies have shown that fenugreek seed extract was effective in modulating the ethanol-induced alterations in the CYP2E1, ADH 2, ALDH 2 and cellular heat shock proteins-HSP70, HSC70, HSC92, and mitochondrial protein mtHSP70.⁴⁸ Additionally, studies with cultured hepatocytes have also shown that the extract of fenugreek seed was effective in preventing the ethanol-induced cell death, apoptosis, to prevent leakage of LDH from the cells and to concomitantly increase the ratio of GSH/GSSG.^{46,49}

***Murraya koenigii* (L.) Sprengel (Family Rutaceae; common name curry leaves)**

Murraya koenigii, commonly known as the curry tree is an important spice in India. The leaves are used as a seasoning agent for various curries. The major phytochemicals of curry leaves are tannins, alkaloids, saponins, glycosides and flavonoids. These phytochemicals possess antioxidant, antimicrobial, anti-diabetic, anti-hyperlipidemic and anti-inflammatory properties.⁵⁰ With regard to the hepatoprotective effects, *in vitro* studies have shown that carbazole alkaloid and tannin-rich fractions of curry leaves were effective in preventing alcohol-induced damage. When compared to the alcohol-treated cohorts, the investigators observed that the co-treatment with the curry leaf extract reduced the ethanol-induced lipid peroxidation, enhanced the antioxidants SOD, CAT and GSH, and restored the normal histology.⁵⁰

***Ocimum gratissimum* L. (Family Lamiaceae; common name wild basil)**

Ocimum gratissimum is an important spice as well as a medicinal plant. The leaves are used with vegetables, meat, fish, sauces, stews, dressings, herbal teas, liqueurs, and mixed drinks. The plants are also of use in the various traditional systems of medicine in Asia, South America and Africa. They are used to treat bacterial infections, diarrhoea, diabetes, respiratory-tract infections, pneumonia, fever and coughs. Preclinical studies have shown that *Ocimum gratissimum* decreased the alcohol-induced increase in the levels of TBARS, AST and ALT in the serum, restored hepatic antioxidant levels and reduced the levels of lipid peroxidation in rats.^{51,52} Histopathological studies have also

shown that administering the wild basil extract was effective in reducing the alterations in the liver cell.⁵³

***Piper betle* L. (Family Piperaceae; common name betel leaf)**

Piper betle commonly known as betel vine is an important recreational and medicinal plant in Southeast Asia. The betel leaf is a valued masticator and is a good mouth freshener and mild vitalizer.⁵⁴ Scientific studies have shown betel leaf to possess antioxidant, anti-inflammatory, immunomodulatory, anti-hyperglycemic and antimicrobial properties.⁵⁴ Saravanan *et al.*,⁵⁴ have shown that administering the beetle leaf extract protects rats against ethanol-induced hepatotoxicity. The authors observed that when compared to the alcohol-treated cohorts, administering betel leaf extract decreased AST, ALT and lipid peroxides in the serum and increased the levels of hepatic antioxidants SOD, CAT, GSH-Px, GSH, vitamin C and vitamin E.⁵⁴

***Prunus armeniaca* L (Family Rosaceae; common name apricot)**

Apricot belonging to the plum category of fruits is rich in carotenoids, flavonoids and phenols.⁵⁵ Animal studies have shown that administering apricot to rats chronically feeding on ethanol decreased the levels of ALT and AST in the serum; and reduced oxidative stress and lipid peroxidation in the liver by increasing the levels of antioxidant enzymes.⁵⁵ Studies have also shown that supplementation of β -carotene (Fig. 1), which is present in apricot, prevented ethanol-induced increase in the serum aminotransferases and inhibits the depletion of the antioxidant molecule GSH in the liver.⁵⁶ Additionally, *in vitro* studies with the hepatocytes isolated from the ethanol-fed rats have also shown that β -carotene improved the cell viability, increased catalase activity and level of GSH.⁵⁷ Mechanistic studies performed with hepatocytes isolated from the ethanol-fed rats have also shown that β carotene ameliorated the oxidative stress, enhanced antioxidant, and decreased the expression of CYP2E1 and apoptosis.⁵⁸

Additionally, lutein (Fig. 1) and *meso*-zeaxanthin (Fig. 1) present in apricot in minor quantities are also effective against alcohol-induced damage.⁵⁹ When compared to the alcohol-treated cohorts, administering lutein and *meso*-zeaxanthin are also shown to reduce the elevated serum levels of aminotransferases, alkaline phosphatase, bilirubin and to decrease the levels of lipid peroxidation, conjugated diene and hydroperoxides in rat liver.⁵⁹ Histopathological studies have also shown that administering lutein and *meso*-zeaxanthin to ethanol-treated rats reversed the histopathological abnormalities and reduced the levels of hydroxyproline (indicator of fibrosis).⁵⁹

***Vitis vinifera* L. (Family Vitaceae; common name grapes)**

For thousands of years, *Vitis vinifera*, commonly referred to as grapes has been grown and harvested for medicinal, nutritional and economic purposes. The major constituents of grape are epicatechin gallate, procyanidin dimers, trimers, tetramers, catechin, epicatechin, and gallic acid, procyanidin pentamers,

hexamers, and heptamers and their gallates, resveratrol, phenolics, flavonoids and anthocyanins.⁶⁰ Grapes are reported to possess anti-inflammatory, anti-aging, potent antioxidant, anti-mutagenic, anti-inflammatory, hepatoprotective, anticancer, antidiabetic, cardioprotective, nephroprotective, neuroprotective and anti-carcinogenic properties.⁶⁰ With respect to the hepatoprotective effects, studies have shown that co-administration of grapes to rats treated with ethanol caused a decrease in the levels of AST, ALT, ALP and GGT in the liver.⁶¹ Grapes also decreased the levels of lipid peroxidation in the liver and concomitantly increased the levels of hepatic enzymatic and nonenzymatic antioxidants.⁶¹ The extract of grape leaf is also shown to restore the normal histological architecture of liver in alcohol-fed rats, confirming the hepatoprotection observation of the biochemical assays.⁶¹ Additionally, studies have also shown that the red wine prepared from grapes ameliorates oxidative stress in the liver of alcohol-fed rats, and to prevent fatty liver and hepatic fibrosis.⁶²

With regard to phytochemicals, studies have shown that co-treatment with resveratrol (Fig. 1), reduced ethanol-induced lipid peroxidation^{63,64} and to restore the levels of the antioxidant enzymes SOD, CAT and GSH-Px in the rat liver.⁶⁴ Feeding resveratrol reduced ethanol-induced macrovesicular steatosis, necrosis and fibrosis of the liver in rats.⁶⁵ Studies with mice subjected to ethanol-induced toxicity have also shown that administering 4-hydroxystilbenes (Fig. 1) and resveratrol were effective in reversing the ethanol-induced liver cell injury and to inhibit the oxidation of PUFA.⁶⁶ When compared to the ethanol treated cohorts, administering resveratrol to mice reduced AST, ALT, GST, IL-10, TNF- α , IFN- γ , VEGF- α and TGF- β 1 activities and levels of TBARS and nitrite; increase the albumin content, GSH level and activities of SOD, CAT, GR and GPx.⁶⁷ Resveratrol is a potent activator of SIRT1 and AMPK, two critical signalling molecules regulating the pathways of hepatic lipid metabolism. It increased the SIRT1 expression, stimulated the AMPK activity, suppressed SREBP-1 and activated PGC-1 α in the liver of ethanol-fed mice.⁶⁸ Resveratrol increased the circulating adiponectin levels and enhanced mRNA expression of hepatic adiponectin receptors (AdipoR1/R2) in the ethanol treated mice. Together all these observations indicate that resveratrol treatment reduces alcohol treatment induced increase in lipogenesis and fatty liver, thereby prevented the alcoholic liver steatosis in mice.⁶⁸

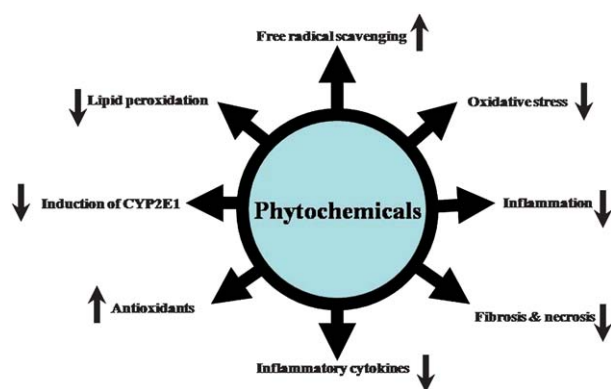


Fig. 2 Mechanisms responsible for the hepatoprotective effects (arrows up = increase; arrows down = decrease).

Conclusions

Numerous preclinical studies have demonstrated the hepatoprotective actions of some of the dietary agents like garlic, tea, turmeric, Indian gooseberry, asafoetida, Malabar tamarind, soyabean, curry leaves, beetle leaf, apricot, wild basil, cocoa, fenugreek and grapes are effective against the ethanol induced damage. A combination of factors like antioxidant effects, inhibition of lipid peroxidation, and decreasing expressions of proinflammatory cytokines, matrix metalloproteinases and anti-inflammatory actions would have contributed to the hepatoprotective effects (Fig. 2). While most studies have been with laboratory animals and validate the clinical applicability to humans, future studies should be planned with humans to understand the efficacy of these dietary agents and their phytochemicals. The major advantage of these ingredients over the synthetic drugs lies in the fact that most of them have a low effective dose to high toxic dose ratio. This property gives an immense advantage as it can be easily recommended for human trials and at lesser costs. Preliminary observations indicate that these dietary agents have great potential as hepatoprotective agents, thus validating Hippocrates statement 'Let food be thy medicine and medicine be thy food' proclaimed 25 centuries ago. However, detailed studies are needed with humans to understand the optimal dose for protection.

Abbreviations

ADH	Alcohol dehydrogenase
ALDH	Aldehyde dehydrogenase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMP	Adenosine monophosphate.
AMPK	AMP-activated kinase
AST	Aspartate aminotransferase
CAT	Catalase
COX-2	Cyclooxygenase-2
CPT-1	Carnitine palmitoyl-transferase 1
CYP 1A2	Cytochrome P450 1A2
CYP 2E1	Cytochrome P450 2E1
CYP	Cytochrome P 450
GGT	Gamma glutamyl transferase
GR	Glutathione reductase
GSH	Glutathione
GSHPx/GPx	Glutathione Peroxidase
GST	Glutathione S-transferase
IFN- γ	Interferon gamma
IL	Interleukin
i-NOS	Inducible NO synthase
LDH	Lactate dehydrogenase
MAPK	Mitogen-activated protein Kinase
NF- κ B	Nuclear Factor kappaB
p-ACC	Phospho-acetyl CoA carboxylase
PGC-1 α	Peroxisome proliferator-activated receptor γ coactivator α
PPAR	Peroxisome proliferator-activated receptor
ROS	Reactive oxygen species
SDH	Succinate dehydrogenase

SIRT1	Sirtuin 1
SOD	Superoxide dismutase
SREBP-1	Sterol regulatory element binding protein 1
TAG/TG	Triglycerides
TBARS	Thiobarbituric acid-reactive substances
TGF- β	Transforming growth factor beta1
TNF	Tumor necrosis factor
VEGF-A	Vascular endothelial growth factor A
VLDL	Very low density lipoprotein

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