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A critical review on hepatoprotective effects of bioactive food components

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ABSTRACT

Background: Bioactive food components are nonessential biomolecules, which help to give beneficial effects to human being against several diseases. Natural bioactive food components derived from plants and animals, such as phytosterols, carotenoids, polyphenols and fatty acids, have been proposed as valuable substitutions for anticipation and management of hepatotoxic effects and its chronic complications based on *in vitro* and *in vivo* studies.

Objectives of the study: To summarize drugs and chemical-induced hepatotoxicity and review how various bioactive food components attenuate the hepatotoxicity via cellular mechanisms.

Results: Remarkable studies demonstrated that the health promoting effects of bioactive components originated from plants have been frequently attributed to their antioxidant properties and facilitate to increase cellular antioxidant defense system and thereby scavenge free radicals, inhibit lipid peroxidation, augment anti-inflammatory potential, and further protect the liver from damage.

Conclusion: In this critical review, we summarize current progress in clarifying the molecular mechanism in hepatotoxicity and curative potential of the bioactive food components and its successive clinical outcomes in the field of drug discovery and overcome the problems of medication and chemical-induced hepatotoxic effects.

Abbreviations: AKR: aldo-keto reductase; Akt: protein kinase B or serine/threonine-specific protein kinase; ALT: alanine transaminase; ARE: antioxidant response element; AST: aspartate transaminase; CAT: catalase; CCl₄: carbon tetrachloride; COX: cyclooxygenase; Cu: copper; CYP: cytochrome P450; DMH: 1,2-dimethylhydrazine; DNA: deoxyribonucleic acid; ERK: extracellular regulated kinase; GGT: gamma glutamyl transferase; GPx: glutathione peroxidase; GR: glutathione reductase; GSH: reduced glutathione; GSH-R: glutathione reductase; GSSG: oxidized glutathione; GST: glutathione s-transferase; H₂O₂: hydrogen peroxide; HBC: hepatitis C-virus; HBV: hepatitis B virus; HO-1: heme oxygenase; IF: interferon; IL: interleukin; Keap: Kelch-like ECH-associated protein; MDA: malondialdehyde; MEK: mitogen-activated protein/extracellular signal regulated kinase; Mn: manganese; MPO: myeloperoxides; mRNA: messenger RNA; NADP: nicotinamide adenine dinucleotide phosphate; NADPH: nicotinamide adenine dinucleotide phosphate hydrogen; NDEA: N-nitrosodiethylamine; NF-κB: nuclear factor kappa B; NQO-1: (NAD(P)H quinone dehydrogenase); Nrf2: nuclear factor-erythroid-2-related factor; O₂^{•-}: superoxide anion radical; OH[•]: hydroxyl radical; PGE: prostaglandins E; PI3K: phosphoinositide 3-kinase; PIP3: phosphatidylinositol (3,4,5)-triphosphate; PMN: polymorphonuclear cells; PTEN: phosphatase and tensin homolog; RAF: rapidly accelerated fibrosarcoma; RAS: family of related protein; RBC: red blood cells; RNA: ribonucleic acid; RNS: reactive nitrogen species; ROS: reactive oxygen species; SOD: superoxide dismutase; STZ: streptozotocin; SP: specificity protein; TNF: tumor necrosis factor; UDPGT: uridine diphosphate glucuronosyltransferase; UDP: uridine diphosphate; WHO: world health organization

KEYWORDS

Bioactive food components; hepatotoxic agents; antioxidants; anti-inflammatory; hepatoprotective

Introduction

The liver is the chief and the most significant metabolic organ of the human body, having an average weight of 1.5 kg for 70 kg body weight person, located in the upper right-hand side of the abdomen. It is the center of different metabolic reactions, which occur in the body. More than 75% of the hepatic parenchyma is made up of hepatocytes, which is the most accountable for maintaining each function of the liver and needs to support the body physiological functions. It executes more than 500 significant functions such as conversion of food components to critical blood components, storage of vitamins and minerals, manufacture of many vital plasma proteins and minerals, maintenance of hormonal balance and

metabolism, and detoxification of toxic wastes of the body. It secretes bile that helps in lipid digestion (Ghany and Hoofnagle, 2005). Further, it is responsible for synthesizing the blood-clotting factors prothrombin, fibrinogen, and heparin, which prevents the blood from clotting within the blood circulation (Saleem et al., 2010). In addition, Liver is noteworthy infunctions such as metabolisms of lipids, proteins, and carbohydrates (Worman, 1999; Vuda et al., 2012). The liver helps in regulating the normal glucose concentrations during fasting. It also plays a fundamental role in glycogen metabolism, thereby; it clears insulin and suppresses glucose production, and enhances hepatic glucose production by glycogenolysis (Michael et al., 2000).

Liver diseases

Any clinical defects or conditions which rise to impairment of liver are known as liver diseases. Liver diseases are mainly classified into two types: acute and chronic liver diseases. The acute liver disease occurs rapidly and usually exists for a very short duration. Chronic liver diseases are typically long term, generally over 6 months. In the clinical circumstances, the chronic disease causes periodical destruction and regeneration of liver parenchyma generates fibrosis and cirrhosis of the liver (Crawford, 2007). Eventually, it causes an extensive degree of inflammation in the liver producing chronic hepatitis, cirrhosis, and liver carcinoma.

Liver diseases and their global burden

The liver is accountable for biotransformation of drugs and chemicals, thereby protecting the body against toxic foreign materials. In this mechanism, the liver is exposed to high concentration of toxic chemicals and their metabolites which may cause liver injury. There are over hundreds of etiology cause hepatic diseases. The majority of the hepatic diseases causing agents include microorganisms (hepatitis virus A, B, C; cytomegalovirus, Epstein-Barr virus, and yellow fever virus), metabolic diseases (obesity related fatty liver disease, hemochromatosis and Wilson's disease), xenobiotics (alcohol, drugs, and chemicals), inherited related hepatic diseases, autoimmune diseases (biliary cirrhosis, hepatitis and sclerosing cholangitis), and liver malignancies (Daniel, 2009). Hepatic diseases result in loss of workdays, reduced quality of life, decreased life span, and also pose an economic burden to the individual as well as to the society (WHO, 2002).

Globally, hepatic diseases are dreaded disease cause greater morbidity and mortality. Among them, about 1.3 million populations die due to acute and chronic viral hepatitis. Over 350 million people are suffering chronically by HBV and 170 million people are infected with HCV (Lok et al., 2001; Daniel, 2009). Each year, HBV causes approximately 600,000 deaths and HBC cause 350,000 people deaths (Sharma and Patni, 2012). The recent statistics clearly show that the global burden of liver disease has increased over time with a huge impact on the overall world population.

It is proposed that compensated cirrhosis and liver cancer will reach more than 80 percent in the year 2020. Davis et al. (2003) showed their statistical analysis that decompensated cirrhosis will enhance more than 100 per cent and hepatic injury-related deaths will enhance by 181 percent. In spite of viral infections, increase rates of obesity and alcohol ingestion globally predict that the burden of hepatic diseases associated with alcohol and non-alcoholic diseases are set to two folds. Moreover, those individuals having chronic hepatic diseases are more vulnerable to develop a severe illness like HIV infection and hepatic carcinoma (WHO, 2002).

Treatment for hepatotoxicity

Healing choices for widespread liver diseases are inadequate due to the deficient hepatoprotective drugs in modern medicine. In addition, drugs developed along the principle of

advanced medicine are often ineffective, carry the danger of undesirable effects, and are generally so expensive, especially for the populations of the developing nations. For example, the effectiveness of treatments such as those using corticosteroids and interferon is inconsistent, carried the risk of adverse events, and is often too costly (Girish and Pradhan, 2012). Alternatively, bioactive food compounds derived from plants are easily accessible and affordable. It is a strong conviction that plant therapy represents protection due to natural and risk-free, which are alternative to artificial drugs. Herbal remedies are again in staging as Renaissance in the world. Many current surveys from the US and Europe have confirmed that the usage of herbal therapy for hepatic diseases will shoot up with up to 65 percent within a few years. The truth is that consistent hepatoprotective drugs are obviously too little and then investigate for natural herbal drugs have deeper in the current decades.

Bioactive food components

Dietary management tenders a realistic alternative for prevention and healing of various hepatic diseases. The quantity and composition of the food and frequency of intake could influence the progression or prevention of pathological conditions. A better understanding of nutrients and non-nutritional compounds in the food and knowledge about their mechanisms for biological activities in the context of health and diseases are necessary for adopting nutrition as a tool to manage health.

Bioactive food components are nonessential biomolecules, extensively present in diets and show the capability to control more than one metabolic pathway, which helps to give beneficial effects for several diseases and target tissues in humans. Generally, it is found in plants and animal products. In plants, it is widely present in the forms of alkaloids, phytosterols, organosulfur compounds, carotenoids, polyphenols and nitrogen-containing compounds. Fatty acids are animal bioactive compounds abundantly found in fish and milk.

Bioactive food components from plants are often products of a plant's secondary metabolism. Most of these constituents in plants produce defense system against pests, pathogens, and predators (Cowan, 1999). Examples of bioactive compounds obtained from plants are polyphenols, tocopherols, tocotrienols, carotenoids, alkaloids, flavonoids, glycosides, saponins, terpenoids, phytosterols, sesquiterpene lactones, organosulfur compounds, fibers, inulin, and pectins. Among them, polyphenols are the largely available bioactive compounds. There are over 7500 polyphenols present in the plant kingdom (Opara and Rockway, 2006) of which, flavonoids, isoflavones, and catechins are therapeutically important. Cereals, legumes, nuts, grains, fruits, spices, and vegetables are rich sources of polyphenols (Opara and Rockway, 2006). Milk and whey protein are excellent sources of bioactive compounds that are of animal origin. Fermented milk products contain various beneficial bacteria that are favorable to an individual's health. These fermented bacteria are known as probiotic and that are designated as bioactive food compounds (Ghosh and Playford, 2003).

Many of these food components have been part of the human diet for ages, their use for prevention and treatment of various diseases is a relatively new concept in 'nutrition and health' research. Many *in vivo*, *in vitro* and clinical

experimental trials, have been shown that the bioactive compounds are potential to control acute and chronic hepatic diseases (Opara and Rockway, 2006).

Mechanism of bioactive food components in hepatoprotection

Free radical scavenging effects

Free radicals are molecules with unpaired electrons and very reactive in nature. Therefore, they could damage the surrounding molecules. In the normal condition, a certain level of free radicals is found everywhere in the human body, produced as the result of irradiation, metabolic processes, and toxic substances. Free radicals will commence chain reaction of oxidation, causes rupture of carbohydrates, DNA, lipids, and proteins.

The electron-deficient reactive oxygen species (ROS) and the reactive nitrogen species (RNS) are free radicals cause oxidative stress when produced in excess. Among the ROS and RNS, the hydroxyl radical (OH^\bullet), superoxide anion radical (O_2^\bullet), hydroperoxyl radical (HOO^\bullet), lipid peroxide radical (ROO^\bullet), hydrogen peroxide (H_2O_2), singlet oxygen ($^1\text{O}_2$), ozone (O_3), nitric oxide (NO^\bullet), alkoxy (RO $^\bullet$), nitrogen dioxide (NO_2), nitronium ion (NO_2^+), and peroxy nitrite (ONOO^\bullet), are the most noteworthy elements as they can cause cell membrane damage (Krishnakantha and Lokesh 1993). Out of this, hydrogen peroxide, ozone, nitrogen dioxide and singlet oxygen are not free radicals (they do not have a superscript dot). However, because of their extreme activity, they are included in the group of reactive oxygen species. Free radicals are implicated in the etiopathogenesis of many diseases and conditions such as aging, cancer, cardiovascular diseases, diabetes, neurodegenerative diseases, and the toxic effects of many xenobiotic compounds. Free radical generation causes cellular damage, aging and cell death depicted in Figure 1.

Many hepatotoxic compounds such as alcohol, CCl_4 , paracetamol, antibiotics, organophosphates, mycotoxins and heavy metals are known to induce the generation of free radicals in the liver and lead to liver impairment (Krishnakantha and Lokesh 1993). On the other hand, free radicals are valuable since they play a significant role in many biochemical processes. For instance, white blood cells participate as phagocytes and also alleged to act as cellular messengers in a biochemical process called redox signaling. However, the unhealthy lifestyle and diet are believed to create the excessive amount of free radicals. Diabetes, cancer, cardiovascular disease and other neurodegenerative diseases are believed to cause as a result of such severe oxidative stress. Nevertheless, free radical scavenging enzymes such as CAT, SOD, GPx, and GSH-R play a vital role in a chain reaction to reduce the effect of oxidative stress and damage in cell structures, depicted in Figure 2.

Prevention of free radical generation is important, and studies have shown that many medicinal herbs, vegetables, fruits, spices and condiments, and dietary compounds are effective to conquer this problem. Bioactive food components derived from plants are antioxidants, play important roles in ROS and RNS metabolism and avoidance of uncontrolled oxidation of essential biomolecules.

The name 'antioxidant' is known as a chemical substance that banned the utilization of oxygen (Burneo-Palacios, 2009); therefore, antioxidants are molecules, whose function is to postpone or avert oxidation of oxidizable biomolecules such as protein, lipids, DNA and carbohydrates (Halliwell, 2007). Antioxidants play in their task to stop oxidation reactions and impede new oxidation reactions. In nature, there are two classes of antioxidants namely endogenous and exogenous. Endogenous antioxidants can be synthesized within a cell (e.g., reduced GSH, CAT, SOD, GPx, GSH-R etc.). Exogenous antioxidants can be taken as dietary antioxidants (e.g., carotenoids, flavonoids, saponins, vitamin A, C, E, selenium, glycine etc. (Sies

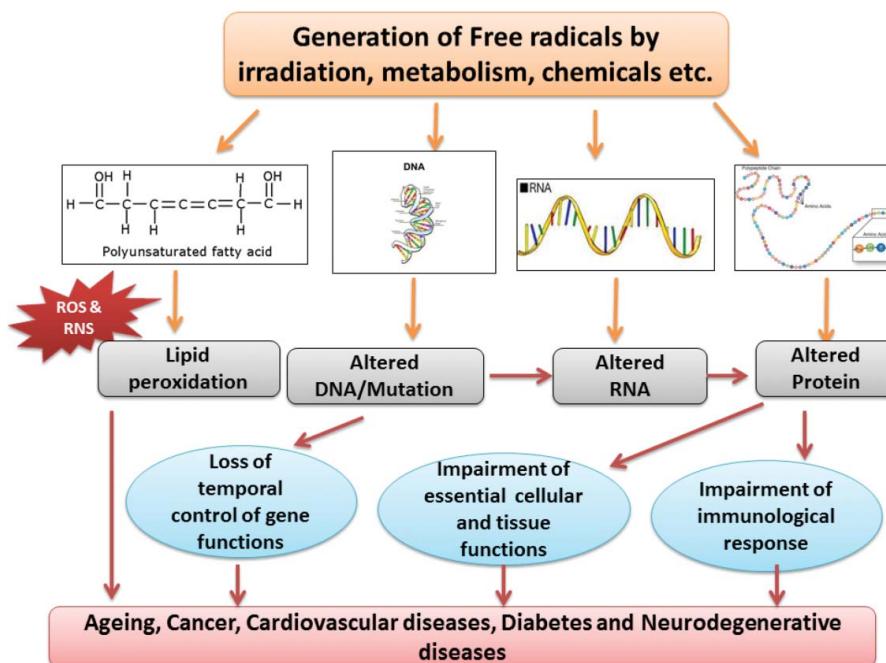


Figure 1. Free radical generation causes aging, cancer, cardiovascular diseases, diabetes, and neurodegenerative diseases.

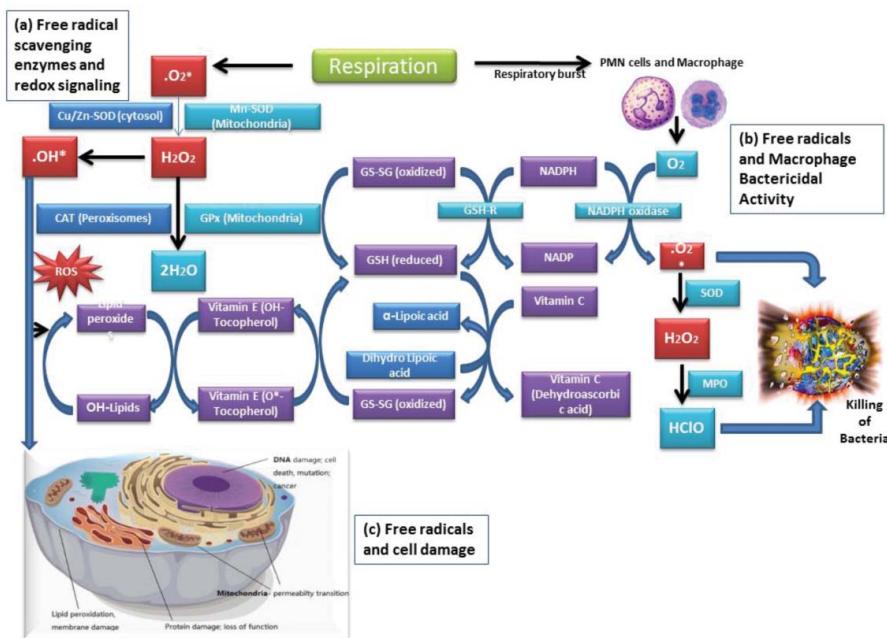


Figure 2. (a) Free radical scavenging enzymes and redox signaling: The free radicals are inactivated by enzyme systems containing SOD, CAT, Gpx, GSH-R, lipoic acid, vitamin E & C. Reduced GR is regenerated with the help of NADPH. (b) ROS and macrophage bactericidal activity: NADPH is required for production of reactive oxygen-species (ROS) (superoxide anion radical) by macrophages to kill bacteria (c) ROS and cell damage: Free radicals (super oxide, hydrogen peroxide) are continuously produced in all cells. These will destroy DNA, proteins, fatty acids and all biomolecules, and in turn cells are destroyed.

1997; Krishnaiah et al., 2011). The addition of exogenous antioxidants in the diet or enhance the endogenous antioxidant defenses in the body has been initiated to be a promising technique of eradicating the adverse effects of oxidative stress (Kasote et al., 2013).

Based on solubility, antioxidant compounds are divided into two categories namely hydrophilic (such as phenolic compounds and vitamin C) and lipophilic (such as carotenoids and vitamin E). Antioxidant activities of bioactive phenolic compounds have principally redox potential, which has reducing properties. Ascorbic acid (vitamin C) is one among the significant antioxidant; possess two free electrons that could be

utilized by the generation of free radicals. The antioxidant activity of retinol (vitamin A) is described by donation of hydrogen ion and prevent chain reactions (Camacho-Luis and Mendoza-Pérez, 2009; Hernández-Ceruelos et al., 2009; Muñoz Sánchez, 2009).

However, an amount of free radicals exceeds the production of antioxidants in the human system under abnormal/diseased conditions. Increase the antioxidant potential of human system by optimizing the natural antioxidants consumption in dietary intake is one of the best approaches to attain equilibrium between free radical and antioxidant activity in the human system.

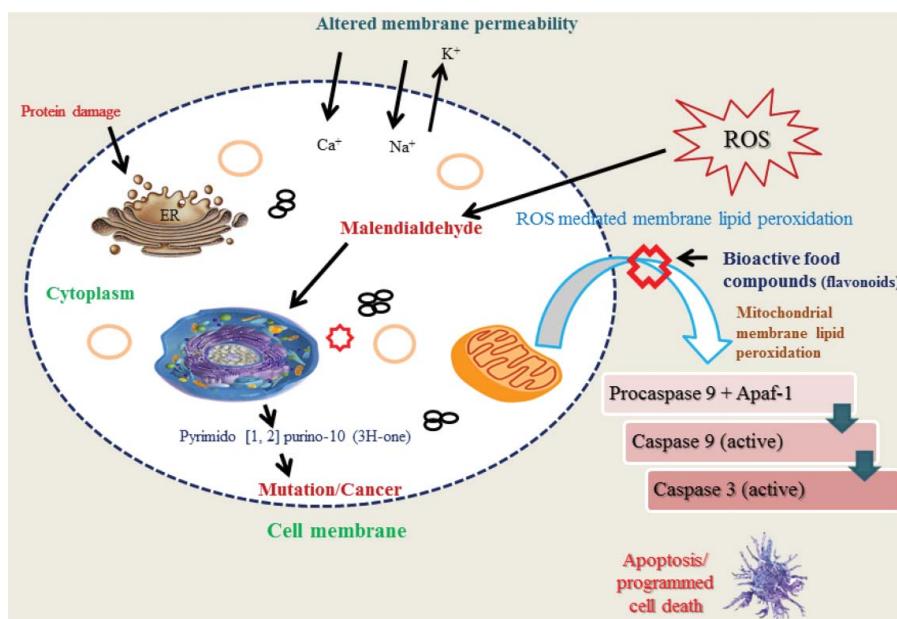


Figure 3. Mechanism of bioactive food compounds on lipid peroxidation and apoptosis.

Inhibition of lipid peroxidation and inflammation

Subcellular organelles containing lipids are extremely vulnerable to free radical injury to generate vast amounts of toxic products. The process of lipid peroxidation produces a fluid loss, reduces membrane potential, enhances permeability for hydrogen and calcium ions, and eventual loss of plasma membrane integrity. It occurs in membranes of both cell wall and mitochondria, subsequently initiate the cell death through apoptosis and/or autophagy mechanisms (Choi et al., 2007). To avoid or nullify the actions of ROS and RNS, usually, cells are equipped with enzymatic and nonenzymatic antioxidant mechanisms. In addition, the major bioactive food components such as secondary metabolites play a significant role in scavenging free radicals and protect the cell organelles (Saleem et al., 2010). Bioactive food components inhibit the lipid peroxidation and apoptosis depicted in Figure 3.

Generally, hepatic diseases are caused by xenobiotics, which trigger the inflammatory pathways via the activation of prostaglandin (Srivastava, 1984) and leukotriene synthesis (Ojewole, 2006). Studies showed that bioactive food components (green tea, turmeric, and omega 3- fatty acids) reduced prostaglandin synthesis by inhibiting the actions of cyclooxygenase-1, cyclooxygenase-2, and inhibit the biosynthesis of leukotriene by 5-lipoxygenase (Ojewole, 2006) and reduce the mediators influencing proinflammatory cytokines (Figure 4).

Bioactive food components protect against various liver toxicants

Hepatic damage is a major health crisis that challenges not only medical professionals but also the drug regulatory authorities and pharmaceutical industries. It is caused by diverse noxious chemicals like acetaminophen, antibiotics, chemotherapeutic

agents, CCl_4 , thioacetamide, chronic alcoholism, viral infections, and malaria (Roy et al., 2014). One of the most common causes of liver disease is inflammation, which often results from the abuse of alcohol, poor diet or even malnutrition (Roy et al., 2014). Over 50% hepatic injuries are caused by an overdose of acetaminophen, isoniazid, sulphonamides, toxic ingestion, and other drugs (Micheale and Cynthia, 2006). Generally, drugs are metabolized by the CYP system in the hepatic cells to yield spontaneous metabolites trichloromethyl radicals that can commence the progression of lipid peroxidation and cause hepatic injury (Srivastava and Shivanandappa, 2010).

The liver is the exclusive organ for the metabolism of xenobiotics and it is also a dumping site for toxic compounds and, thus many times, a victim of their toxic sign. Hepatotoxicity is caused chiefly by drugs which are the most common causative factors for hepatic diseases. The most common hepatotoxic drugs are acetaminophen, alcohol, isoniazid, sulfonamides, some antibiotics, pesticides, insecticides, fungicides, rodenticides, CCl_4 , and numerous carcinogens. The pathophysiology of hepatotoxicity represents in the form of vascular lesions, necrosis, fatty infiltration, centrilobular necrosis, and cholestasis (Ghany and Hoofnagle, 2005; Saleem et al., 2010). Normally drug-induced hepatotoxicity may be asymptomatic sign and elevate the levels of serum transaminases, GGT, bilirubin, and urea lead to liver dysfunction, necessitate hepatic transplantation.

Liver cirrhosis is another complicated liver injury caused due to chronic alcoholism, hepatitis B, and hepatitis C infection. The incidence of liver injury depends on the age and gender of the patients and the number of drugs consumed. Older patients, female sex, and the presence of concomitant diseases, such as immune deficiency states, all put the patient at higher risk. Mortality rate may go over 50 percent if liver

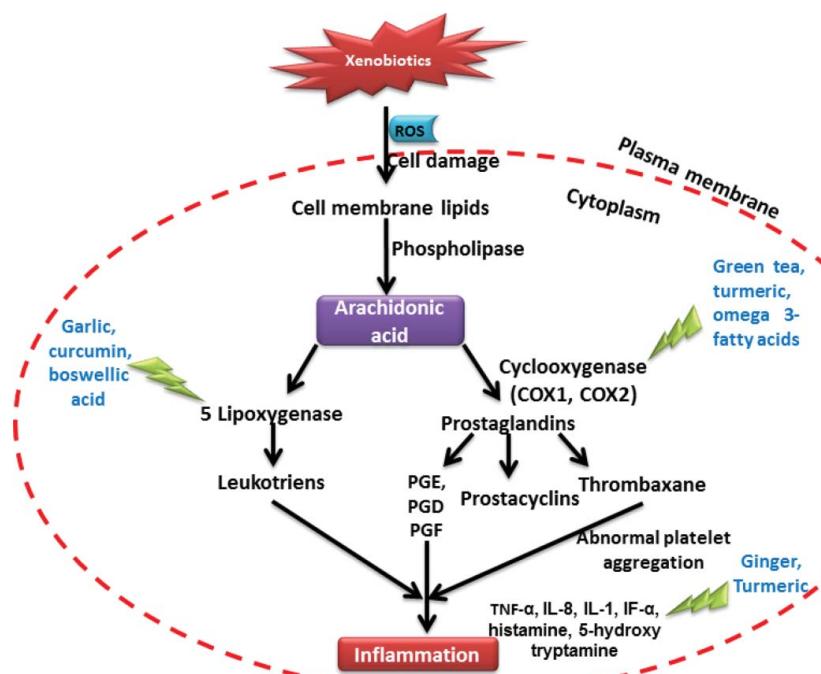


Figure 4. Overview of mediators influencing pro-inflammatory process and anti-inflammatory roles of bioactive food components.

transplantation is not performed in time. Liver cancer is usually observed in 20–30 years subsequent findings of cirrhosis of the liver. Most of the patients only survive 6–20 months after the diagnosis of liver cancer and die from either liver failure or tumor progression.

Bioactive components are antioxidants and anti-inflammatory biomolecules, which have a vital role in averting acute liver injury. Generally, they are abundantly present in plants in the form of alkaloids, polyphenols, glycosides, and saponins. Numerous *in vivo*, *ex vivo*, and *in-vitro* studies have revealed bioactive components have a potential of antioxidant, hypoglycemic, hypolipidemic, anti-inflammatory, antimicrobial, gastroprotective, antimutagenic, anticancer, chemopreventive, and immunomodulatory effects (Bhandari et al., 2003; Ajith et al., 2007; Ali et al., 2012; Shati and Elsaied, 2009; Khaki and Khaki, 2010). Bioactive food components inhibit the effects of drugs/chemicals induced oxidative stress. Bioactive components facilitate intra cellular signaling pathways and activate of Nrf2 through initiation of the P1K3/AKt and ERK and thereby it regulates various transcription factors. Furthermore, bioactive components negatively regulate SP/NR1 signaling pathways. Overall, bioactive food components have a significant role in drugs/chemicals induced oxidative stress and regulates intracellular enzymes, protects cell toxicity, and detoxify various metabolites from the cell (Figure-5).

Protects against paracetamol-induced hepatotoxicity

Paracetamol (acetaminophen) chemically known as N-acetamide, is used as a pain reliever and fever reducing agent worldwide (Girish et al., 2009). Nevertheless, prolonged

administration of acetaminophen at high concentration is evidenced to cause liver toxicity in both experimental animals and humans (Ajith et al., 2007). In the cell, the ingestion of acetaminophen produces toxic metabolites, N-acetyl-p-benzoquinone imine by the enzymes of CYP phase I system. These noxious products generate free radicals in the liver and diminish the level of GSH, thereby leading to hepatotoxicity (Yassin et al., 2010).

In vitro studies with cultured rat hepatocytes and several *in vivo* studies showed that bioactive food components are greater effective in acetaminophen-induced hepatic damage. Preclinical studies have conclusively shown that soybean, sesame, picroliv, cucumber, ginger, turmeric, and carrot caused a concentration-dependent decrease in the levels of serum AST, ALT, ALP, bilirubin, and urea (Singh et al., 1992; Bishayee et al., 1995; Kampkotter et al., 2008; Yassin et al., 2010; Munish et al., 2011; Gopalakrishnan and Kalaiarasi, 2013). Studies have shown that, when compared to only paracetamol treated rats, administration of single dose of carrot, drumstick, yam, ginger, turmeric and other spices and condiments reduced the levels of serum ALT, AST, and ALP, and increase the levels of SOD, GST, and CAT activities (Ruckmani et al., 1998; Kumar et al., 2004, 2005; Hurkadale et al., 2012).

In addition, when compared with silymarin many bioactive components isolated from vegetables and fruits showed decreased levels of serum MDA, AST, ALT, and ALP (Girish et al., 2009; Abdel-Azeem et al., 2013; Fan et al., 2013; Hashem et al., 2013). Additionally, concomitant increase in the levels of antioxidants was also observed, indicating that the observed hepatoprotection was mediated through the antioxidant and anti-inflammatory mechanisms (Hashem et al., 2013).

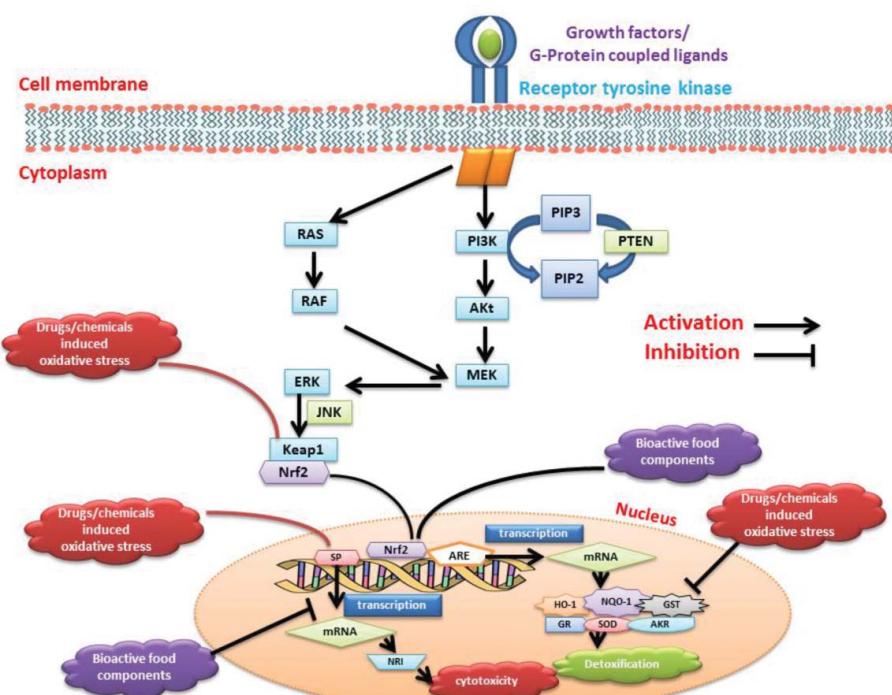


Figure 5. Antioxidant effects of bioactive components in drugs/chemicals induced oxidative stress. Bioactive components facilitate to activate of Nrf2 through activation of the P1K3/AKt and ERK signaling pathways which contributes to increasing expression of Nrf2 regulated enzymes that prevent drugs/chemicals induced oxidative stress. In addition bioactive components negatively regulate SP/NR1 signaling pathways.

Protects against CCl_4 -induced hepatotoxicity

Carbon tetrachloride (CCl_4) is a distinguished toxin commonly used in preclinical *in vivo* and *in-vitro* experiments for xenobiotic-induced hepatic damage (Dwivedi et al., 1992a, b). CCl_4 is a nonflammable organic solvent, broadly utilized as a fire extinguisher, households cleansing agents and preparation of Freon in refrigerants. CCl_4 is very noxious and fixed with greenhouse gas and have ozone-depleting potential. Humans and animals are exposed to CCl_4 through inhalation, ingestion, and absorption. Based on the doses in human, the toxicity effect of CCl_4 generally affects the respiratory tract, cardiovascular, gastrointestinal tract, renal, nervous system, endocrine and reproductive system (Yemitan and Izegbu, 2006). Administration of CCl_4 generates oxidative stress by the production of free radicals, cause acute hepatocellular injury, centrilobular necrosis, and steatosis. Normally, CCl_4 is degraded into highly reactive trichloromethyl radical by CYP phase I enzyme system in the hepatic cell (Patrick-Iwuanyanwu et al., 2007).

In vitro studies have shown that drumstick, picroliv and lemon were effective in causing a concentration-dependent decrease in the CCl_4 -induced cytotoxic effects and to restore the levels of AST, ALT, and ALP of rat hepatocytes (Visen et al., 1998; Bhavsar et al., 2007; Kumar and Santhi, 2012). *In vitro* studies have further validated that turmeric, picroliv and taro were more effective against the CCl_4 - induced liver toxicity (Dwivedi et al., 1990; Naik et al., 2004; Patil and Ageely, 2011).

Studies demonstrated in *in vivo* showed that the pretreatment of rats with broccoli, bitter melon, beetroot and onion to reduce the CCl_4 -induced increase in the level of serum ALT, AST, and ALP and levels of serum bilirubin (Al-Howiriny, 2008; Rawat and Dutt, 2007; Semiz and Sen, 2007; Rose et al., 2014). Moreover, CCl_4 -induced hepatotoxicity is nullified by the bioactive components such as vegetables and fruits thereby increase the levels of antioxidants such as SOD, CAT and GSH observed, indicated that vegetables and fruits proved as a hepatoprotective potential which mediated through the antioxidant and anti-inflammatory mechanisms (Kumar et al., 2010; Alqasoumi, 2012).

Protects against alcohol-induced hepatotoxicity

Alcoholism is one of the world's primary health problems and ingesting of high doses of ethanol is evidenced to cause cirrhosis of the liver and malignancy (Rastogi et al., 1996; Saraswat et al., 1999). Alcohol is chiefly metabolized in the liver by alcohol dehydrogenase and aldehyde dehydrogenase in a two-step reaction to form water and carbon dioxide. Cytochrome P450 phase I enzyme system is also identified to break down alcohol to acetaldehyde. Further, the acetaldehyde is highly toxic and carcinogenic. This reaction normally generates free radicals and lipid peroxidation leads to liver toxicity (Mallikarjuna et al., 2008).

Several *in vivo* studies have shown that the oral administration of cereals and grains- black rice bran (Hou et al., 2010), foxtail millet (Pang et al., 2014); pulses- chestnut (Noh et al., 2011), black gram (Nitin et al., 2012); vegetables-curry leaf (Sathaye et al., 2011), wild mint (Radhika et al., 2011; Patil and Mall, 2012), *Ginkgo biloba* (Yao et al., 2007); and fruits

-Chinese date (Dahiru and Obidoa, 2007) were effective in ameliorating the ethanol-induced chronic hepatotoxicity in rats. Studies with *in vitro* hepatocytes have also shown that turmeric, picroliv, garlic, and ginger were effective in protecting against the cytotoxic effects of ethanol and to decrease the levels of alcohol-metabolizing enzymes (Saraswat et al., 1999). These experiments obviously showed the efficacy of bioactive food components on ethanol-induced liver injury and rejuvenate the bile, which facilitated through the antioxidant and anti-inflammatory mechanisms.

Protects against thioacetamide-induced hepatotoxicity

Thioacetamide is also known as thioacetimidic acid or acetothioamide, a vital organosulfur compound with extensive industrial applications. It is used as a motor fuel stabilizer and rubber vulcanizing accelerator in leather, fabrics, and paper productions (Dwivedi et al., 1991). It is an important experimental carcinogen and induces hyperplastic liver nodules and liver cell adenomas and hepatocarcinoma in mice, hepatocellular neoplasms and cholangio-cellular neoplasms in rats (Visen et al., 1998). Cell culture studies have shown that eugenol, picroliv and corn (*Zea mays*) protected the rat hepatocytes against the thioacetamide-induced cytotoxicity (Visen et al., 1998; Yogalakshmi et al., 2010; Lv et al., 2013).

Studies *in vivo* showed that the pretreatment of rats with guava and papaya to reduce the thioacetamide-induced increase in the level of serum ALT, AST, and ALP and levels of serum bilirubin (Roy et al., 2006; Roy and Das, 2010; Manikandaselvi et al., 2012). Moreover, thioacetamide-induced hepatotoxicity is nullified by the fruits thereby increase the levels of antioxidants such as SOD, CAT and GSH observed, indicated that fruits proved as a hepatoprotective potential which mediated through the antioxidant and anti-inflammatory mechanisms (Adeneye et al., 2009; Manikandaselvi et al., 2012).

Protects against galactosamine-induced hepatotoxicity

D-galactosamine is one of the significant drugs to study hepatotoxic effects in experimental animal models, which cause acute hepatitis. Biochemically, D-galactosamine disturbs UDP-glucose and UDP-galactose metabolism in the liver leads to loss of intracellular calcium and avert the synthesis of energy. Alterations in calcium homeostasis affect cell membranes, organelles and inhibit the synthesis of protein & DNA thereby causes hepatic dysfunction (Visen et al., 1998). *In vitro* and *in vivo* studies with hepatocytes have shown that eggplant, horsegram, picroliv, turmeric, and betulinic acid possesses hepatoprotective effects against galactosamine-induced cytotoxicity. These bioactive compounds restore the galactosamine-induced hepatic changes in the levels of serum AST, ALT, ALP, and bilirubin (Visen et al., 1998; Chattopadhyay et al., 2006; Zheng et al., 2011; Parmar et al., 2012; Nuevo and Banzon, 2013b). Turmeric, carvacrol, and picroliv increased the activities of enzymatic antioxidants such as SOD, CAT, and GPx and nonenzymatic antioxidants such as vitamin C, A, E, and GSH in the serum, RBC, hepatocytes, and kidney, thereby inhibit and restore the effects of the D-galactosamine-intoxicated liver injury. Further, the histopathological observations showed

significant improvement adds strength to the biochemical results, which facilitated through the antioxidant and anti-inflammatory mechanisms (Dwivedi et al., 1992a; Dwivedi et al., 1993a; Aristatile et al., 2009).

Protects against aflatoxin-induced hepatotoxicity

Aflatoxin is a class of mycotoxins mainly produced by the *Aspergillus flavus* and *A. parasiticus* and proved as one of the recognized pollutant, hepatotoxin, and cancer inducing chemical (Banu et al., 2009a, b). Contact of aflatoxin mostly occurs through ingestion of peanuts, walnuts, almonds, grains, sunflower, black pepper and coriander maintained in conditions favoring fungal growth (El-Nezami et al., 2006). Studies showed that the oral treatment with turmeric and picroliv reversed the aflatoxin-induced hepatic damage there diminish the activity of hepatic glucose-6-phosphatase CYP, and levels of DNA, RNA, proteins, and glycogen (Govindarajan, 1980; Dwivedi et al., 1993b). Further, the histopathological studies also exhibited that administering turmeric and picroliv reduced the aflatoxin-induced hepatic changes and endorse the hepatoprotective effects. Biochemical and histopathological results clearly exhibit the protective effects of turmeric and picroliv, which mediated through the antioxidant and anti-inflammatory mechanisms (Dwivedi et al., 1993b; Rastogi et al., 2000, 2001a).

Protects against cadmium-induced hepatotoxicity

Heavy metals (cadmium, arsenic, mercury etc.) possess severe menace to human health due to their toxic effects on various vital organs including the liver. Due to industrialization, cadmium is extensively distributed in the environment and cause occupational hazards (Ramesh and Satakopa 2006). Cadmium is one of the most significant noxious hepatotoxic agents generates free radicals; thereby it initiates lipid peroxidation cause cell necrosis and death (Yadav et al., 2005; Yadav and Khandelwal, 2006; 2009). Animal studies have shown that oral administration of garlic juice, tulsi, picroliv, drumstick, and onion before administering a single dose of cadmium chloride (3 mg/kg b.w, i.p.) was effective in protecting rats against the impending hepatotoxicity (Yadav et al., 2005; Ramesh and Satakopan 2006; Ige et al., 2009; 2011; Lawal et al., 2011; Toppo et al., 2015). Administering tulsi, picroliv and drumstick ameliorated the cadmium chloride-induced hepatotoxicity and decreased the levels of serum MDA, ALT, AST, GGT, LDH and concurrently enhanced the levels of serum antioxidant parameters SOD, CAT, GSH, GPx, and ascorbic acid (Yadav et al., 2005; Ramesh and Satakopan, 2006; Yadav and Khandelwal, 2006; 2009; Bharavi et al., 2010). Histopathological studies also clearly exhibited a reversal of the cadmium-induced damage by the administration of tulsi, picroliv and drumstick, which arbitrated through the antioxidant and anti-inflammatory mechanisms (Yadav et al., 2005).

Protects against oxytetracycline-induced hepatotoxicity

Oxytetracycline is a tetracycline class of antibiotics, regularly used for the management of various microbial infectious diseases such as anthrax, chlamydia, cholera, typhus, Lyme

disease, tularemia, relapsing fever, malaria, plague, mycoplasma, syphilis, respiratory infection, rickettsia, and streptococcal infection (Jayanthi and Subash, 2010). Excess oxytetracycline may contribute various adverse effects in human such as hepatic injury and microvesicular steatosis leads to death (Saraswat et al., 1997). Caffeic acid, *Nigella sativa* oil, picroliv and naringenin caused a dose-dependent hepatoprotective activity against oxytetracycline (200 mg/ kg b.w)-induced hepatic damage in rats (Gnanasoundari and Pari, 2006; Abdel-Daim and Ghazy, 2015). Histopathology studies also showed that caffeic acid, *Nigella sativa* oil, picroliv, and naringenin ameliorate the cytotoxic effects of oxytetracycline and thereby increased the number of viable hepatocytes and increased the secretion of bile (Saraswat et al., 1997). These studies showed a reversal of the damage by bioactive compounds provided hepatic tissues protection, which mediated through the antioxidant and anti-inflammatory mechanisms (Abdel-Daim and Ghazy, 2015).

Protects against monocrotaline-induced hepatotoxicity

Monocrotaline is a pyrrolizidine alkaloid abundantly distributed in *Crotalaria* plant species and causes respiratory and liver toxicity in both humans and animals. It is accidentally ingested during the consumption of food grain along with *Crotalaria* contamination or through herbal medicine preparations (Copple et al., 2003). In Asia and Africa, the studies proposed that the feeding of herbal medicines containing pyrrolizidine alkaloids might cause to the high incidence of chronic hepatic injury and liver cancer (Copple et al., 2003; Wiedenfield and Edgar, 2011). Prevalence of monocrotaline-related human deaths happened in Asia and Afghanistan owing to food contaminants in wheat, rice, milk, honey, herbal teas and herbal medicines (Dwivedi et al., 1991a). Monocrotaline containing toxic metabolites causes cell explosion, veno-occlusive defectives in liver endothelium, respiratory hypertension, and right ventricular hypertrophy in heart (Klaassen, 2001). These noxious metabolites usually escape from the blood stream and reach target organs thereby induce organ injury.

Animal studies have shown that oral administration of N-acetyl cysteine and picroliv ameliorated the effects of monocrotaline-induced hepatic injury (Dwivedi et al., 1991a,b; Karagoz et al., 2013). Both compounds reduced the activities of hepatic succinate dehydrogenase, ribonuclease, acid phosphatase, GGT, and 5-nucleotidase. In addition, they reduced the abnormal levels of DNA, RNA, glycogen, and proteins. Hepatoprotective activity of N-acetyl cysteine and picroliv was further confirmed by the quantitative decrease in the histopathological changes. These studies have shown a reversal of the damage by bioactive compounds provided hepatic tissues protection, which mediated through the antioxidant and anti-inflammatory mechanisms (Karagoz et al., 2013).

Protects against 1, 2-dimethylhydrazine-induced hepatotoxicity

1,2-Dimethylhydrazine (DMH), a potent laboratory chemical, is a familiar DNA methylating agents and experimental colon carcinogen. During liver metabolism, DMH yield noxious

metabolites such as carbonium ions and alkyl free radicals. These metabolites cause severe hepatic injury, necrosis, fatty infiltration and DNA methylation leads to impairment of protein synthesis (Sharma, 2011). Oral administration of DMH causes distract the intestinal villi and inhibit intestinal absorption (Sharma et al., 1995a, b). Normally DMH abundantly present in tobacco, wild mushrooms, and other food items (Wilbert et al., 1990). DMH induces hepatic injury due to its mutagenic properties. It is metabolized in the liver and generate several carcinogenic metabolites such as azoxymethane, methyl azoxy methanol, and methyldiazonium which induce DNA alkylation leads to DNA mutations and cell death (Rajeshkumar and Kuttan, 2003; Eboh et al., 2015). Oral administration of kola virion, Triphala and picroliv reduces the DMH-induced hepatotoxicity and necrosis. Biochemical and histological studies showed that kolaviron, Triphala and picroliv decreased the levels of lipid peroxides, hepatic GGT, restored the levels of anti-oxidant enzymes, viability of the hepatic cell, hepatic cell necrosis, and cystic hyperplasia proved the hepatoprotective effects. These studies showed a reversal of the damage by bioactive compounds provided hepatic tissues protection, which mediated through the antioxidant and anti-inflammatory mechanisms (Rajeshkumar and Kuttan, 2003; Sharma and Sharma, 2011; Eboh et al., 2015).

Protects against N-nitrosodiethylamine-induced hepatotoxicity

N-Nitrosodiethylamine (NDEA) is a potent hepatocarcinogenic compound widely present in the products of milk, meat, soft drinks, alcoholic beverages, and tobacco. Normally, NDEA is used as xenobiotic agent in experimental animal model study (Dakshayani et al., 2005). During liver metabolism, some therapeutic drugs are also produce NDEA. It is degraded by the action of CYP produce reactive electrophiles; cause oxidative stress leads to mutation, cytotoxic, and carcinogenesis (Shaarawy et al., 2009). Umbelliferone, esculetin, picroliv ellagitannins, and garlic are shown to effectively inhibit the hepatocarcinogenesis induced by NDEA in rats. Oral administration of the bioactive compounds reduced the NDEA-induced elevation of GGT, bilirubin, ALP, ALT, and peroxides, and to normalize the altered levels of GSH and GST (Rajeshkumar and Kuttan, 2000; Hussein and Khalifa, 2014; Subramaniam and Ellis, 2016). This strongly indicates the chemopreventive potential of active principles, umbelliferone (active principle obtained from carrot, coriander, *Apium graveolens* L., *Lavandula angustifolia* Mill., and garden angelica), esculetin (*Cichorium intybus*, *Crataegus oxyacantha* L., and *Centarea cyanus* L.), picroliv (*Picrorhiza kurroa*), ellagitannins (*Rubus idaeus*) and garlic against chemically induced liver tumors. These studies showed a reversal of the damage by bioactive compounds provided hepatic tissues protection, which mediated through the antioxidant and anti-inflammatory mechanisms (Hussein and Khalifa, 2014; Subramaniam and Ellis, 2016).

Bioactive food components is effective in viral hepatitis

Several *in vitro* and *in vivo* preclinical results have demonstrated that epigallocatechin-3-gallate, curcumin, sodium

butyrate, caffeic acid, allyl isothiocyanate, and resveratrol, inhibit the activity of hepatocellular carcinoma (Lea et al., 2001; Lee and Zhu, 2006; Bishayee and Dhir, 2009; Darvesh et al., 2012; Darvesh and Bishayee, 2013; Wang et al., 2013). The development of hepatocellular carcinoma in humans is associated with the well-identified main risk factors, including chronic virus HBV and HBC infection (Moreno et al., 2016),

In worldwide, hepatitis caused by hepatotropic viruses is the most common cause of various liver diseases and cancers. Among the viral diseases, the hepatitis B and C are predominant, responsible for most diseases. People find rely on alternative medicine due to the ineffectiveness of modern medicine. *In vitro* studies showed picroliv has a potent similar like anti-hepatitis-B actions while kept along with the positive samples of serum of HBV (Mehrotra et al., 1990). In addition, clinical studies showed that oral administration of *Picrorhiza kurroa* root decreased the levels of AST, ALT, and bilirubin, and thereby protect the liver from infected HBV individuals (Vaidya et al., 1996).

Bioactive food components reduces the ischemia–reperfusion injury of liver

ROS have been implicated in the pathophysiology of ischemia–reperfusion injury in liver transplantation. Preclinical studies demonstrated that resveratrol, green tea, flavonoids, picroliv and diosmin were effective in ameliorating injury following ischemia–reperfusion in Sprague–Dawley rats (Singh et al., 2000; Giovannini et al., 2001; Rah et al., 2007; Tanrikulu et al., 2013; Yildiz et al., 2015). The investigators observed that the pretreatment with resveratrol, green tea, flavonoids, picroliv and diosmin for seven consecutive days prior to hepatic ischemia caused a decrease apoptotic mechanism and reduce liver glycogen. Studies showed that administering resveratrol, green tea, flavonoids, picroliv and diosmin decreased neutrophil infiltration, the levels of proinflammatory cytokines, transcription of caspase-3 and Fas, liver malondialdehyde, and concomitantly increased the levels of SOD and cell proliferation (Singh et al., 2000; Fengsu et al., 2003). These findings suggested that bioactive compounds are potent to reduce the ischemia–reperfusion injury and this protective effect mediates by antioxidant and antiapoptotic mechanisms.

Hepatoprotective effect of bioactive food components

Many dietary foods and supplements possess hepatoprotective activity. The bioactive components of different plant and animal products are taking center stage in the treatment of various liver illnesses. Many food ingredients possess potential ability to prevent liver injuries or restore the liver functions. Numerous studies have been conducted at preclinical level, and many bioactive compounds have been identified as potential hepatoprotective agents.

Hepatoprotective effects of cereals

In vivo and *in vitro* experimental animal model studies provided that cereals exert potent hepatoprotective activities, as summarized in Table 1.

Table 1. Hepatoprotective effects of cereals and grains.

cereals and grains	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Barley	<i>Hordeum vulgare</i> L. (Poaceae)	isoflavones, and β -glucan	Antioxidant and anti-inflammatory	cholesterol-enriched diet-induced wistar albino rats		El-Mageed, 2011
Barley	<i>Hordeum vulgare</i> L. (Poaceae)	isoflavones, and β -glucan	Antioxidant and anti-inflammatory	Azoxymethane-induced wistar albino rats		Lahouar et al., 2011; 2014
Cacao	<i>Theobroma cacao</i> L.	flavan-3-ols, catechin and epicatechin, anthocyanin, quercetin glycosides	Antioxidant and anti-inflammatory	cholesterol-enriched diet-induced wistar albino rats		Lecumberri et al., 2007
Wheat grass	<i>Triticum aestivum</i> (Poacea)	isoflavones	Antioxidant and anti-inflammatory	CCl ₄ -induced wistar albino rats		Jain et al., 2007; Kamboj et al., 2011
Black rice bran	<i>Oryza sativa</i> L. <i>japonica</i> (Poacea)	Anthocyanin	Antioxidant and anti-inflammatory	CCl ₄ -induced wistar albino mice		Hou et al., 2013

Black rice bran	<i>Oryza sativa</i> L. Japonica (Poaceae)	Anthocyanin		Hou et al., 2010
Rice	<i>Oryza sativa</i> L.(Poaceae)	Anthocyanin	Antioxidant and anti-inflammatory	Alcohol-induced wistar albino mice
Foxtail millet	<i>Setaria italica</i> (Poaceae)	Hydroxybenzoic acids, hydroxycinnamic acids and flavonoids	Antioxidant and anti-inflammatory	tert-butyl hydroperoxide-induced wistar albino mice
Finger millet or ragi	<i>Eleusine coracana</i> L. (Poaceae)	phenolic acids phytic acid, flavonoids and tannins	Antioxidant and anti-inflammatory	CCl ₄ -induced wistar albino rats
				Bhusan et al., 2011

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Table 1. (Continued)

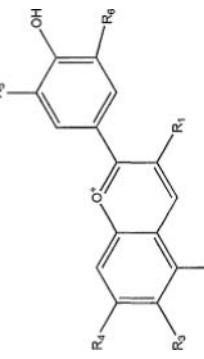
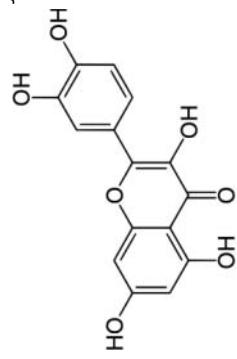
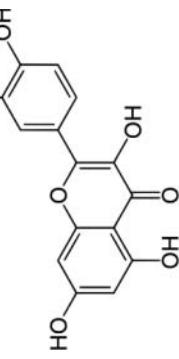
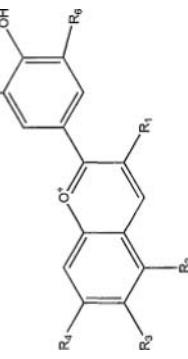
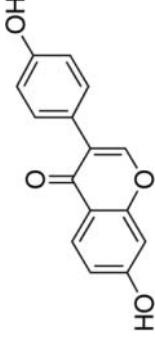
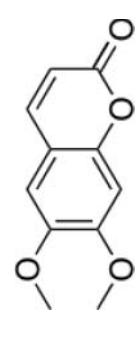
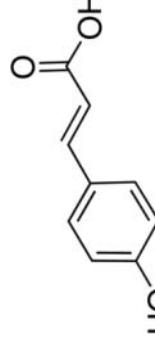
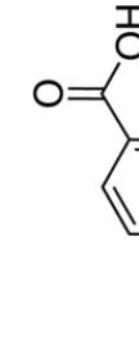
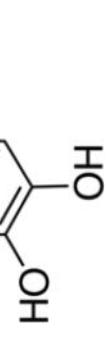
cereals and grains	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Common Wheat	<i>Triticum aestivum</i> (Poaceae)	Anthocyanin	Antioxidant and anti-inflammatory	CCl_4 -induced wistar albino rats		Ebeid et al., 2015
Maize	<i>Zeamays</i> L(Gramineae)	Phenolics and flavonoid	Antioxidant and anti-inflammatory	CCl_4 -induced wistar albino rats		Jayachitra et al., 2013
corn	<i>Zeamays</i> L(Gramineae)	Phenolics and flavonoid	Antioxidant and anti-inflammatory	thioacetamide (TAA)-induced liver fibrosis in wistar albino rats		Ly et al., 2013
Cassava	<i>Manihot esculenta</i> Crantz (Euphorbiaceae)	Anthocyanin	Antioxidant and anti-inflammatory	CCl_4 -induced wistar albino rats		Ly et al., 2013

Table 2. Hepatoprotective effects of pulses.

Fruits	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Tofu (Curdle Soymilk)	<i>Glycine max</i> (Leguminaceae)	isoflavones, and antioxidants (carotenoids, vitamins C and E, phenolic and thiol (SH) compounds, and essential amino acids	Antioxidant and anti-inflammatory	Acetaminophen-induced wistar albino rats		Mujeeb et al., 2011; Yakubu et al., 2013
Soy bean	<i>Glycine max</i> (Leguminaceae)	Daidzein	Antioxidant and anti-inflammatory	Acetaminophen-induced hepatoma cells		Kampkötter et al., 2008
Chestnut	<i>Castanea crenata</i> (Fagaceae)	Scoparone, Tannins and polyphenol	Antioxidant and anti-inflammatory	Ethanol-induced C57BL/6 mice		Noh et al., 2011
Fermented sea tangle	<i>Laminaria japonica</i> (Laminariaceae)	Phenolic compounds	Antioxidant activity	CCl ₄ -induced Sprague-Dawley rats		Lee et al., 2010
Horse gram	<i>Macrotyloma uniflorum</i> (Lam.) Verdc (Fabaceae)	phenolic acids, namely, 3,4-dihydroxybenzoic, 4-hydroxybenzoic, vanillic, caffeic, <i>p</i> -coumaric, ferulic, syringic and sinapic acids	Antioxidant activity	Paracetamol and d-galactosamine-induced wistar albino rats		Parmar et al., 2012

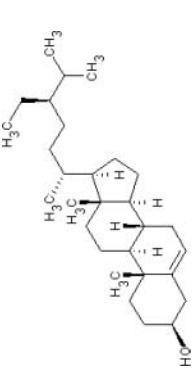
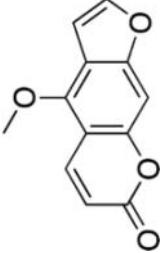
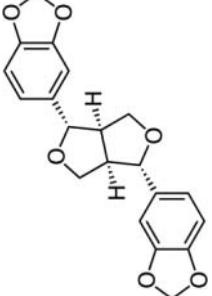
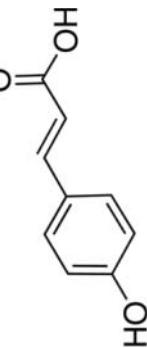
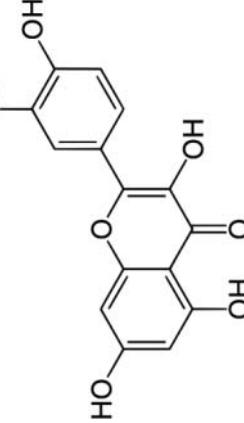
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Table 2. (Continued)

Fruits	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Black beans Phaseolus vulgaris L (Fabaceae)	polyphenols, flavonoids, and tannins, phytosterols, and triterpenoids	Antioxidant activity	CCl_4 -induced wistar albino rats	Lopez-Reyes et al., 2008		
adzuki bean hulls Vigna angularis L. (Fabaceae)	Saponin, phenolics flavonoids tannin	Antioxidant activity	Paracetamol-induced wistar albino rats	Han et al., 2004		
Sesame Sesamum indicum Linn. (Pedaliaceae)	sesamin and sesamolin	Antioxidant activity	CCl_4 -induced wistar albino rats	Kumar et al., 2011; Cengiz et al., 2013		
Sesame Sesamum indicum Linn. (Pedaliaceae)	sesamin and sesamolin	Antioxidant activity	Lead-induced wistar albino mice	Azab, 2014		

Sesame	<i>Sesamum indicum</i> Linn. (Pedaliaceae)	sesamin and sesamolin in addition to glycerides of oleic and linoleic acid	Antioxidant activity	Paracetamol induced wistar albino rats	Munish et al., 2011
Black gram	<i>Vigna mungo</i> L. (Fabaceae)	steroids, flavonoids, tannins, alkaloids and glycosides	Antioxidant activity	Ethanol-induced wistar albino rats	Nitin et al., 2012
Black gram	<i>Vigna mungo</i> L. (Fabaceae)	n-hentriacontane, ferulic acid, 4-hydroxycinnamic acid, querectin-3-rhamnoside and kaempferol-3-glucoside	Antioxidant activity	CCl ₄ -induced wistar albino rats	Anitha et al., 2012
Black gram	<i>Vigna mungo</i> L. (Fabaceae)	beta-sitosterol, beta-sitosterol-glucoside and d-mannitol	Antioxidant activity	Paracetamol-induced wistar albino rats	Solanki and Jain, 2011
Moth bean	<i>Vigna aconitifolia</i> L. (Fabaceae)	Flavonoids, tannins, and saponins	Antioxidant activity	smokeless tobacco mixed diet and CCl ₄ - induced wistar albino rats	Cheekuramelli et al., 2014

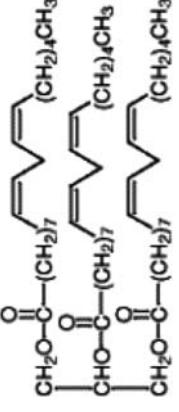
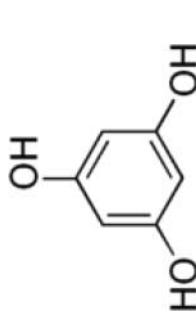
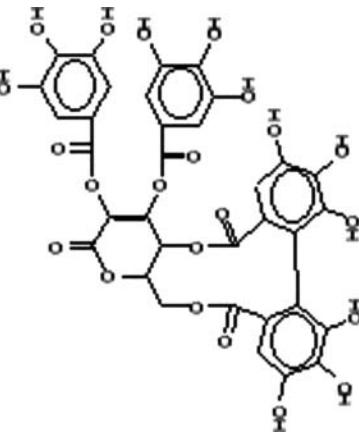
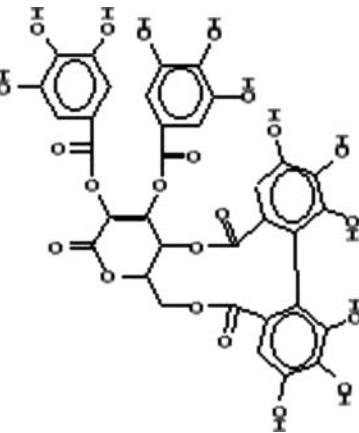
Table 3. Hepatoprotective effects of fruits.

Fruits	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Common Fig	<i>Ficus carica</i> (Moraceae)	flavonoids, beta-sitosterol, vitamins, nicotinic acid, tyrosine, ficusin, psoralen, bergapten, rutin, stigmastanol, furocoumarin, taraxasterol, and saponin	Antioxidant and anti-inflammatory	CCl_4 -induced wistar albino rats		Singab et al., 2010; Mujeeb et al., 2011
Common Fig	<i>Ficus carica</i> (Moraceae)	bergapten, rutin, stigmastanol, furocoumarin, taraxasterol, and saponin	Antioxidant and anti-inflammatory	Rifampicin-induced wistar albino rats		Gond and Khadabadi, 2008
Fig tree	<i>Ficus hispida</i> L.f. (Moraceae)	sesamin	Antioxidant and anti-inflammatory	Paracetamol-induced wistar albino rats		Mandal et al., 2000
Indian fig tree	<i>Ficus racemosa</i> L. (Moraceae)	Phenolic compounds	Antioxidant and anti-inflammatory	CCl_4 -induced wistar albino rats		Mandal et al., 1999
Avocado	<i>Persea Americana</i> (Lauraceae)	Ferulic, salicylic, syringic, p-coumaric and cinnamic acids and Flavonoids (quercetin, luteolin, rutin, kamferol and hypersoloid acid)	Antioxidant and anti-inflammatory	CCl_4 -induced wistar albino male rats		Mahmoed et al., 2013

Grape	<i>Vitis labrusca</i> L. (Vitaceae)	Polyphenolic compounds	Buchner et al., 2014
Grape vine, wild grape	<i>Vitis vinifera</i> L. (Vitaceae)	Flavonoids, tannins, poly phenols, saponins, cardiac glyco sides, terpenoids, phytosterols	Antioxidant and anti-inflammatory High fat diet-induced wistar albino rats
Cucumber	<i>Cucumis sativus</i> ; (Cucurbitaceae)	n-Hexadecanoic acid	Sharma et al., 2012
Cucumber	<i>Cucumis sativus</i> ; (Cucurbitaceae)	n-Hexadecanoic acid	Gopalakrishnan and Kalaiarasu, 2013
Cherry	<i>Laurocerasus officinalis</i> Roem; (Rosaceae)	Phenolic and flavonoid compounds	Heidari et al., 2012
Mango	<i>Mangifera indica</i> L. (Anacardiaceae)	Mangiferin	Mirzaei and Rezanejad, 2015
			Rodeiro et al., 2008

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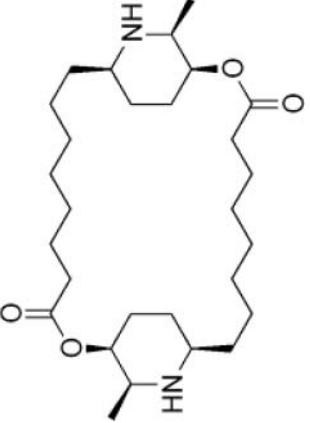
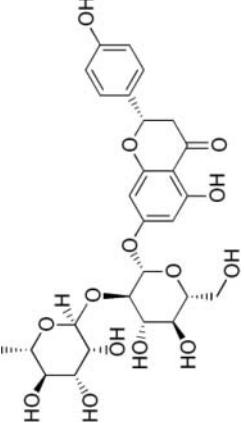
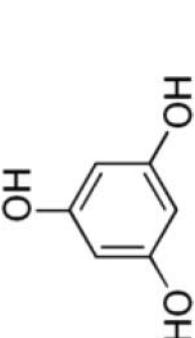
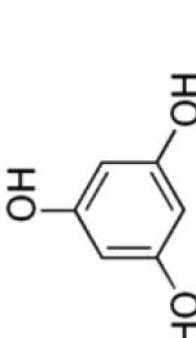
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Fruits	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Blacknightshade	<i>Solanum nigrum</i> L (Solanaceae)	Trilinolein, Ursic acid monoacetate, Niclofen and 8-Azabicyclo [3.2.1] octane-2-carboxylic acid, 3-hydroxy-8-methyl,(2-endo,3-ex)	Antioxidant and CCl ₄ -induced wistar albino rats anti-inflammatory			Raju et al., 2003
Amla	<i>Emblica officinalis</i> Gaertn (Euphorbiaceae)	Ascorbic acid and tannins (emblicans A and B)	Antioxidant and L-thyroxine-induced mice anti-inflammatory			Panda and Kar, 2003
Amla	<i>Emblica officinalis</i> Gaertn (Euphorbiaceae)	Tannins and flavonoids	Antioxidant and anti-inflammatory			Malar and Bai, 2009
Amla	<i>Emblica officinalis</i> Gaertn (Euphorbiaceae)	emblicanins A and B	Antioxidant and tert-butyl hydroperoxide (t-BH)-induced toxicity in HepG2 cells anti-inflammatory			Srirama et al., 2012

Indian gooseberry <i>Phyllanthus amarus</i> (Phyllanthaceae)	Ascorbic acid and tannins (emblicanins A and B)	Liu et al., 2001; Tasduq et al., 2005	Antioxidant and CCl ₄ -induced wistar male rats anti-inflammatory	
Flaxseed <i>Linum usitatissimum</i>	3-omega (n3) oil, alpha-linolenic acid; and lignans	Hemmings and Barker, 2004	Antioxidant and 10% flax chow-induced Fischer 344 rats anti-inflammatory	
Papaya <i>Carica papaya</i> L.	Carpainecarposide (Caricaceae)	Raj Kapoor et al., 2002; Sadeque and Begum, 2010; Sadeque et al., 2012;	Antioxidant and CCl ₄ -induced wistar albino rats anti-inflammatory	
Papaya <i>Carica papaya</i> L.	Carpaine carposide (Caricaceae)	Manikandaselvi et al., 2012; Adeneye et al., 2009	Antioxidant and CCl ₄ vapor-induced wistar albino rats anti-inflammatory	

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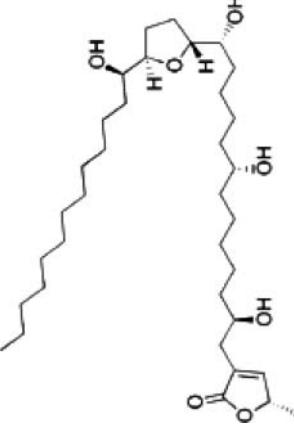
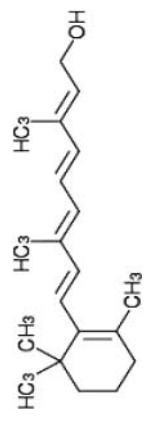
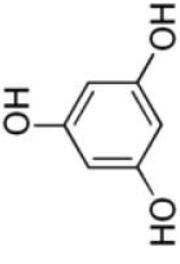
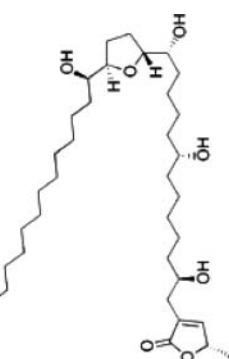
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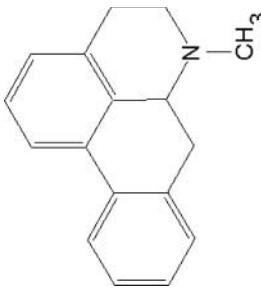
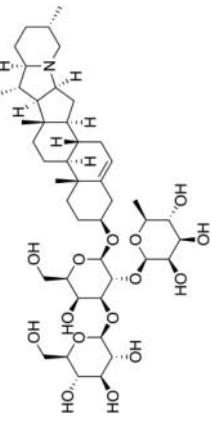
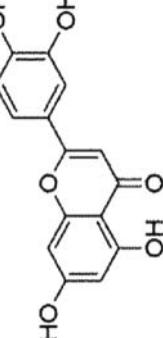
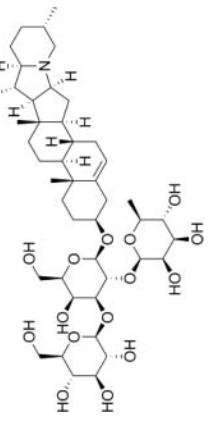
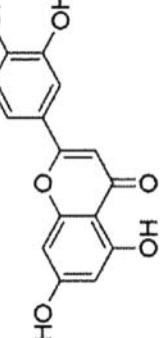
Fruits	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Papaya	<i>Carica papaya</i> L. (Caricaceae)	Carpaine carposide	Antioxidant and anti-inflammatory	Paracetamol and Thioacetamide-induced wistar albino rats		Manikandaselv et al., 2012; Adeneye et al., 2009
Lemon	<i>Citrus limon</i> . (L.) Burm. (Rutaceae)	Eriocitrin and c-glucosyl flavones, Eriodictyol Naringin	Antioxidant and anti-inflammatory	CCl_4 exposed human liver-derived HepG2 cell line		Bhavasar et al., 2007
Chinese orange	<i>Citrus microcarpa</i> Bunge (Rutaceae)	Tannins, glycosides, flavonoids	Antioxidant and anti-inflammatory	Paracetamol-induced male BFAD-Sprague Dawley rats		Francesca et al., 2010
Bergamot orange	<i>Citrus bergamia</i> (Rutaceae)	Tannins, glycosides, flavonoids	Antioxidant and anti-inflammatory	CCl_4 -induced female wistar albino rats		Karaca et al., 2005

Guava	<i>Psidium guajava</i> L. (Myrtaceae)	caryophyllene oxide, caryophyllene, tannins Antioxidant and CCl ₄ , paracetamol, thioacetamide-induced wistar albino rats		Roy et al., 2006; Roy and Das, 2010
Guava	<i>Psidium guajava</i> L. (Myrtaceae)	caryophyllene oxide, caryophyllene, tannins Antioxidant and Paracetamol-induced wistar albino rats		Tajua et al., 2011; Tajua et al., 2010
Banana	<i>Musa paradisiaca</i> L. (Musaceae)	caryophyllene Antioxidant and Paracetamol-induced wistar albino rats		Iweala et al., 2011; Radhika et al., 2012

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Table 3. (Continued)

Fruits	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Banana	<i>Musa paradisiacaL</i> (Musaceae)	Acetogenin	Antioxidant and anti-inflammatory	CCl_4 -induced Paracetamol-induced wistar albino rats		Dikshit et al., 2011; Nirmala et al., 2012
Pineapple guava	<i>Feijoa sellowiana</i> (Myrtaceae)	Polyphenols, carbohydrates, vitamin A	Antioxidant and anti-inflammatory	3, 4-methylene dioxymethamphetamine (MDMA or ecstasy)-induced liver damage		Karami M et al., 2013
wood-apple, monkey fruit, elephant-apple	<i>Feronia limonia</i> (Rutaceae)	Flavonoid, tannin, phenols	Antioxidant and anti-inflammatory	CCl_4 -induced hepatotoxicity in rats & CCl4 treated HepG2 cells		Jain et al., 2012
Custard apple	<i>Annona squamosa</i> (Annonaceae)	Acetogenin, Aporphine, glycoside, squamoline	Antioxidant and Isoniazid and rifampicin-induced wistar albino rats	Antioxidant and anti-inflammatory		Saleem et al., 2008

Custard apple	<i>Annona squamosa</i> (Annonaceae)	Aporphine alkaloids, terpine, Glycosides, diazepine, squamolannetemoyin-1, Annetemoyin-2, Squamocin, Cholesteryl Glucopyranoside, Bullatacin		Rai et al., 2009
Baby Water melon	<i>Coccinia indica</i> (Cucurbitaceae)	Tannins, saponins and phenolic compounds		Kumar et al., 2010
Baby Water melon	<i>Coccinia indica</i> (Cucurbitaceae)	Polyphenols		Sanapala and Kumar, 2013
Chinese date/Chinee <i>Ziziphus mauritiana</i> apple/Indian plum	<i>Ziziphus mauritiana</i> (Rhamnaceae)	Tannins, saponins and phenolic compounds		Dahiru, D.; Obidao, 2007
Apple	<i>Pyrus malus</i> (Rosaceae)	Polyphenols		Miura et al., 2007; Yang et al., 2010

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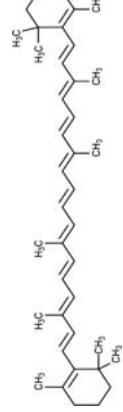
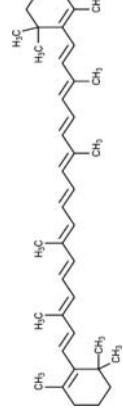
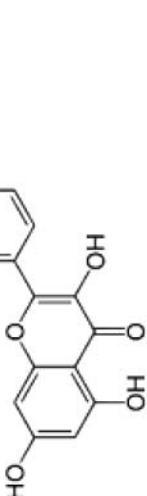
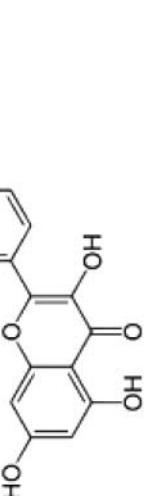
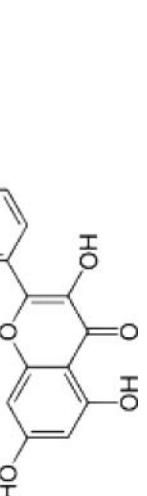
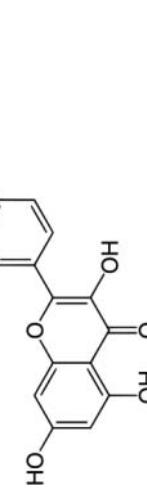
Fruits	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Pomegranate	<i>Punica granatum</i> (Lythraceae)	Polyphenols	Antioxidant and CCl ₄ -induced wistar albino mice anti-inflammatory			Faria et al., 2007; Toklu et al., 2007
Sea buckthorn	<i>Hippophae rhamnoides</i> (Elaeagnaceae)	Carotenes	Antioxidant and CCl ₄ -induced wistar albino rats anti-inflammatory			Zhao et al., 1987; Gao et al., 2003

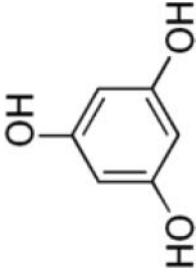
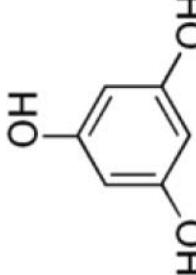
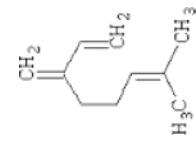
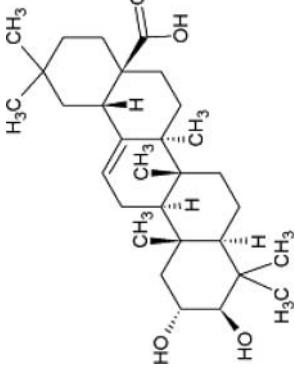
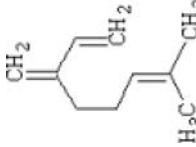
Table 4. Hepatoprotective effects of vegetables.

Vegetables	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Carrot	<i>Daucus carota L.; (Apiaceae)</i>	Beta-carotene	Scavenge the free radicals	Paracetamol-induced wistar albino rats		Kumar et al., 2005
Carrot	<i>Daucus carota L.; (Apiaceae)</i>	Carotenes	Antioxidants	Paracetamol, Isoniazid and Alcohol-induced male wistar albino rats		Shoba et al., 2008
Carrot	<i>Daucus carota L.; (Apiaceae)</i>	Carotenes	Antioxidants	Lindane-induced male wistar albino rats		Bala Subramaniam et al., 1998
Carrot	<i>Daucus carota L.; (Apiaceae)</i>	B-carotene, α -carotene, γ -carotene, lycopene, cryptoxanthin, leutein, abscisic acid, trisporic acid, B-epo-carotenals, crocetin, violaxanthin	Minimize the deleterious effects of peroxy radicals	CCl ₄ -induced Swiss albino mice		Bishayee et al., 1995
Drumstick	<i>Moringa oleifera Lam; (Moringaceae)</i>	alkaloids, anthocyanins, β -carotene, protein, vitamin C, phenolics	Antioxidant and anti-inflammatory	antitubercular drugs (isoniazid, rifampicin, and pyrazinamide)-induced wistar albino rats		Pari and Ashok Kumar, 2004; Ajijore et al., 2012
Drumstick	<i>Moringa oleifera Lam; (Moringaceae)</i>	alkaloids, anthocyanins, β -carotene, protein, vitamin C, phenolics	Antioxidant and anti-inflammatory	Paracetamol-induced wistar albino rats		Ruckmani et al., 1998

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Table 4. (Continued)

Vegetables	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Drumstick	<i>Moringa oleifera</i> Lam; (Moringaceae)	quercetin and kaempferol, vitamin A, ascorbic acid	Antioxidant and anti-inflammatory	Cadmium-induced wistar albino rats		Toppo et al., 2015
Drumstick	<i>Moringa oleifera</i> Lam; (Moringaceae)	quercetin, isoquercetin, kaempferol, zeatin, rutin, β-carotene and ascorbic acid	Antioxidant and anti-inflammatory	High fat diet-induced wistar albino rats		Das et al., 2012
Drumstick	<i>Moringa oleifera</i> Lam; (Moringaceae)	quercetin, kaempferol,	Antioxidant and anti-inflammatory	CCl ₄ -induced wistar albino rats		Ezeonwu and Ugonna, 2012
Lady's finger	<i>Hibiscus esculentus</i> L. (Syn. <i>Abelmoschus esculentus</i> ; (Malvaceae))	Quercetin derivatives, flavonoids, tannins, sterols and triterpenes	Antioxidant and anti-inflammatory	CCl ₄ -induced wistar albino rats		Alqasouni, 2012

curry tree/curry leaf	<i>Murraya koenigii</i> (Rutaceae)	Carbazole alkaloid and tannin	Gupta and Nigam, 1970		Antioxidant and anti-inflammatory	Ethanol-induced wistar albino rats
curry tree/curry leaf	<i>Murraya koenigii</i> (Rutaceae)	Carbazole alkaloid and tannin	Sathaye et al., 2011		Antioxidant and anti-inflammatory	Ethanol-induced liver carcinoma cell lines
Ginkgo	Ginkgo biloba (Ginkgoaceae)	Terpenes and flavonol	Yao et al., 2007		Antioxidant and anti-inflammatory	Ethanol-induced wistar albino rats
Comfort root/ Big Thicket Hibiscus/Pine Hibiscus	<i>Hibiscus hispidissimus</i> Griff; (<i>Malvaceae</i>)	Triterpenes (hibiscatin, gossypitrin) and flavonoids	Krishnakumar et al., 2008		Antioxidant and anti-inflammatory	paracetamol and CCl4-induced Wistar rats
bulbs of onion	<i>Allium cepa L</i> (Liliaceae)	Terpenes and flavonol	Rawat and Dutt, 2007		Antioxidant and anti-inflammatory	CCl4 ethyl acetate & paracetamol-induced wistar albino rats

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Table 4. (Continued)

Vegetables	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
bulbs of onion	<i>Allium cepa L</i> (Liliaceae)	Luciosides A–R, triterpenoid saponins, and Apigenin	Antioxidant and anti-inflammatory	Cadmium-induced wistar albino rats		Ige et al., 2009; 2011
bulbs of onion	<i>Allium cepa L</i> (Liliaceae)	S-alanyl cystine, S-alanyl mercaptocysteine and allin	Antioxidant and anti-inflammatory	CCl ₄ & Paracetamol-induced wistar albino rats		Shaik et al., 2012
Ridgedgourd	<i>Luffa acutangula</i> (Cucurbitaceae)	vitamin E, beta-carotene, flavonols, and flavonoids,	Antioxidant and anti-inflammatory	CCl ₄ & Rifampicin-induced wistar albino rats		Jadhav et al., 2012
Ridgedgourd	<i>Luffa cylindrica L</i> (Cucurbitaceae)	Luciosides A–R, triterpenoid saponins, and Apigenin	Antioxidant and anti-inflammatory	Paracetamol-induced wistar albino rats		Pal and Manoj, 2011
Garlic	<i>Allium sativum</i> (Liliaceae)	S-alanyl cystine, S-alanyl mercaptocysteine and allin	Antioxidant and anti-inflammatory	Lead-induced female wistar albino rats		Senapati et al., 2001; Ajayi, et al., 2008

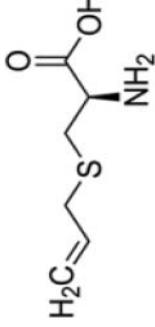
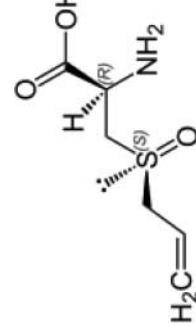
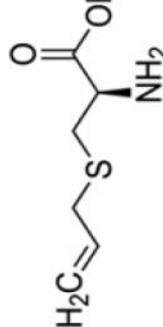
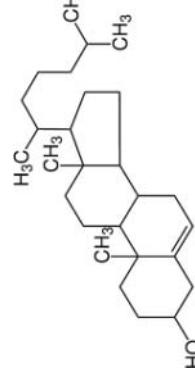
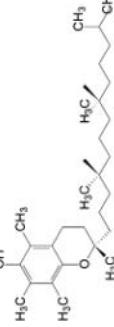
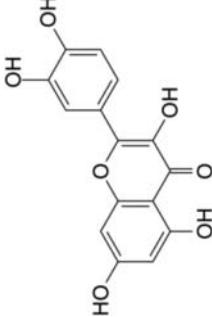
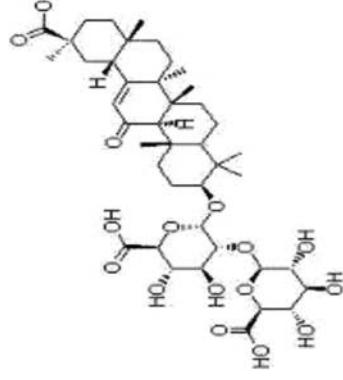
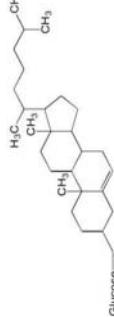
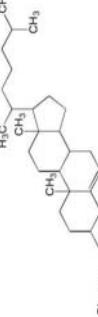
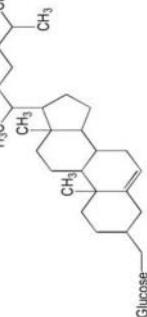
Garlic	<i>Allium sativum</i> (Liliaceae)	S-allyl cystine, S-allyl mercaptocysteine and allin	Antioxidant and anti-inflammatory	Paracetamol-induced wistar albino rats		Ebenyi et al., 2012
Garlic	<i>Allium sativum</i> (Liliaceae)	S-allyl cystine, S-allyl mercaptocysteine and allin	Antioxidant and anti-inflammatory	Alloxan-induced wistar albino rats		Asaduzzaman et al., 2012
Garlic	<i>Allium sativum</i> (Liliaceae)	S-allyl cystine, S-allyl mercaptocysteine and allin	Antioxidant and anti-inflammatory	isoniazid-induced wistar albino rats		Ilyas and Sadiq, 2011
Yam	<i>Amorphophallus paeoniifolius</i> (Araceae)	flavonoids and steroids	Antioxidant and anti-inflammatory	Paracetamol-induced wistar albino rats		Hurkdale et al., 2012
Winter melon	<i>Benincasa hispida</i> (Thunb.) (Cucurbitaceae)	vitamin E, beta-carotene, flavonols, and flavonoids,	Antioxidant and anti-inflammatory	Nimesulide-induced wistar albino rats		Das and Roy, 2011 (Continued on next page)

Table 4. (Continued)

Vegetables	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Common beet	<i>Beta vulgaris</i> (Amaranthaceae)	Betaxanthines and Betalins	Antioxidant and anti-inflammatory	CCl_4 -induced wistar albino rats		Agarwal et al., 2006; Pal et al., 2010
Common beet	<i>Beta vulgaris</i> (Amaranthaceae)	Betalins	Antioxidant and anti-inflammatory	CCl_4 -induced wistar albino rats		Rose et al., 2014
Common beet	<i>Beta vulgaris</i> (Amaranthaceae)	Betalins	Antioxidant and anti-inflammatory	Ethanol-induced wistar albino rats		Jain et al., 2012

Bitter gourd	<i>Momordica dioica</i> Roxb (Cucurbitaceae)	Flavonoids		Antioxidant and anti-inflammatory	CCl_4 -induced wistar albino rats	Jain et al., 2008
Bitter gourd	<i>Momordica charantia</i> L (Cucurbitaceae)	charantin, charine, cryptoxanthin, cucurbitin, cucurbitacins, cucurbitanes, cycloartenols, diosgenin, elaeostearic acids, erythroidol, galactouronic acids, gentisic acid, goyaglycosides, goyasaponins		Antioxidant and anti-inflammatory	Alloxan-induced wistar albino rats	Hossain et al., 2011
Bitter melon	<i>Momordica charantia</i> L (Cucurbitaceae)	momocharin, momordicin		Antioxidant and anti-inflammatory	CCl_4 -induced wistar albino rats	Semiz and Sen, 2007
Bitter melon	<i>Momordica charantia</i> L (Cucurbitaceae)	momocharin, momordicin, momordicin, momordicin, momordicin, momordicin, momordicin, momordol, charanthin, charine, cryptoxanthin, cucurbitins, cucurbitacins, cucurbitanes, cycloartenols, diosgenin, elaeostearic acids, erythroidol, galactouronic acids, gentisic acid, goyaglycosides, goyasaponins and multiflorenol		Antioxidant and anti-inflammatory	Ammoniumchloride-induced wistar albino rats	Thenmozhi, and Subramanian, 2011
Mustard	<i>Brassica juncea</i> (Brassicaceae)	Coumarin, Triterpenoids Glycoside		Antioxidant and anti-inflammatory	CCl_4 -induced wistar albino rats	John and Soba, 2011
Broccoli,	<i>Brassica juncea</i> (Brassicaceae)	momocharin, momordicin		Antioxidant and anti-inflammatory	CCl_4 -induced wistar albino rats	Al-Howiriny, 2008

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Table 4. (Continued)

Vegetables	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Broccoli, <i>Brassica oleracea</i> L. var. <i>Italica</i>	<i>Cucurbitacin, Cucurbitacin A, B, E</i> (Brassicaceae)		Antioxidant and anti-inflammatory	Paracetamol-induced wistar albino rats		Hashem et al., 2013
Cabbage var. <i>capitata f. alba</i>	Flavonoids		Antioxidant and Antihyperlipidemic	Alloxan-induced wistar albino rats		Asadujjaman et al., 2011
Snake gourd <i>Trichosanthes cucumerina</i> Var <i>cucumerina</i> L. (cucurbitaceae)	<i>Cucurbitacin, Cucurbitacin A, B, E</i>		Antioxidant and anti-inflammatory	CCl_4 -induced wistar albino rats		Kumar et al., 2009
Taro/Elephant ear <i>Colocasia antiquorum</i> (Araceae)	cyanidin-3-glucoside, pelargonidin-3-glucoside and cyanidin-3-rhamnoside		Antioxidant and anti-inflammatory	Paracetamol and CCl_4 -induced wistar albino rats and Swiss albino mice		Tuse et al., 2009

Taro	<i>Colocasia esculenta</i> (L)Schott (Araceae)	Cyanoglucoside, arabinogalactan and mono and digalactoyl diacylglycerols	Antioxidant and anti-inflammatory	paracetamol and CCl_4 using in vitro liver slice	Patil and Agreely, 2011
Bitter gourd	<i>Cucumis trigonus</i> Roxb. (Cucurbitaceae)	Cucurbitacin, Cucurbitacin A, B, E	Antioxidant and anti-inflammatory	CCl_4 -induced female wistar albino rats	Patil et al., 2011; Gopalakrishnan and Kalaiarasi, 2013
Bottle gourd	<i>Lagenaria siceraria</i> (Molina) Standl. (Cucurbitaceae)	cucurbitacins, fibers and polyphenols, flavoneglycosides Lagenin,	Antioxidant and anti-inflammatory	CCl_4 -induced female wistar albino rats	Lakshmi et al., 2011
Bottle gourd	<i>Lagenaria siceraria</i> (Molina) Standl. (Cucurbitaceae)	Lagenin, fucosterol and compesterolsflavonoids, cucurbitacins, saponins and polyphenolic triterpenoids and C-flavone glycosides and ellagitannins	Antioxidant and anti-inflammatory	CCl_4 -induced Sprague-Dawley rats and Swiss albino mice	Deshpande et al., 2008

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Table 4. (Continued)

Vegetables	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Wild mint	<i>Mentha arvensis</i> L. (Lamiaceae)	menthone, isomenthone, neomenthol, limonene, methyl acetate, piperitone, beta-caryophyllene, alpha-pinene, beta-pinene, tannins and flavonoids.	Antioxidant and anti-inflammatory	Alcohol- CCl ₄ -induced wistar albino rats		Radhika et al., 2011; Patil and Mall, 2012
Eru	<i>Gnetum africanum</i> (Gnetaceae)	Flavonoids, Nasunin	Antioxidant and anti-inflammatory	Paracetamol-induced wistar albino rats		Iweala and Osundiya, 2010
Tomato	<i>Solanum lycopersicum</i> L (Solanaceae)	Lycopene, β-carotene, vitamin C, quercetin glycosides, naringenin chalcone and chlorogenic acid	Antioxidant and anti-inflammatory	CCl ₄ -induced wistar albino rats		Weremfo et al., 2011
Eggplant	<i>Solanum melongena</i> L. (Solanaceae)	Flavonoids	Antioxidant and anti-inflammatory	CCl ₄ -induced wistar albino rats		Nuevo and Banzon, 2013; Hamzah et al., 2016

Eggplant	<i>Solanum melongena</i> L. (Solanaceae)	Flavonoids, Nasunin	Antioxidant and anti-inflammatory	Galactosamine-induced wistar albino rats	Nuevo and Banzon, 2013
Spinach	<i>Spinacia oleracea</i> L (Amaranthaceae)	β -carotene, lutein, zeaxanthine, flavonoids, vitamin C, Antioxidant and anti-inflammatory p-coumaric acid	β -carotene, lutein, zeaxanthine, flavonoids, vitamin C, Antioxidant and anti-inflammatory p-coumaric acid	CCl_4 -induced wistar albino rats	Gupta and Singh, 2006; Jain et al., 2012
Spinach	<i>Spinacia oleracea</i> L (Amaranthaceae)	β -carotene, lutein, zeaxanthine, flavonoids, vitamin C, Antioxidant and anti-inflammatory	β -carotene, lutein, zeaxanthine, flavonoids, vitamin C, Antioxidant and anti-inflammatory	Radiation-induced wistar albino rats	Gupta and Singh, 2006
Veldt Grape or Devil's Backbone	<i>Cissus quadrangularis</i> (Vitaceae)	β -carotene	β -carotene	Rifampicin-induced hepatotoxicity in rats	Swamy et al., 2012
Sweet corn	<i>Zea mays</i> var. <i>saccharata</i> (Grasses)	Corn peptide	Corn peptide	Bacillus Calmette–Guerin/lipopolysaccharide-induced hepatotoxicity in mice	Guo et al., 2009

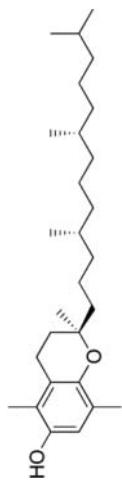
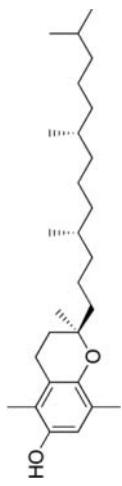
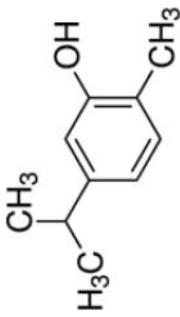
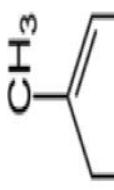
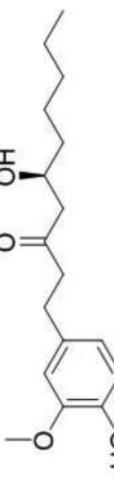
**Table 5.** Hepatoprotective effects of spices and condiments.

Spices and condiments	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Turneric	<i>Curcuma longa</i> L. (Zingiberaceae)	Polyphenolic curcuminooids including curcumin I, curcumin II, and curcumin III	Antioxidant properties; decrease the formation of proinflammatory cytokines	CCl_4 -induced wistar albino rats		Sakuntala Behura et al., 2002
Turneric	<i>Curcuma longa</i> L. (Zingiberaceae)	Curcumin	Antioxidant properties; decrease the formation of proinflammatory cytokines	CCl_4 -induced Swiss albino mice		Sengupta et al., 2011
Turneric	<i>Curcuma longa</i> L. (Zingiberaceae)	Polyphenoliccurcuminooids -demethoxycurcumin	Antioxidant properties; decrease the formation of proinflammatory cytokines	Galactosamine-induced wistar albino rats		Chattopadhyay et al., 2004
Turneric	<i>Curcuma longa</i> L. (Zingiberaceae)	Polyphenoliccurcuminooids -bis-demethoxycurcumin	Antioxidant properties; decrease the formation of proinflammatory cytokines	paracetamol induced wistar albino rats		Eigner et al., 1999
Turneric	<i>Curcuma longa</i> L. (Zingiberaceae)	Reversed biliary hyperplasia, fatty changes, and necrosis induced by aflatoxin production	Antioxidant properties; decrease the formation of proinflammatory cytokines	Aspergillusflavotoxin-induced wistar albino rats		Govindarajan, 1980
Kokum	<i>Garcinia indica</i> Choisy (Family: Clusiaceae/ Guttiferae)	Garcinol, hydroxycitric acid, citric acid, malic acid, polyphenols, anthocyanin pigments and ascorbic acid	Antioxidant properties	Ethanol-induced wistar albino rats		Panda et al., 2012

Cinnamon	Cinnamomum verum; Lauraceae	essential oil containing cinnamaldehyde and eugenol	Antioxidant properties	CCl_4 -induced wistar albino rats	Moselhy and Ali, 2009
Fenugreek	<i>Trigonella foenumgraecum</i> (Fabaceae)	Vitexin, tricin, naringenin, quercetin, and tricin- 7-O-beta- d -glucopyranoside	Antioxidant properties	Ethanol-induced wistar albino rats	Shang et al., 1998
	Propolis (mixture <i>Propolis/sanguolosa</i> ofgums, resins, and balsms)	Cinnamic acid, benzoic acid and their esters, substituted phenolic acid and ester, flavonoid glycones, bee wax, and caffeic acid phenylethylester	Antioxidant properties	Econazole-induced wistar albino rats	Su et al., 1994
Wild basil	<i>Ocimum gratissimum</i> ; (Lamiaceae)	eugenol, camphene, Licorice, anethole	Antioxidant properties	Ethanol-induced wistar albino rats	Chaturvedi et al., 2007
Chinese Magnolia bark	<i>Magnolia officinalis</i> ; (Magnoliaceae)	Honokiol and Magnolol	Antioxidant properties	Ethanol-induced RAW 264.7 cells	Yin et al., 2009

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Table 5. (Continued)

Spices and condiments	Botanical name and family	Bioactive food components	Specific mechanism	Model	Structure	References
Coriander	<i>Coriandrum sativum</i> L (Umbelliferae)	Tocopherols, carotenoids and phospholipids	Antioxidant properties	Lead nitrate-induced male Swiss albino mice		Kansal et al., 2011
Chinese parsley	<i>Coriandrum sativum</i> L (Umbelliferae)	Essential oils	Antioxidant properties	Lead nitrate-induced male ICR mice		Aga et al., 2001
Caraway	<i>Carum carvi</i> L. (Apiaceae)	carvacrol, carvone, α -pinene, limonene, γ -terpinene, linalool, carvenone, and p-cymene	Antioxidant properties	CCl ₄ -induced Male NMRI mice		Samoilik et al., 2010
Cumin	<i>Cuminum cyminum</i> (Apiaceae)	cuminaldehyde, limonene, α - and β -pinene, 1,8-cineole, o- and p-cymene, α - and γ -terpinene, safranal and linalool	Antioxidant properties	Profenofos-induced female Swiss albino mice		Kumar et al., 2011
Ginger	<i>Zingiber officinale</i> L (Zingiberaceae)	6-gingerol, 8-gingerol and zingerone	Antioxidant properties	Paracetamol-induced Sprague-Dawley albino rats		Yasin et al., 2010; Abdel-Azeem et al., 2013
Ginger	<i>Zingiber officinale</i> L (Zingiberaceae)	6-gingerol, 8-gingerol and zingerone	Antioxidant properties	CCl ₄ -induced wistar albino rats		Atta et al., 2010; Ezza et al., 2011

Ginger	Zingiber officinale L (Zingiberaceae)	6-gingerol,8-gingerol and zingerone	Antioxidant properties	adriamycin-induced wistar albino rats
				Sakr et al., 2011

Green tea	Camellia sinensis (Theaceae)	Catechins	Antioxidant properties	diethyl nitrosamine-induced wistar rat model
				Luper, 1999

Table 6. Hepatoprotective effects of bioactive compounds isolated from food.

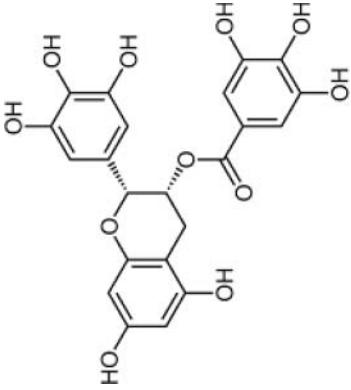
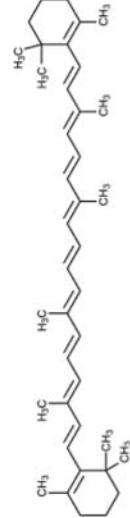
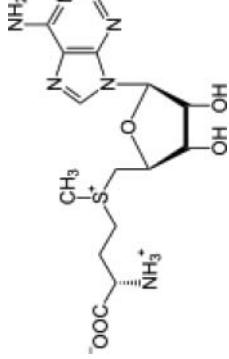
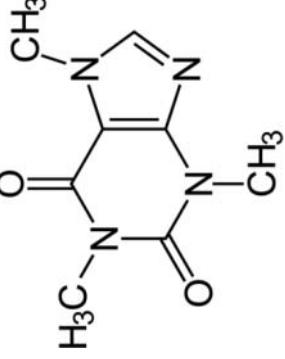
Sources of Bioactive food components	Active principle	Specific mechanism	Model	Structure	References
Carotenoid	Lutein	Antioxidant properties	Paracetamol-, carbon tetrachloride- and ethanol-induced wistar albino rats		Sindhu et al., 2010
Tomatoes, sweet corn, rice bran	Ferlic acid	Antioxidant properties	Alcohol- and heated PUFA-induced wistar albino rats		Rukkumani et al., 2004
Earthworm powder	Vitamin C and vitamin K	Antioxidant properties	Alcohol-induced wistar albino rats		Prakash et al., 2008
Flavonoids	(+)-cyanidanol-3	Antioxidant properties	Alcohol-induced male CFY rats		Varga and Buris, 1989; 1990
Vitamin B3	nicotinic acid amide	Antioxidant properties	Acetaminophen-induced female NMRI mice		Kröger et al., 1996

Berries of grapevine)	Resveratrol (3,5,4'-trihydroxystilbene)	Antioxidant properties	Seitz and Stickel, 2006; Assunção et al., 2009
Rheum	Resveratrol, Piceatannol, Rhapontigenin, Deoxyrhapontigenin	Antioxidant properties	Raal et al., 2009
Cherry tomato, onion, broccoli, tea, red wine, berries	Quercetin	Antioxidant properties	Yao et al., 2007; Yao et al., 2009
Turmeric	Curcumin	Antioxidant properties	Bao et al., 2010

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Table 6. (Continued)

Sources of Bioactive food components	Active principle	Specific mechanism	Model	Structure	References
Turmeric	Curcumin	Antioxidant properties	Lipopolysaccharide/D-galactosamine-induced liver injury in rats		Cerny et al., 2011
Turmeric	Curcumin	Antioxidant properties	In vitro liver slice		Naik et al., 2004
Hurricane weed	phyllanthin	Antioxidant properties	Alcohol-induced wistar albino rats		Chirddhupunserree and Pramyothin, 2010
green tea leaves	epigallocatechin gallate	Antioxidant properties	Alcohol-induced toxicity in HepG2 cells		Augustyniak et al., 2005; Lee et al., 2008

Green tea leaves	epigallocatechin gallate	Antioxidant properties		Quine, and Raghu, 2005
Carrot, coriander leaves	Beta carotene	Antioxidant properties		Lin et al., 2009
Spinach	Sadenosyl methionine	Antioxidant properties		Gong et al., 2008
Coffee	Caffeine	Antioxidant properties		Lv et al., 2010

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Table 6. (Continued)

Sources of Bioactive food components	Active principle	Specific mechanism	Model	Structure	References
Garcinia kola,	Kolaviron	Antioxidant properties	Alcohol-induced wistar albino rats		Adaramoye et al., 2009
Citrus fruits	Ascorbic acid	Antioxidant properties	CCl ₄ -induced wistar albino rats		Ozturk et al., 2009
Spinach	Vitamin E	Antioxidant properties	CCl ₄ -induced male wistar albino rats		Parola et al., 1992
Vegetable oil, seeds, nuts	Omega 3-polyunsaturated fatty acids	Antioxidant properties	Diabetic rats fed on a high fat thermolyzed diet		De Assis et al., 2012
Drumstick, Thymbra spicata	haw pectic oligosaccharide	Antioxidant properties	High fat diet-induced mice		Das et al., 2012; Li et al., 2014

Vegetable oil, seeds, nuts	Apolipoprotein A-I	Antioxidant properties	High fat diet-induced rabbits	Wang et al., 2013
Cabbage	Black cabbage sprout	Antioxidant properties	High fat diet-induced wistar albino rats	Melega et al., 2013
Citrus fruits and spinach	Vitamin C and E	Antioxidant properties	STZ-induced wistar albino rats	Naziroglu et al., 2011
Vegetable oils	Stobadine	Antioxidant properties	STZ-induced wistar albino rats	Cumaooglu et al., 2007
Berberis	Berberine	Antioxidant properties	STZ-induced wistar albino rats	Zhou and Zhou, 2011

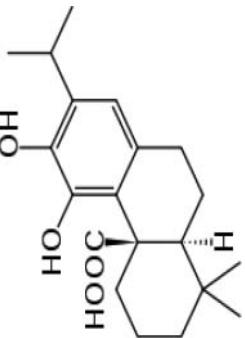
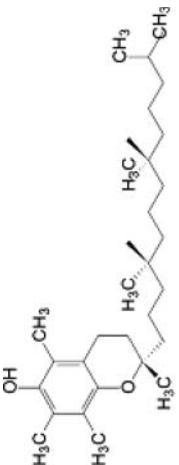
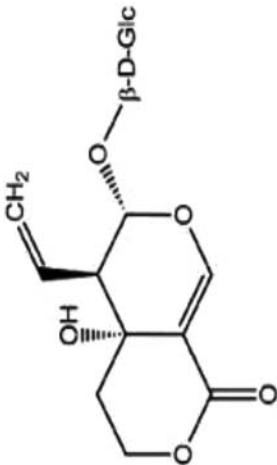
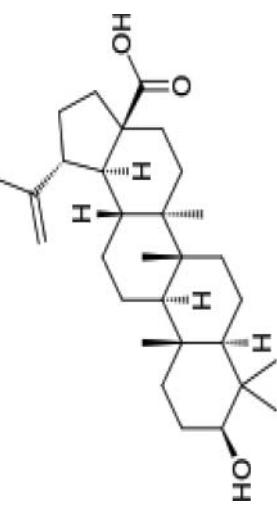
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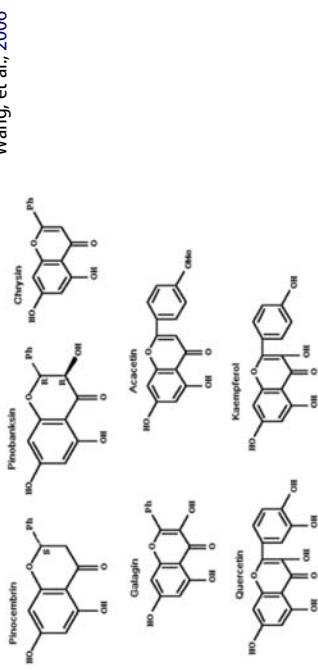
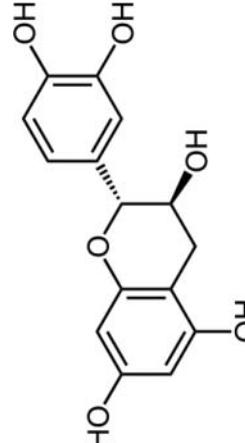
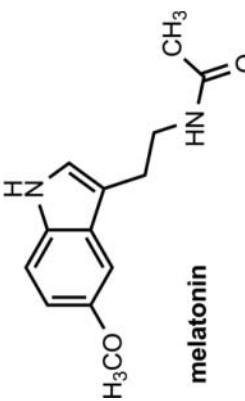
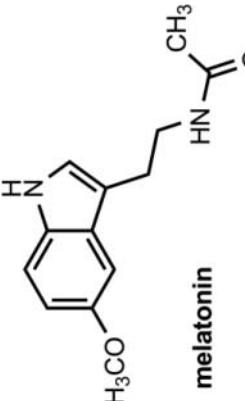
Sources of Bioactive food components	Active principle	Specific mechanism	Model	Structure	References
Pulses	N-Acetylcysteine	Antioxidant properties	STZ-induced wistar albino rats		Lei et al., 2012
Pulses	N-acetylcysteine	Doxorubicin-induced liver injury in rats			Kockar et al., 2010
olive-pomace oil	Maslinic acid	Antioxidant properties	STZ-induced wistar albino rats		Mkhwanazi et al., 2014
Wine, grapes, blueberries	Resveratrol	Antioxidant properties	STZ-induced wistar albino rats		Sadi et al., 2014

Berries, Onion	Galllic acid	Antioxidant properties	Paracetamol-induced liver toxicity in mice Rascol et al., 2010	
Lizard's tail	Sauchinone	Antioxidant properties	Paracetamol-induced liver toxicity in mice Kay et al., 2011	
Soy products, peas	Genistein	Antioxidant properties	Paracetamol-induced liver toxicity in mice Fan et al., 2013	
Gypsophila trichotoma	Saponarin	Antioxidant properties	Paracetamol-induced liver toxicity in rats Simeonova et al., 2013	

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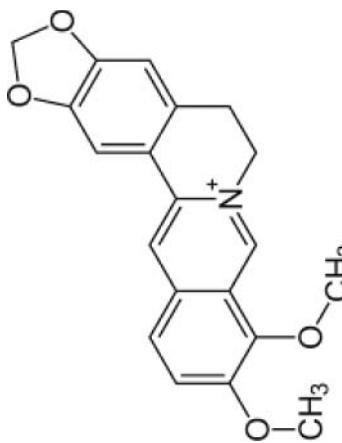
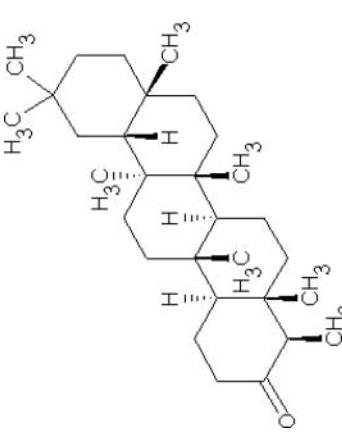
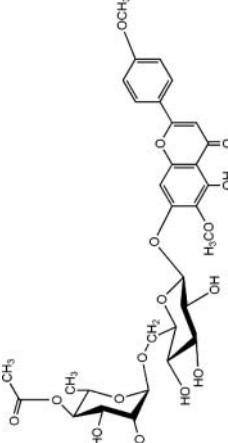
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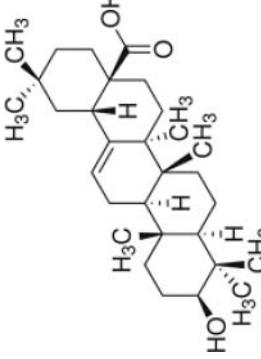
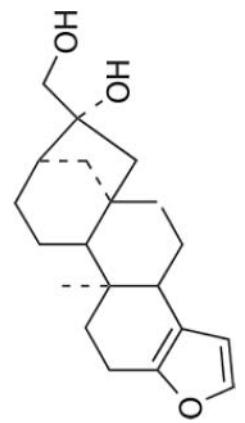
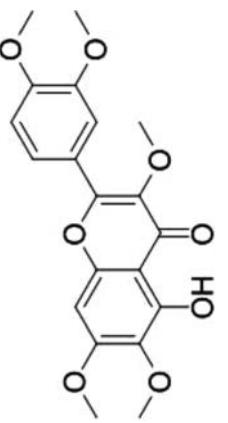
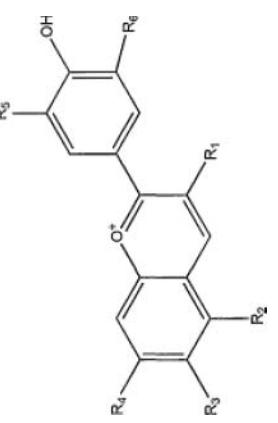
Sources of Bioactive food components	Active principle	Specific mechanism	Model	Structure	References
Rosemary and common sage	Carnosic acid	Antioxidant properties	Lipopolysaccharide-induced liver injury in rats		Xiang et al., 2013
Carrot and spinach	Combination of selenium, ascorbic acid, carotene, and tocopherol	Antioxidant properties	D-Galactosamine-induced liver injury in rats		Catal and Bolken, 2008
Ericostemma axillare	Swertiamarin	Antioxidant properties	D-Galactosamine-induced liver injury in rats		Jaishtree et al., 2010
bark of Betula alba, (white birch)	betulinic acid	Antioxidant properties	Lipopolysaccharide/D-galactosamine-induced liver injury in rats		Zheng et al., 2011

Gums, resins, honey combs, tree buds, bee glues	Propolis	Antioxidant properties	Tert-butyl hydroperoxide-induced liver injury in rats		Wang, et al., 2006
Tea	Catechin	Antioxidant properties	Tamoxifen-induced liver injury in mice		Tabassum et al., 2007
bananas and grapes, rice, wheat, barley, and oats	Melatonin	Antioxidant properties	Hepatic steatosis stimulated with tunicamycin		Kim et al., 2015
bananas and grapes, rice, wheat, barley, and oats	Melatonin	Antioxidant properties	Ethionine-induced liver injury in mice		Ferraro and Lopez-Ortega, 2008

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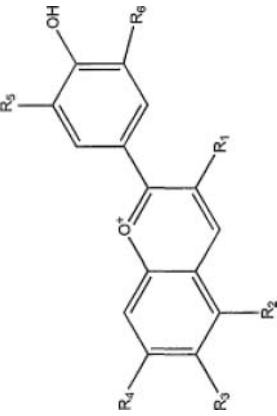
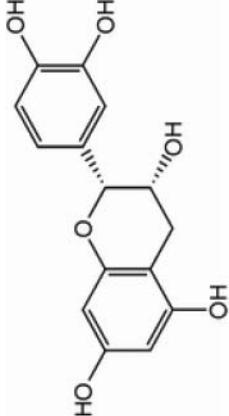
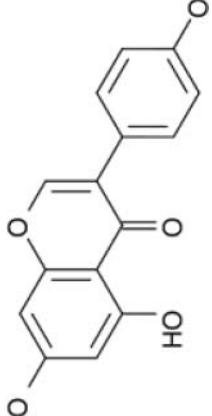
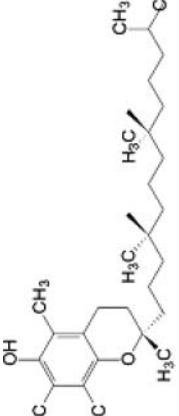
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Sources of Bioactive food components	Active principle	Specific mechanism	Model	Structure	References
Coptidis rhizome	berberine	Antioxidant properties	CCl ₄ -induced liver damage in rats		Feng et al., 2011
Azima tetraacantha	Friedelin	Antioxidant properties	CCl ₄ -induced liver damage in rats		Adegbesan et al., 2007
Morus bombycis	2,5-dihydroxy-4,31-di(α-D-glucopyranosyloxy)-trans-stilbene	Antioxidant properties	CCl ₄ -induced liver damage in rats		Jin et al., 2005; 2006

Actinidia deliciosa	Oleanolic acid	Antioxidant properties		Bai et al., 2007
Coffee	Kahweol and cafestol	Antioxidant properties		Lee et al., 2007
Vitex	Artemetin	Antioxidant properties		Sridhavi et al., 2012
Blueberry	Blueberry anthocyanins	Antioxidant properties		Chen et al., 2007

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Table 6. (Continued)

Sources of Bioactive food components	Active principle	Specific mechanism	Model	Structure	References
Blackrice bran	Anthocyanins	Antioxidant properties	CCl ₄ -induced liver damage in mice		Hou et al., 2013
Grape seeds	Proanthocyanidins	Antioxidant properties	CCl ₄ -induced liver damage in rats		Dai et al., 2014
Soy products, peas	Genistein	Antioxidant properties	TAA-induced liver injury		Saleh et al., 2014
Spinach	Vitamin E and selenium	Antioxidant properties	Cigarette smoking induced oxidative damage in liver of mice		Ozkan et al., 2007

Vegetable oils	Vitamin E	Antioxidant properties	Atrazine exposure rats	Singh et al., 2014
Green leafy vegetables and citrus fruits	Vitamins C and E	Antioxidant properties	Methidathion-induced liver injury in rats	Sutcu et al., 2006
Vegetable oils	Vitamin E	Antioxidant properties	Polychlorinated biphenyl-induced hepatic damage in rats	Banudevi et al., 2006
clove oil, nutmeg, cinnamon, basil, Eugenol and bay leaf.		Antioxidant properties	Thioacetamide-induced hepatic damage in rats	Yogalakshmi et al., 2010
purple sweet potato	Anthocyanins	Antioxidant properties	Dimethylnitrosamine-induced hepatic damage in rats	Hwang et al., 2011

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Table 6. (Continued)

Sources of Bioactive food components	Active principle	Specific mechanism	Model	Structure	References
Garlic juice	ascorbic acid	Antioxidant properties	Cadmium-induced hepatic injury in rats		Lawal et al., 2011
Wine, grapes, blueberries	Resveratrol	Antioxidant properties	As2O3-induced hepatotoxicity in cat		Zhang et al., 2014
Morinda pubescens	Hyoscyamine	Antioxidant properties	Human liver cancer cell line		Kumar and Santhi, 2012; Choi et al., 2013
Pleurotus pulmonarius (edible mushroom)	Flavonoids, triterpenoids	Antioxidant properties	Liver cancer of mice		Xu et al., 2014

Silimaricin	Silybin	Antioxidant properties	Rat with secondary biliary cirrhosis		Serviddio et al., 2014
Green tea	Catechin	Antioxidant properties	Cholestatic rats with bileduct ligation		Kobayashi et al., 2010
Tea	Epigallocatechin-3-gallate	Antioxidant properties	Bile duct-ligated cholestatic rats		Yu et al., 2015
Volatileoil of black seed	Thymoquinone	Antioxidant properties	Bile duct-ligated cholestatic rats		Oguz et al., 2012

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Table 6. (Continued)

Sources of Bioactive food components	Active principle	Specific mechanism	Model	Structure	References
Soy bean	N-acetylcysteine	Antioxidant properties	Bile duct-ligated cholestatic rats		Galicia-Moreno et al., 2012
Bananas/grapes, rice, wheat, barley, and oats	Melatonin	Antioxidant properties	Bile duct-ligated cholestatic rats		Ohta et al., 2003
Bananas/grapes, rice, wheat, barley, and oats	Melatonin	Antioxidant properties	Ischemia/reperfusion in obese rats with fatty liver		Kireev et al., 2013

Hepatoprotective effects of pulses

In vivo and *in vitro* experimental animal model studies provided that pulses exert potent hepatoprotective activities, as summarized in Table 2.

Hepatoprotective effects of fruits

In vivo and *in vitro* experimental animal model studies provided that fruits exert potent hepatoprotective activities, as summarized in Table 3.

Hepatoprotective effects of vegetables

In vivo and *in vitro* experimental animal model studies provided that vegetables exert potent hepatoprotective activities, as summarized in Table 4.

Hepatoprotective effects of spices and condiments

In vivo and *in vitro* experimental animal model studies provided that spices and condiments exert potent hepatoprotective activities, as summarized in Table 5.

Hepatoprotective effects of bioactive compounds isolated from food

In vivo and *in vitro* experimental animal model studies provided that various bioactive compounds isolated from food exert potent hepatoprotective activities, as summarized in Table 6.

Conclusion and future perspective

Several studies in the last decade have clearly demonstrated that bioactive food components possess hepatoprotective activity against diverse xenobiotic agents. Numerous mechanisms are likely to interpret pharmacological effects. However, the most imperative mechanism of hepatoprotection, which are mediated by free radical scavenging, antioxidant, and anti-inflammatory effects and thereby bioactive food compounds elevate the endogenous antioxidant enzymes in the body. Besides, bioactive food compounds augment the metabolism of hepatotoxic drugs and by mitochondrial CYP phase, I & II enzymes and finally all active metabolites detoxified by bile kidney. This comprehensive review will be helpful to begin anew avenue and to investigate further clinical applications of bioactive compounds as chemotherapeutic agents. Since it's plenty of availability, cheap, and safety of ingestion, bioactive compounds remain in a dietary food with remarkable potential and uncountable promises for further investigation. However, a great number of investigations have been directed at preclinical level, and numerous bioactive food compounds have been recognized as an effective hepatoprotective agent, more clinical studies are mandatory for authentication. Further, it is an appropriate time to cover the possibility of the study of the hepatoprotective potential of new bioactive food compounds for human health.

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Conflict of interest

None

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