

## Review of natural products with hepatoprotective effects

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### Abstract

The liver is one of the most important organs in the body, performing a fundamental role in the regulation

of diverse processes, among which the metabolism, secretion, storage, and detoxification of endogenous and exogenous substances are prominent. Due to these functions, hepatic diseases continue to be among the main threats to public health, and they remain problems throughout the world. Despite enormous advances in modern medicine, there are no completely effective drugs that stimulate hepatic function, that offer complete protection of the organ, or that help to regenerate hepatic cells. Thus, it is necessary to identify pharmaceutical alternatives for the treatment of liver diseases, with the aim of these alternatives being more effective and less toxic. The use of some plants and the consumption of different fruits have played basic roles in human health care, and diverse scientific investigations have indicated that, in those plants and fruits so identified, their beneficial effects can be attributed to the presence of chemical compounds that are called phytochemicals. The present review had as its objective the collecting of data based on research conducted into some fruits (grapefruit, cranberries, and grapes) and plants [cactus pear (*nopal*) and cactus pear fruit, chamomile, silymarin, and spirulina], which are consumed frequently by humans and which have demonstrated hepatoprotective capacity, as well as an analysis of a resin (propolis) and some phytochemicals extracted from fruits, plants, yeasts, and algae, which have been evaluated in different models of hepatotoxicity.

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**Key words:** Hepatoprotection; Grapefruit; *Vaccinium* spp; *Vitis vinifera* L; *Opuntia ficus-indica*; Spirulina; Propolis; Glucans; Alcoholic liver disease

**Core tip:** Currently, diverse natural products have been studied, in attempts to identify protective effects against agents that cause disease. In this paper, we conduct a review of diverse natural products which, by means of their antioxidant activity, protect the liver

from the damage caused by substances such as ethanol, acetaminophen, carbon tetrachloride, thioacetamide, *etc.*

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## INTRODUCTION

The liver is one of the most important organs of the body. It performs a fundamental role in the regulation of diverse physiological processes, and its activity is related to different vital functions, such as metabolism, secretion, and storage. Its capacity to detoxify endogenous (waste metabolites) and/or exogenous (toxic compounds) substances of organisms, as well as for synthesize useful agents, has been analyzed since the 1970s by many researchers<sup>[1-4]</sup>.

The liver is also involved in the biochemical processes of growing, providing nutrients, supplying energy, and reproducing. In addition, it aids in the metabolism of carbohydrates and fats, in the secretion of bile, and in the storage of vitamins<sup>[5]</sup>.

Because of all of these functions, hepatic diseases continue to among the principal threats to public health, and they are a problem worldwide<sup>[4,6]</sup>. Hepatic disease is a term that indicates damage to the cells, tissues, structure, or liver function, and this damage can be induced by biological factors (bacteria, virus, and parasites) and autoimmune diseases (immune hepatitis, primary biliary cirrhosis), as well as by the action of different chemicals, such as some drugs [high doses of paracetamol (PCM) and antitubercular drugs], toxic compounds [carbon tetrachloride (CCl<sub>4</sub>), thioacetamide, dimethylnitrosamine (DMN), D-galactosamine/lipopolysaccharide (GalN/LPS)], and unquestionably, excessive consumption of alcohol<sup>[7-9]</sup>. Despite enormous advances in modern medicine, there are no completely effective drugs that stimulate hepatic function, offer complete protection to the organ, or aid in regenerating hepatic cells<sup>[10]</sup>. Additionally, some drugs can induce adverse or side effects. Thus, it is necessary to identify alternative pharmaceuticals for the treatment of hepatic diseases, with the aim of these agents being more effective and less toxic.

The use of some plants and the consumption of different fruits have played fundamental roles in human health care. Approximately 80% of the world's population has employed traditional medicine for health care, which is based predominantly on plant materials<sup>[4,9]</sup>. Diverse scientific investigations of medicinal plants and the ingestion of fruits have indicated that the properties

that are responsible for their beneficial effects could be attributed to the presence of chemical compounds or substances that are biologically active and that are non-essential nutrients for life, called phytochemicals<sup>[11]</sup>.

In the literature, studies can be found that have examined the impact that different phytochemicals exert on health. Among the most frequently cited examples, we find the following: (1) the vinca alkaloids (vincristine, vinblastine, and vindesine); (2) the betalain pigments (betanin and indicaxanthine); (3) the anthocyanins (cranberries); and (4) and resveratrol; all of these have generally been analyzed based on their chemoprotective properties against cancer<sup>[4,12-14]</sup>. All of the medicinal plants, as well as the ingestion of certain fruits, have demonstrated different effects on living systems. Although there have been diverse studies directed toward the evaluation of their hepatoprotective potential, the majority of investigations have been directed at analysis of their sedative, analgesic, antipyretic, cardioprotective, antibacterial, antiviral, anti-protozoal, and anticarcinogenic capacities<sup>[15]</sup>.

In addition to these studies, empirical evidence for the use of natural remedies for the treatment of hepatic diseases has a long history, and this field has become an innovative field of study, with the principal aim of analyzing the consumption of traditional fruits and medicinal plants by a great number of people and the different phytochemicals that are extracted from these foods. In general, liver-protective fruits, as well as plants, contain a variety of chemical compounds, such as phenols, coumarins, lignans, essential oils, monoterpenes, glycosides, alkaloids, carotenoids, flavonoids, organic acids, and xanthenes<sup>[16]</sup>.

This present review had as its objective the gathering of data based on works conducted in some fruits and plants that are consumed frequently by humans and that have demonstrated hepatoprotective capacity, as well as analysis of a resin and some phytochemicals extracted from fruits, plants, yeasts, and algae that have been evaluated in different models of hepatotoxicity. With these goals in mind, the authors of this paper have attempted to provide information and bibliographic support to researchers who are exploring compounds with this potential and to encourage the development of new investigations in this area of study.

## HEPATOPROTECTIVE FRUITS

### Grapefruit (*Citrus paradisi*)

**Overview:** The grapefruit is an important member of the genus *Citrus* of the Rutaceae family, the scientific name of which is *Citrus paradisi*. The grapefruit originated on Barbados Island, but it is currently cultivated in Mexico, Spain, Morocco, Israel, Jordan, South Africa, Brazil, and Jamaica and on the Asian continent<sup>[17]</sup>. In addition to its being consumed as a seasonal fruit or in juice to accompany other foods, it has been used in many countries in popular and traditional medicine as an antimicrobial, antifungal, anti-inflammatory, antioxidant, and antiviral, as an astringent solution, and as a preservative agent<sup>[18]</sup>.

Studies conducted over past decades have suggested that the grapefruit might be active in cellular regeneration, cholesterol reduction, the detoxifying process, and the maintenance of heart health, in rheumatoid arthritis, for the control of body weight, and in cancer prevention<sup>[17-19]</sup>. Grapefruit juice is an excellent source of many phytochemicals and nutrients that contribute to a healthy diet. It contains significant levels of vitamin C, folic acid, phenolic acid, potassium, calcium, iron, limonoides, terpenes, monoterpenes, and *D*-glucaric acid. The red and pink varieties also contain beta-carotene and lycopene, antioxidants that the body can convert into vitamin A<sup>[17]</sup>. However, the flavonoid that has the greatest concentration is naringin, which humans metabolize into naringenin<sup>[20,21]</sup>.

**Hepatoprotective evidence for naringin and naringenin:** Despite the common consumption of the grapefruit as a fresh fruit or in juice, there have been no studies that have directly analyzed its protective effects against the damage produced by hepatotoxic substances. The main evidence that is able to suggest its hepatoprotective potential has emerged from the study of naringenin and naringin.

One of the first studies was the investigation performed by Parmar<sup>[22]</sup>, who evaluated in rats the antiulcer activity of inhibiting histidine decarboxylase in retention ulcers and in phenylbutazone- and aspirin-induced pyloric ligatures. Their results showed that naringenin significantly reduced mucosa damage in both models, with a greater effect observed in ulcers with pyloric ligation, suggesting that the protective mechanism of naringenin involved inhibition of the formation and release of endogenous histamine in the gastric mucosa of rats.

These results motivated other investigations specifically into hepatoprotective effects; thus, the protective capacity of naringenin on dimethylnitrosamine (DMN)-induced hepatic damage in rats was investigated in 2004. Oral administration of naringenin (20 and 50 mg/kg daily over 4 wk) notably diminished DMN-induced damage when the weight of the liver was evaluated, as well as alanine transaminase (ALAT), aspartate transaminase (ASAT), alkaline phosphatase (ALP), and bilirubin levels. Naringenin also restored natural protein levels in serum and albumin and hepatic malondialdehyde (MDA) levels. In conclusion, it was demonstrated that naringenin had antifibrogenic and hepatoprotective effects, suggesting that it could be useful in the treatment of hepatic fibrosis<sup>[23]</sup>.

Taken together, the results of the two most recent studies indicated that this flavonoid is a biologically active compound that is capable of significantly reducing levels of serum ALAT and ASAT, gamma-glutamyl transpeptidase (GGT), thiobarbituric acid-reactive substances (TBARS) tissue, conjugated dienes, lipid hydroperoxides, protein carbonyl content, bilirubin, ALP, lactate dehydrogenase (LDH), and phase I enzymes and of increasing the activity of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GRx), glutathione-S-transferase (GST), alco-

hol dehydrogenase (ADH), and aldehyde dehydrogenase (ALDH), as well as the levels of vitamins C and E in tissues and phase II enzymes in rats with ethanol-treated hepatic damage in comparison to animals not receiving treatment<sup>[24,25]</sup>.

With respect to naringin, the sole study that found evidence of the hepatoprotective capacity of this flavonoid was the investigation of Seo *et al.*<sup>[26]</sup>, who analyzed the role of a naringin supplement in the regulation of lipid and ethanol metabolism in male Sprague-Dawley rats. These animals were organized into six groups based on the following six dietary categories: ethanol- and naringin-free; ethanol (50 g/L) plus low-naringin (0.05 g/L); ethanol plus high-naringin (0.125 g/L); and three corresponding pair-fed groups. The pair-fed control rats received an isocaloric diet containing dextrin-maltose instead of ethanol for 5 wk. Among the ethanol-treated groups, naringin supplements significantly lowered the plasma ethanol concentration, with simultaneous increases in ADH and/or ALDH activity. However, among the ethanol-treated groups, naringin supplementation resulted in a significant decrease in hepatic triglycerides (TGs) and plasma and hepatic total cholesterol (TC), compared with the naringin-free group. Naringin supplementation significantly increased high-density lipoprotein-c (HDL-cholesterol) and HDL-c/TC ratio, while lowering the AI value among the ethanol-treated groups. Hepatic lipid accumulation was also significantly reduced in the naringin-supplemented groups compared with the naringin-free group among ethanol-treated groups, while no differences were found among the pair-fed groups. Among the ethanol-treated groups, low-naringin supplementation resulted in a significant decrease in the levels of plasma and hepatic TBARS, whereas it resulted in higher SOD and GPx activities and higher glutathione (GSH) levels in the liver. Accordingly, naringin would appear to contribute to alleviating the adverse effects of ethanol ingestion by enhancing ethanol and lipid metabolism, as well as promoting the hepatic antioxidant defense system.

### **Blueberries/cranberries (*Vaccinium spp*)**

**Overview:** Among the small, soft-fleshed, colorful fruits, berries make up the largest proportion consumed in our diets. These fruits are not only ingested in their fresh and/or frozen forms, but they also appear in processed products, such as canned fruits, yogurts, beverages, jams, and jellies. Thus, in recent years, the consumption of berry extracts has increased as an ingredient in functional foods and dietary supplements, which might or might not be combined with other colored fruits, plants, and herbal extracts. The berry fruits that are habitually consumed in North America include blackberries (*Rubus spp*), black raspberries (*Rubus occidentalis*), red raspberries (*Rubus idaeus*), strawberries (*Fragaria X ananassa*), blueberries (*Vaccinium corymbosum*), and cranberries (*Vaccinium macrocarpon*)<sup>[14]</sup>.

At the 2007 International Berry Health Benefits Symposium, diverse research from Asia, Europe, New Zealand, Mexico, and North and South America were

presented that demonstrated the potential benefits that could be obtained by consuming these fruits. In general, it was concluded that these benefits could be observed in cardiovascular diseases, neurodegenerative diseases, and other diseases associated with aging, in obesity, and in some human cancers (mainly esophageal and gastrointestinal)<sup>[27]</sup>. It was determined that the agents responsible for these biological properties were diverse phenolic-type phytochemicals, among which the following were highlighted (1) flavonoids (anthocyanines, flavonols, and flavanols); (2) tannins [condensed tannins (proanthocyanidins) and hydrolyzable tannins (ellagitannins and gallotannins)]; (3) stilbenoids; and (4) phenolic acids<sup>[14]</sup>. Of all of these compounds, those that have been most studied are the anthocyanins (pigments are responsible for the berries' attractive colors), which have demonstrated antioxidant, anticarcinogenic, and anti-inflammatory biological activity<sup>[14,28]</sup>.

#### Hepatoprotective evidence for the berry fruits and proanthocyanidins:

Oxidative stress (OS) and dysfunction of cellular immunity are important indicators in the pathogenesis of hepatic diseases caused by diverse xenobiotics<sup>[29]</sup>. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is an important transcription factor that regulates OS reactions and is in charge of controlling two antioxidant enzymes: HO-1 and *Nqo1*<sup>[30-32]</sup>. This antecedent motivated Wang *et al.*<sup>[32]</sup> to evaluate the effects of the blueberry on liver protection and cellular immune function. The authors randomly submitted male Kunming mice 6-8 wk of age to two experiments: in the first, they extracted samples of hepatic RNA with the Trizol reagent (Invitrogen, United States) and determined the expression of Nrf2, HO-1, and *Nqo1* by real-time reverse transcription-polymerase chain reaction, as well as the quantification of SOD and MDA after administering blueberries orally (0.6 g/10 g) over 21 d; in the second experiment, the animals received blueberries over 35 d with the aim of evaluating cellular immune function and quantifying the percentage of CD3<sup>+</sup>, CD4<sup>+</sup>, and CD8<sup>+</sup> T lymphocyte subgroups in peripheral blood by flow cytometry, as well as the thymus index and lymphocyte proliferation in the spleen by MTT tetrazolium-dye assay. The results indicated that treatment with this fruit significantly increased the expression of Nrf2, HO-1, and *Nqo1*, as well as the percentages of the CD3<sup>+</sup> and CD4<sup>+</sup> T lymphocyte subsets. It also increased the spleen index, improving the proliferation of lymphocytes deriving from this organ, increasing hepatic SOD, and reducing MDA. In conclusion, the authors suggested that consuming this berry type protected hepatocytes from OS and could modulate the function of T cells.

As mentioned in the overview, different types of berries are consumed frequently, and among these, the cranberry was the topic of an experiment with the primary objective of evaluating its antioxidant and hepatoprotective potential against liver mitochondrial damage induced by acute [0.8 g/kg body weight (*bw*), single injection] and chronic (1.6 g/kg *bw*, 30 d, biweekly injections) CCl<sub>4</sub>

intoxication in rats. Both acute and chronic intoxication negatively affected the mitochondrial respiratory parameters in the liver, and the enzymatic activities of succinate dehydrogenase, GPx, and cytoplasmic catalase were significantly inhibited. However, administration of cranberries (7 mg/kg) was effective in diminishing the toxic effects of CCl<sub>4</sub>, normalizing ALAT and ASAT activity and bilirubin concentrations. Similarly, it prevented accumulation of membrane lipid peroxidation products in the rat liver, resulting in apparent preservation of the mitochondrial ultrastructure<sup>[33]</sup>.

It is important to remember that the anthocyanins and proanthocyanidins are widely available compounds in fruits, vegetables, and seeds of natural origin. Specifically, the proanthocyanidins are a class of phenolic compounds that have demonstrated a broad range of biological effects; therefore, Shin *et al.*<sup>[34]</sup> investigated the protective effects of these compounds against DMN-induced hepatic lesions in rats. Treatment with DMN caused significant increases in the levels of serum ALAT, ASAT, ALP, and bilirubin, but on administering proanthocyanidins orally (20 mg/kg daily over 4 wk), these authors observed a significant reduction in these parameters, as well as the normalization of serum albumin and total protein levels and a reduction in the hepatic level of MDA. In contrast, accumulation of DMN-induced collagen, observed in the histological analysis of Sirius red-stained tissue, was reduced in rats treated with proanthocyanidins. In conclusion, the authors' results demonstrated that these phenols showed hepatoprotective potential *in vivo* and antifibrogenic effects against DMN-induced hepatic lesions, suggesting that the proanthocyanidins (derived from cranberries, as well as from other fruits) could be useful in the prevention of hepatic fibrosis.

#### Grape (*Vitis vinifera* L)

**Overview:** The grape (the scientific name of which is *Vitis vinifera*) is a woody climbing plant that, when growing in its free state, can reach up to 30 m; however, due to the human action of annual pruning, it often remains reduced to a small, 1-m shrub. The grape is a fruit of the vine, it is edible, and it is the raw material for the manufacture of wine and other alcoholic beverages. Viticulture began in Asia and Southeastern Europe, and as a result of this development, the grape is an indispensable element in the feeding of humans, and its cultivation has extended to the American and African continents. There are approximately 3000 varieties of grapes in the world, although not all of these are equally appreciated. According to their final use, grapes are classified into two large groups: (1) those designated for consumption with meals (table grapes); and (2) wine grapes, which are employed for the creation of wine<sup>[35,36]</sup>. The leaves, as well as the fruit, are a stupendous source of vitamins and minerals and other active ingredients (Table 1); medicinal properties have been attributed to these components, which is why some authors have considered the grape to be a drug-food<sup>[37,38]</sup>. From the different parts of this plant,

**Table 1** Main active ingredients of the grape

Active ingredient	Compounds
Carbohydrates	Glucose, fructose, saccharose, dextrose, yeast, and levulose
Vitamins	Vitamin C and vitamin B <sub>6</sub>
Beta-carotene	Vitamin A
Tannins	Resveratrol
Minerals	Potassium, magnesium, calcium, sulfur, iron, and manganese
Flavonoids	Quercetin

particularly from the fruit, different preparations have been obtained that have been used in popular and traditional medicine, highlighting laxative, astringent, diuretic, cicatrissant, immunological stimulant, anti-inflammatory, and hypocholesterolemic activities, as well as chemopreventive activity against cardiovascular disease and some cancers (mainly prostate and colon)<sup>[39,40]</sup>.

**Hepatoprotective evidence for the grape and its phytochemicals:** Diverse studies have shown that grape juice and grape seeds (GS) are rich sources of flavonoids, such as catechins, epicatechins, anthocyanidins, proanthocyanidins, and resveratrol<sup>[39,40]</sup>, compounds, which, similar to the fruit and juice, have aroused great interest due to their biological effects. The first studies on hepatoprotection conducted on grapes were focused on the analysis of the antioxidant capacity of the skin and seed using TBARS testing in laboratory animals intoxicated with alcohol. The experimental design, developed by Peruvian scientists of the Universidad Nacional Mayor de San Marcos, consisted of comparing a group of animals that freely consumed a triturated and dry mixture of grape skin-seeds, which they ingested from a drinking fountain in a 5% alcohol solution, against two experimental lots of animals treated only with 5% alcohol (positive control) or with the dry mixture of grape seeds. The evaluation of hepatic tissue to measure OS levels consisted of extracting the animals' livers, weighing them, evaluating them for hepatomegaly, and analyzing their lipoperoxidation by means of TBARS at 24, 48, and 72 h, as well as later, on days 5 and 7 of treatment. Their results showed that hepatomegaly presented from 24 h (36.68% increase in hepatic mass) in the alcohol group, which was less than in the skin-seeds lot. A very similar phenomenon was seen with the TBARS test, and additionally, the skin-seeds plus alcohol group exhibited a reduction in this parameter as the treatment time advanced, obtaining the best protection on days 5 and 7<sup>[39]</sup>. These results motivated further exploration in this field of study; thus, in 2008, the antioxidant activity of two different types of grape was investigated (the juice of the organic purple grape and the juice of the conventional purple grape). The antioxidant activity of both juices was evaluated using an animal model of three groups: control, organic, and conventional. After 30 d, the animals were sacrificed, and their blood and livers were recovered to evaluate lipid peroxidation

levels (TBARS assay), protein oxidative levels (carbonyl assay), and CAT and superoxide dismutase (SOD) activities. The group treated with organic grape juice exhibited the highest SOD and CAT activity in the plasma and liver, compared with the conventional and control groups. Both types of juice were capable of reducing carbonyl and lipid peroxidation levels in the plasma and liver. However, in the plasma, the organic group showed lower carbonyl and TBARS levels, compared to the conventional grape juice group. This finding demonstrated that the ingestion of black grape juice, especially of organic juice, induced better antioxidant effects compared with conventional juice and that this difference could be an important problem for future investigations in the area of functional biochemical foods. Similarly, secondary data from this same investigation showed that in plasma, there was a positive correlation among SOD and CAT activities, resveratrol, and the content of anthocyanins; thus, it was suggested that these polyphenols could be, at least in part, responsible for this increase in antioxidant defense and protection against alcohol<sup>[41]</sup>.

In a study recently performed by Dogan and Celik<sup>[42]</sup>, the authors evaluated the hepatoprotective effects and antioxidant role of GS against ethanol-induced OS by measuring the liver damage serum marker enzymes ASAT, ALAT, GGT, and LDH and antioxidant defense systems, such as GSH, GRx, SOD, GST, GPx, and MDA, in rats. The results that the authors obtained from the four experimental groups [I (control), II (20% ethanol), III (15% GS), and IV (20% ethanol + 15% GS)] indicated that the levels of serum marker enzymes were significantly increased in the ethanol-treated group (II) compared with group I and that this level notably decreased with both compounds (group IV). Additionally, they observed that administration of GS-supplemented food restored ethanol-induced MDA, which was increased to near the control level. These results newly confirmed that GS, as well as grape juice, could be an important antioxidant supplement in the diet for the prevention of oxidative damage to tissues, by reducing lipoperoxidation or inhibiting the production of ethanol-induced free radicals.

With regard to the grape's phytochemicals, resveratrol has been the most studied of these compounds as a possible hepatoprotective agent. In this regard, there has been evidence that resveratrol exerts a protective effect by controlling chronic intoxication due to ethanol<sup>[43]</sup> and by reducing the damage caused by hepatocarcinogens, such as azoxymethane (AOM)<sup>[44]</sup>. In the first study, the authors evaluated whether a dietary supplement of resveratrol could attenuate lipid peroxidation, the result of oxidative damage induced by the chronic administration of 35% ethanol. The results that the authors obtained after daily intraperitoneal (*ip*) administration of ethanol for 6 wk were that MDA levels increased in liver, heart, brain, and testicles. However, when the animals were treated with ethanol plus resveratrol (5 g/kg), the increase in MDA levels was significantly reduced in all of the organs. Based on these results, the authors concluded that

this tannin was capable of inhibiting ethanol-induced lipoperoxidation, and it exerted a protective effect against oxidative damage. Very likely with the aim of confirming these results, Gürocak *et al.*<sup>[44]</sup> conducted a new study, the principal objective of which was to evaluate whether resveratrol could protect liver tissues against the effects of AOM, a chemical carcinogen that causes *de novo* hepatic damage. Their study was organized into four groups, each of which consisted of seven rats; group 1 only received AOM (twice weekly, 5 mg/kg); group 2 was treated with AOM plus resveratrol (twice weekly, 20 mg/kg); group 3 was considered the control group; and the animals in group 4 were administered resveratrol alone. At the end of the seven week, the animals were sacrificed to perform a biochemical analysis of MDA, nitric oxide (NO), and GSH levels in the liver. In general, it was found that the group concomitantly administered resveratrol had significantly reduced MDA and NO levels and that they had increased GSH, resulting in the new conclusion that this tannin most likely could exert protective effects against the oxidative damage caused by chemical carcinogens, including AOM.

## HEPATOPROTECTIVE PLANTS

### *Nopal (Cactus pear) and tuna (Cactus pear fruit) "Opuntia ficus-indica"*

**Overview:** Plants of the genus *Opuntia* are the most abundant of the Cactaceae family, which is cultivated throughout the American continent, as well as in the central zone of the Mediterranean, Europe, Asia, Africa, and Australia. The majority of *Opuntia* spp. present flat stems called *penca*s or cladodes (paddles), and the most common variety is the cactus pear (*nopal*)<sup>[45]</sup>. The fruits of this plant [called cactus pear fruits (*tunas*) or prickly pear fruits] are oval berries with a large number of seeds and a semihard bark containing thorns, and they are grouped by their different colors (red, purple, orange/yellow, and white). Generally, fruit with white pulp and green skin is preferred for consumption as food, and its domestic production corresponds to nearly 95% of the total production worldwide. Mexico is the primary producer of cactus pear fruits, representing more than 45% of world production; however, only 1.5% of this production is exported<sup>[45]</sup>. Cactus pear fruit, as well as prickly pear fruit, has been employed for a long time in traditional medicine as a treatment for different pathologies, such as ulcers, dyspnea, and glaucoma, as well as for liver diseases, wounds, and fatigue<sup>[45,46]</sup>.

Different studies performed in European and Asiatic prickly pear varieties have demonstrated antioxidant activities, with significant reductions in OS in patients and prevention of chronic pathologies<sup>[45]</sup>. Some preparations of the fleshy stems (cladodes) have been tested for the treatment of the symptomatology of diabetes in humans and in animal models<sup>[47-49]</sup>. Some authors have also reported that the fresh stems and the prickly pear are good sources of fiber and that these materials also reduce

blood sugar and cholesterol levels in the plasma<sup>[50,51]</sup>. The prickly pear fruit can be considered a functional food, which is a property that has been attributed to its bioactive compounds, such as vitamin C and vitamin E, polyphenols, carotenoids, flavonoid compounds (for example, kaempferol, quercetin, and isorhamnetin), taurine, and pigments<sup>[45,52-54]</sup>. The betalains are water-soluble pigments. Two betalainic derivatives are present in prickly pears: betacyanin, responsible for its purplish-red color; and betaxanthine, responsible for its yellowish-orange color. These pigments have demonstrated beneficial effects in the redox-regulated pathways implicated in cellular growth and inflammation, and no toxic effects have been observed in humans<sup>[45,55,56]</sup>.

### **Hepatoprotective evidence for *Opuntia ficus-indica*:**

Despite the diverse therapeutic uses that, for many years, have been attributed to plants of the genus *Opuntia*, prickly pear and cactus pear fruits (*tunas*) were ignored by the scientific world until the beginning of the 1980s, when they started to receive attention, and different investigations and symposia were initiated, resulting in publications, books, and book chapters. However, the scientific research into the hepatoprotective capacity of this food continues to be insufficient<sup>[57]</sup>. The first scientific evidence for the use of *Opuntia ficus-indica* against hepatotoxic substances was described by Wiese *et al.*<sup>[58]</sup>, who reported that this cactaceous species was useful for reducing the symptoms of hangovers after consuming alcohol in excess. Their data indicated that the severity of the hangover produced by alcohol consumption might be caused by inflammation induced by the impurities in beverages or by alcoholic metabolism subproducts and that an extract of *Opuntia ficus-indica* could diminish nausea, dry mouth, and anorexia, which are characteristic signs of alcoholic hangovers in humans.

Years later, Ncibi *et al.*<sup>[59]</sup> demonstrated that an extract of *Opuntia ficus-indica* cladodes (CCE) could reduce the hepatic toxicity of the organophosphorous insecticide chlorpyrifos (CPF), which was a conclusion that these authors obtained in observing whether combining CPF plus CCE could significantly normalize biochemical parameters, such as ALAT, ASAT, ALP, LDH, cholesterol, and albumin, in contrast with animals treated with the pesticide alone, in which the biochemical parameters were notably affected. In more recent years, investigations developed by the el Hassen Bacha scientific group explored the hepatoprotective effects of a CCE against two compounds with hepatocarcinogenic capacity in Balb/C mice: benzo(*a*)pyrene [B(*a*)P]<sup>[60]</sup> and aflatoxin B1 (AFB1)<sup>[61]</sup>. In both studies, it was observed that the two carcinogens significantly altered markers of oxidative stress, such as MDA level and CAT activity, and increased of the expression of heat shock proteins (Hsp 70 and Hsp 27). In addition, they induced fragmentation of the DNA in the liver and chromosomal aberrations in bone marrow cells, increased the expression of the bcl2 antiapoptotic proteins, and decreased the expression of

**Table 2** Main components of the essential oil of chamomile

Component	RT <sup>a</sup>	Area in the plant
(E)- $\beta$ -farnecene	38.46	28.17%
Germacrene-D	39.23	2.19%
Unidentified sesquiterpene	40.07	1.40%
Unidentified sesquiterpene	41.17	0.78%
(Z,E)- $\alpha$ -farnecene	41.35	1.59%
Unidentified sesquiterpene	48.52	0.71%
$\alpha$ -bisabolol oxide A	54.46	41.77%
$\alpha$ -bisabolol oxide B	49.28	4.31%
$\alpha$ -bisabolol oxide	50.65	5.30%
$\alpha$ -bisabolol	51.18	2.31%
Chamazulene	52.80	2.39%
1,6-dioxaspiro[4,4]non-3-ene,2-(2,4 hexadyn-1-ylidene)	60.73	2.19%
Hexatriacontane	67.49	0.50%

RT<sup>a</sup>: Retention time obtained with gas chromatography.

bax. Additionally, the authors proved that the treatment with CCE prior to or after treatment with B(a)P or AFB1 resulted in a total reduction in oxidative damage induced in all of the markers tested, and they demonstrated that CCE had an antigenotoxic effect by reducing the damage to the genetic material of the liver and to the bone marrow caused by both toxins. Similarly, it was observed that CCE was capable of inhibiting the toxic effects of B(a)P and/or AFB1 by differential modulation of the expression of *p53*, which increased in its associated genes, such as *bax* and *bcl2*. Based on these results, the scientific group concluded that the cactus cladode extract was effective in protecting against the dangers of both carcinogens and suggested that *Opuntia ficus-indica* could be considered a plant with hepatoprotective capacity.

Due to the majority of the studies available in the literature, including those previously mentioned, being centered on analysis of the extracts of the fruit, the nopal or the cladodes and these generally being consumed as fresh fruit or juice and, to a lesser degree, as dried fruits, candies, jams, jellies, and/or wines, an experiment was undertaken in 2012 with the aim of investigating the effects of *Opuntia ficus-indica* f. *inermis* prickly pear juice (PPJ) against ethanol-induced liver injury in rats. Chronic ethanol administration (3 g/kg *bw*) over 90 d in Wistar rats significantly increased liver lipid and protein oxidation, reduced glutathione (GSH) content and the activities of liver antioxidant enzymes, such as SOD, CAT, and GPx, and conversely elevated liver injury biochemical markers, such as ASAT, ALAT, ALP, GGT, LDH, cholesterol, and TGs, thereby causing severe histopathologic injury. In contrast, pre-treatment of ethanol-fed rats with PPJ (20 and 40 mL/kg *bw*, orally) interestingly reduced liver lipid and protein oxidation, decreased histopathologic lesions, and inhibited alterations in antioxidant enzymes and the release of biochemical markers. The hepatoprotective effects of PPJ could be due to its capacity to end free radical chain reactions or to enhance endogenous antioxidant activities<sup>[62]</sup>.

### Chamomile (*Matricaria chamomilla* or *Chamomilla recutita*)

**Overview:** While there is an extensive literature suggesting health benefits associated with drinking teas prepared with *Camilla sinensis* (i.e., black and green teas)<sup>[63]</sup>, evidence-based information regarding the effects of the majority of herbal teas, or tisanes, has been quite limited. One of the most commonly consumed single-ingredient herbal teas is chamomile<sup>[64]</sup>.

Chamomile (*Matricaria chamomilla* or *Chamomilla recutita*) is an Asteraceae plant native to Europe, and it is distributed throughout the world, except in tropical and polar regions. This plant has been used for its curative properties since the ancient Egyptian and Greek civilizations, and it currently is frequently used as an antiseptic, antiphlogistic, diuretic, expectorant, febrifuge, sedative, anti-inflammatory, and anticarcinogenic<sup>[18]</sup>. The pharmacological activities of various components of the plant have been reported, for example, the anti-inflammatory capacity and the modulating effects of Hsp on apigenin and quercetin flavonoids, as well as the anti-inflammatory, antioxidant, and antiseptic activities detected in  $\alpha$ -bisabolol, guargazulene, and chamazulene<sup>[18,65,66]</sup>. The essential oil extracted from the chamomile flower ranges from 0.42% to 2% and consists of compounds such as bisabolol, chamazulene, cyclic sesquiterpenes, bisabolol oxides, and other azulenes and terpenes<sup>[18,67]</sup>.

Madrigal-Bujaidar *et al.*<sup>[68]</sup> conducted an investigation with the primary purpose of evaluating the chemoprotective capacity of chamomile. These authors determined the inhibitory effect of three doses of chamomile essential oil (CEO) on the sister chromatid exchanges (SCE) produced by daunorubicin and methyl methanesulfonate in mouse bone marrow cells. Initially, the authors obtained the CEO from flowers of *Chamomilla recutita* by steam distillation, and then they analyzed this oil by gas chromatography to identify the chemical species. Thirteen compounds were determined with this assay, including bisabolol and its oxides,  $\beta$ -farnecene, chamazulene, germacrene, and sesquiterpenes (Table 2). In general, the results indicated dose-dependent inhibition of SCE formed by both mutagens and that its antioxidant capacity could induce this effect. This study, in addition to others that have provided evidence for its spectrum of biological activities, as well as the more than 100 components identified to date, promote chamomile as an ideal candidate for possessing hepatoprotective capacity.

### Hepatoprotective evidence for chamomile and its phytochemicals:

As mentioned in the general comments, chamomile is one of the most popular teas in the world, consumed as a sole herbal ingredient, or tisane, and it has been utilized traditionally with medicinal aims. It has been studied by a great number of investigators with the purpose of fully demonstrating its therapeutic potential. With regard to its gastroprotective potential, this property began to be explored in the 1980s, when

the antispasmodic effects were analyzed of different preparations of chamomile in isolated guinea-pig ileum. In agreement with Achterrath-Tuckermann *et al.*<sup>[69]</sup>, the compounds contained in aqueous and oil extracts of the plant were effective antispasmodics in this experimental model. In comparison with papaverine, a smooth muscle relaxant drug,  $\alpha$ -bisabolol was 91% as effective in barium chloride-induced spasms, while bisabolol A and B oxides were 46%-50% effective. Utilizing the same experimental model, the effectiveness of an ethanolic extract of chamomile in histamine- and acetylcholine-induced spasms. At 2.5- and 10-mL/L doses (of a 31% w/w solution), the chamomile extract shifted to the right the dose response curves of both acetylcholine and histamine, reflecting an increase in their median effective doses, compared with an ethanol control solution. Atropine (7.0  $\mu$ g/L) similarly shifted the dose response curves, but unlike chamomile, this antispasmodic drug was unable to decrease the maximal contraction in response to either acetylcholine or histamine. In rats, both apigenin and  $\alpha$ -bisabolol inhibited the development of gastric ulcers induced by indomethacin, stress, and alcohol<sup>[67]</sup>.

Similar to black or green tea, chamomile tea demonstrated that it could modulate the activity of hepatic cytochrome P<sub>450</sub>. Maliakal *et al.*<sup>[70]</sup> provided Wistar rats with free access to a solution of 2% chamomile tea over 4 wk, finding that CYP1A2 isoform activity was 39% lower in the control group, which received only water. Based on these data, Gupta *et al.*<sup>[71]</sup> evaluated the hepatoprotective activity of an aqueous ethanolic extract of *Chamomile recutita capitula* against PCM-induced damage in albino rats. To determine this protection and to ascertain the possible mechanism of action, the extract was evaluated via blood and liver glutathione, Na<sup>+</sup> K<sup>+</sup>-ATPase activity, serum marker enzymes, bilirubin, glycogen, and TBARS assay. Their results confirmed that the chamomile extract had reversal effects on the levels of the above-mentioned parameters of paracetamol hepatotoxicity, and the authors concluded that the extract served as a hepatoprotective agent and that this hepatoprotective activity of chamomile might be due to the normalization of impaired membrane function activity. Because paracetamol (PCM) is not the only hepatotoxic compound to which humans have free access, Al-Hashem (2010) investigated the gastroprotective effects of an orally administered aqueous extract of *Chamomilla recutita* (ACE) against ethanol-induced gastric ulcers in male Wistar rats, which were organized into five experimental lots: one group was treated with deionized water alone (control group), and four groups received 0, 0.5, 1.0, and 2.0 g/kg ACE, respectively, for 27 d. Stomach ulcerations were induced by orally administering a single dose of 70% ethanol on day 28. Lesions in the gastric mucosa were examined macroscopically to calculate the ulcer index (UI) and the estimated GSH for each animal. On comparing the control group with the remainder of the experimental lots, it was observed that the UI was significantly reduced in a dose-dependent manner. In contrast, GSH levels decreased

after treatment with ethanol, and this reduction was impeded by treatment with ACE, principally at the highest dose (2.0 g/kg). Histological examination revealed that ACE treatment alleviated, or completely resolved, ethanol-induced degenerative alterations, including disorganization of cell nuclei and gland morphology with erosion in the gastric mucosa, and it interrupted muscularis mucosa. In conclusion, this study provided evidence for the regulation of ACE-mediated gastroprotection against ethanol-induced ulceration by GSH<sup>[72]</sup>. Finally, a study that evaluated another extract of *Matricaria chamomilla* L. on lipid peroxidation and antioxidant enzyme systems (ASAT, ALAT, MDA, SOD, GSH levels, GPx, and CAT) in rats treated with CCl<sub>4</sub> for 14 d, demonstrating that depending on the dose of the extract administered (50, 100, and 200 mg/kg), the extract reduced the damage induced by CCl<sub>4</sub> and oxidative stress, thereby positively modifying the antioxidant system<sup>[73]</sup>.

### Silymarin (*Silybum marianum*)

**Overview:** *Silybum marianum* is the scientific name for milk thistle (Mt) or St. Mary's thistle. It is a plant that is native to the Mediterranean region and that belongs to the Asteraceae family. It is characterized by thorny branches, milky sap, and oval leaves that reach up to 30 cm; its flowers are bright pink and can measure up to 8 cm in diameter<sup>[18,74]</sup>. Milk thistle (Mt) grows in its wild form in southern Europe, North Africa, and in the Middle East, but it is cultivated in Hungary, China, and in South American countries, such as Argentina, Venezuela, and Ecuador. In Mexico, it has been consumed as a food supplement for many years<sup>[18,75]</sup>.

In the 1960s, German scientists performed a chemical investigation of the milk thistle fruit, isolating a crude extract formed by active compounds with hepatoprotective capacity; this group of compounds was called silymarin. In 1975, it was found that the main components of silymarin were silybin A, silybin B, isosilybin A, isosilybin B, silychristine A, silychristine B, and silydianine<sup>[18,76]</sup>. Currently, it is known that the chemical constituents of silymarin are flavonolignans, *i.e.*, a combination composed of flavonoids and lignin structures<sup>[18,77]</sup>.

Mt is one of the most investigated plant extracts, with known mechanisms of action for oral treatment of toxic liver damage. Silymarin has been used as a protective treatment in acute and chronic liver diseases<sup>[18,78]</sup>. Its protective capacity is related to different mechanisms, such as suppressing toxin penetration into hepatic cells, increasing SOD activity, increasing the glutathione tissue level, inhibiting lipid peroxidation, and enhancing hepatocyte protein synthesis. The hepatoprotective activity of silymarin can be explained based on its antioxidant properties due to the phenolic nature of its flavonolignans. It also acts by stimulating liver cell regeneration and cell membrane stabilization to prevent hepatotoxic agents from entering hepatocytes<sup>[18,79]</sup>. Silymarin has also been beneficial for reducing the chances for developing certain cancers<sup>[18,80]</sup>. The molecular targets of silymarin for



cancer prevention have been studied. Mt interferes with the expression of cell cycle regulators and of proteins involved in apoptosis to modulate the imbalance between cell survival. These compounds and two other related analogs present in extremely minute quantities were evaluated for antiproliferative/cytotoxic activity against human prostate cancer cell lines. Isosilybin B exhibited the most potent activity<sup>[18,79]</sup>. The isolation of six isomers afforded a preliminary analysis of the structure-activity relationship in terms of prostate cancer prevention. The results suggested that an *ortho* relationship for the hydroxyl and methoxy substituents in silybin A, silybin B, isosilybin A, and isosilybin B was more favorable than a meta relationship for the same substituents in the minor flavonolignans. Silymarin suppressed ultraviolet A (UVA)-induced oxidative stress, which can induce skin damage. Therefore, topical application of silymarin could be a useful strategy for protection against skin cancer<sup>[18,80,81]</sup>.

**Hepatoprotective evidence of silymarin:** As previously noted, silymarin is one of the most investigated plant extracts, with known mechanisms of action for oral treatment of toxic liver damage<sup>[82]</sup>. Silymarin has been employed as a protective treatment in acute and chronic liver diseases<sup>[83]</sup>. In addition, it supports liver cells through multifactorial action, including binding to cell membranes to suppress toxin penetration into hepatic cells, increasing SOD activity<sup>[79]</sup>, increasing glutathione tissue levels<sup>[84]</sup>, inhibiting lipid peroxidation<sup>[85,86]</sup>, and enhancing hepatocyte protein synthesis<sup>[87]</sup>. The hepatoprotective activity of silymarin can be explained by its antioxidant properties deriving from the phenolic nature of flavonolignans. It also acts by stimulating liver cell regeneration and cell membrane stabilization to prevent hepatotoxic agents from entering hepatocytes<sup>[88]</sup>. It has been shown that flavonolignans inhibited leukotriene production; this inhibition explains the anti-inflammatory and antiproliferative activity of flavonolignans<sup>[89]</sup>.

Due to the large number of studies that have demonstrated its hepatoprotective activity and the insufficient space in this review to analyze all of them, we will focus on those investigations in which the combination of silymarin with other compounds has been explored. One of these studies had as its objective the investigation of silymarin, and misoprostol or the co-administration of both against CCl<sub>4</sub>-induced hepatic lesion in rats. Misoprostol (MSP) at 10, 100, and 1000 µg/kg silymarin (25 mg/kg) and the combination of MSP (100 µg/kg) + silymarin (25 mg/kg) were orally administered once daily simultaneously with CCl<sub>4</sub> over 15 d. The authors' results showed that MSP (at all of the doses) exhibited significant protection against the hepatotoxic activity of CCl<sub>4</sub> in the rats, observing reductions in serum ALAT levels of 24.7%, 42.6%, and 49.4%, in comparison to the control group. MSP at doses of 100 and 1000 µg/kg diminished ASAT in 28% and 43.6% and ALP in 19.3% and 53.4%, respectively, while silymarin reduced ALAT, ASAT, and ALP levels, in 62.7%, 66.1%, and 65.1%, respectively. In

contrast, co-administration of both compounds resulted in reductions of 61.4%, 66.1%, and 57.5% in ALAT, ASAT, and ALP levels, respectively.

Histopathological alterations and depletion of hepatocyte glycogen and DNA content by CCl<sub>4</sub> were markedly reduced after treatment with MSP, silymarin, or the combination thereof. Image analysis of liver specimens revealed a marked reduction in liver necrosis, with areas of damage of 32.4%, 24%, and 10.2% after MSP (10, 100, or 1000 µg/kg), of 7.2% after silymarin, and of 10.9% after treatment with both compounds, compared with the CCl<sub>4</sub> control group (46.7%). These results indicate that treatment with MSP and silymarin protected against CCl<sub>4</sub>-induced hepatocellular necrosis. In general, this study suggests that the combination of both compounds demonstrated therapeutic potential for reducing hepatic damage<sup>[90]</sup>.

Another study that has also attracted attention was performed by Kim *et al.*<sup>[91]</sup>, who evaluated the protective effects of a mixture of *Aloe vera* and *Silybum marianum* (the ACTIVAloe N-931 complex) against CCl<sub>4</sub>-induced acute hepatotoxicity and liver fibrosis. Acute hepatotoxicity was induced by an *ip* injection of CCl<sub>4</sub> (50 µL/kg), and ACTIVAloe complex N-931 was administered orally, at doses of 85, 170, and 340 mg/kg at 48, 24, and 2 h before and 6 h after the injection of CCl<sub>4</sub>. Hepatic fibrosis was induced by an *ip* injection of CCl<sub>4</sub> over 8 wk (0.5 mL/kg twice weekly), and the mice were treated with the ACTIVAloe N-931 complex at the same doses once daily. In acute hepatotoxicity, as well as in hepatic fibrosis, serum aminotransferase and lipid peroxidation levels increased, while the hepatic glutathione content was observed as diminished. These changes were impeded by the ACTIVAloe N-931 complex, because it attenuated the tumor necrosis factor-α (TNF-α) levels in nitric oxide synthase, in cyclooxygenase 2 and in the expression of messenger RNA (mRNA) involved in acute hepatotoxicity. In antifibrotic experiments, tissue inhibitor of metalloprotease-1 mRNA expression was attenuated by treatment with the complex. Similarly, hepatic hydroxyproline content and transforming growth factor-beta 1 levels decreased. In summary, these results suggested that the mixture of *Aloe vera* and *Silybum marianum* had hepatoprotective effects against chronic and acute lesions induced by the organochlorine (OC) compound.

More recently, a study in which two plants extracts were combined, namely *Ginkgo biloba* (employed for centuries because of its therapeutic action, especially by Chinese traditional medicine) and *Silybum marianum*, demonstrated that this combination could increase chemoprevention against hepatocarcinogenesis induced by *N*-nitrosodiethylamine (NDEA) through its antioxidant properties and its antigenotoxic and antiangiogenic activity. El Mesallamy *et al.*<sup>[92]</sup> evaluated these activates after organizing male Wistar albino rats into six experimental groups, which included: a control lot; a second group in which NDEA was administered intragastrically (*ig*) at a 10-mg/kg dose five times weekly over 12 wk to induce

hepatocellular carcinoma (HCC); two groups (3 and 4) pre-treated with silymarin and *Ginkgo biloba*, respectively; and finally, two lots (5 and 6) of animals post-treated with each of the extracts. The parameters investigated in the serum were ALAT, ASAT, GGT, and vascular endothelial growth factor (VEGF), while the parameters investigated in hepatic tissue were MDA, GSH, SOD, GPx, GRx, and the Comet assay. On finalizing the experiment, the authors determined that in the NDEA group, the MDA level was elevated, with a subsequent decrease in the GSH level and in the SOD, GPx, and GRx activities. In addition, the NDEA group revealed a significant increase in serum ALAT, ASAT, and GGT levels and in the VEGF level. Furthermore, NDEA-administered animals showed a marked increase in Comet assay parameters. These biochemical alterations induced by NDEA were confirmed by histopathological examination of rat livers intoxicated with NDEA, which disclosed obvious cellular damage and well-differentiated HCC. In contrast, the silymarin + NDEA-treated groups (3 and 5) and the *Ginkgo biloba* + NDEA-treated groups (4 and 6) exhibited a significant decrease in MDA levels and a significant increase in GSH content and in SOD, GPx, and GRx activities, compared with the NDEA group. Silymarin and/or *Ginkgo biloba* also beneficially downregulated the increases in serum ALAT, ASAT, and GGT activities and in the VEGF level induced by NDEA. In addition, both extracts significantly decreased Comet assay parameters and induced an improvement in liver architecture.

#### **Blue green algae spirulina (*Spirulina maxima*, *Spirulina platensis*, and *Spirulina fusiformis*)**

**Overview:** Spirulina is a microscopic blue-green filamentous alga that floats freely; it grows in fresh water, as well as in alkaline salt water. It is a cyanobacterium belonging to the class Cyanophyceae and the order Oscillatoriales. It is an organism with the capacity to store different bioactive molecules, among which are the following: (1) proteins (60%-65% dry weight) with essential amino acids; (2) polyunsaturated fatty acids, such as linoleic acid; (3) vitamins (B<sub>12</sub> and E); (4) polysaccharides; (5) minerals (Na, K, Ca, Fe, Mn, and Se); and (6) pigments (chlorophyll, c-phycocyanin, allophycocyanin,  $\beta$ -carotene, lutein, and zeaxanthin). Generally, the content of the compounds varies in species-to-species proportions, but the phytochemicals that are always present in their biomass are c-phycocyanin (with a content of 12.6% in dry spirulina) and high percentages of dietary zeaxanthin<sup>[93]</sup>.

Spirulina is the sole blue-green alga that is cultivated commercially for food use; there are various species, but those of the greatest commercial importance are *Spirulina maxima*, *Spirulina platensis*, and *Spirulina fusiformis*<sup>[93]</sup>. Spirulina has been consumed for centuries in many parts of the world, ranking from the Aztec civilization in Latin America to the tribes that inhabit the Lake Chad region of central Africa. In 1996, the United Nations World Health Organization declared spirulina the best food for the future, and it has gained in popularity as a food supplement

in recent years thanks to its high content of proteins and natural vitamins<sup>[94]</sup>. Throughout its long history of use as a food and as a result of contemporary scientific discoveries, spirulina is considered safe for human consumption; thus, it has become an important ingredient in many nutraceutical formulations<sup>[93-95]</sup>. Currently, there is varying scientific evidence for its biological effects against health problems. In summary, the results indicated that it was antioxidant, anti-inflammatory, hypolipemic, anti-hypertensive, antidiabetic, antimicrobial, neuroprotective, antianemic, immunostimulant, and anticarcinogenic and a hepatoprotector.

**Hepatoprotective evidence for spirulina:** It is curious that, despite spirulina having been consumed for centuries, studies that have demonstrated its hepatoprotective effects began only in this century, specifically in 2005, when carotenoids were extracted from a mixture of hexane alcohol:isopropyl alcohol (1:1 vol/vol) in two microalgae, among these *S. platensis*. These carotenoids were mixed with olive oil and were administered orally to Wistar rats at a dose of 100  $\mu\text{g}/\text{kg bw}/\text{d}$  (in terms of carotenoids). The degree of hepatoprotection was measured by means of estimating biochemical parameters, such as serum transaminases [serum glutamate oxaloacetate transaminase (GOT) and serum glutamate pyruvate transaminase (GPT)], serum ALP, total albumin, and total protein. The results were compared with those of a control group, a CCl<sub>4</sub>-induced hepatic damage group, and a group treated with synthetic  $\beta$ -carotene at the same dose. The protein content of the CCl<sub>4</sub>-treated group, which received a normal diet, showed a significant decrease (3.92 mg/mL), while the carotenoids from spirulina raised this value to 6.32 mg/mL. The CCl<sub>4</sub>-treated group showed higher transaminase activity (128.68 units/mL GPT and 171.52 units/mL GOT). However, the activity of GPT was 76.83 units/mL with spirulina. For serum ALP, the standard beta-carotene value was 81.52 units/mL, compared with 84.46 units/mL for the CCl<sub>4</sub>-treated group; however, natural algal carotenoids yielded 44.73 units/mL. Similarly, the authors observed this same decrease in the parameter corresponding to total albumin. In summary, their results indicated that the carotenoids derived from spirulina had greater antihepatotoxic effects, compared to synthetic beta-carotene<sup>[96]</sup>. Later, Kuriakose *et al.*<sup>[97]</sup> evaluated the hepatoprotector effect of an ethanolic extract of *Spirulina lonar* (EESLO) on the damage produced by paracetamol (PCM) in rats. These scientists considered analyzing this extract due a *in vitro* prior study having found better antioxidant activity compared to methanolic and aqueous extracts. As in other studies, the authors evaluated parameters such as the degree of lipid peroxidation (TBARS), antioxidant enzymes (SOD, CAT, GPx, and GST) and the activity of ASAT and ALAT, which tends to be altered by high doses of PCM. In general, these indicators of hepatic damage recovered, and consequently, the results suggested that EESLO could act as a hepatoprotective agent and that its mechanism of

action was related to antioxidant phenomena.

These findings motivated other investigators to explore the spectrum of protection, evaluating this property against other compounds, including mercuric chloride (HgCl<sub>2</sub>), cisplatin, and CCl<sub>4</sub>. In the case of the first compound, it was found that albino rats treated with HgCl<sub>2</sub> showed significant increases in the levels of blood hydroperoxide, ASAT, ALAT, ALP, TC, TG, very-low-density lipoprotein-cholesterol (VLDL-c), and MDA. In the same manner, intoxication with mercury induced pathological alterations in the liver, such as necrosis and cytoplasmic vacuolization. In contrast, treatment with *S. platensis* confirmed that the increases in the previously mentioned parameters diminished notably; this treatment attenuated HgCl<sub>2</sub>-induced hepatotoxicity and modified lipid profiles through its antioxidant properties<sup>[98]</sup>.

In contrast, these same species of spirulina, combined with vitamin C and/or administered independently, were capable of reducing the same hepatic markers that were altered after treatment with cisplatin. In the same manner, optic microscopy showed that the hepatic lesions and histopathological abnormalities induced by treatment with cisplatin were impeded by spirulina and by the combination of vitamin C with spirulina. These data newly suggested that the protector effect was related to the antioxidant capacities of the alga and the vitamin<sup>[99]</sup>. The most recent study providing hepatoprotective evidence for spirulina was performed by Kepekçi *et al.*<sup>[100]</sup>, who believe that phenolic compounds constitute the main secondary metabolites, with high pharmaceutical potential, and there have been reports that microalgae contain low amounts of these compounds. These authors decided to investigate the hepatoprotective potential of the biomass of *S. platensis* enriched with phenolic compounds (SP1) and with large amounts of phenolic compounds (SP2) against acute CCl<sub>4</sub>-induced hepatotoxicity in rats. The increases in ALAT, ASAT, and MDA levels, together with the decreases in SOD and CAT activities, were significantly improved by SP2. The histopathological examinations revealed that SP2 was more potent than SP1 in protecting the liver from the toxic lesions caused by CCl<sub>4</sub>, although both compounds preserved the hepatocyte ultrastructure. Lesions including necrosis, lymphocyte infiltration, ballooning degeneration, and hepatocyte injury, as well as irregular lamellar organization, dilation of the endoplasmic reticula, and the presence of great numbers of cytoplasmic vacuolizations, were reversed by SP2.

## NATURAL RESIN

### *Propolis (bee glue)*

**Overview:** Propolis is a resinous substance of natural origin, gathered by bees from different parts of plants, shoots, and exudates<sup>[101]</sup>. Bees utilize it as a sealant for their hives<sup>[102]</sup> and to avoid the decomposition of creatures that have been killed by the bees after hive invasions<sup>[103]</sup>. Chemically, propolis is a lipophilic material that is hard and fragile when cold but soft, flexible, and

very sticky when hot, hence the name bee glue. It has an agreeable aromatic odor, and it varies in color depending on its origin and maturation<sup>[104,105]</sup>. The compounds identified in propolis derive from three sources: plant exudate collected by bees; substances secreted by the metabolism of the bees; and materials that are introduced during the creation of the resin<sup>[104]</sup>. The ethanolic extract of propolis (known as propolis balsam) is the most common, but there are other solvents used to separate and identify many of its components. Among the types of chemical substances found in propolis are waxes, resins, balsams/balms, aromatic oils, pollen, flavonoids, terpenoids, and other organic materials (Table 3). The proportions of these substances are variable and depend on the place and time the propolis is obtained<sup>[104]</sup>.

Propolis has a long history of being utilized in popular medicine, with its employment dating from at least 300 BC<sup>[104,105]</sup>; however, over the last decade, it has been found to possess diverse biological activities, and among the most prominent is its antioxidant, anti-inflammatory, antibiotic, and antifungal potential<sup>[106]</sup>. Recently, propolis has gained popularity as a health beverage; thus, it has been widely utilized in foods and drinks, with the aim of preventing alterations of the heart and chronic degenerative diseases, such as diabetes and cancer<sup>[107]</sup>.

As a consequence of its more than 300 components identified to date and its broad spectrum of biological activities, it has been considered a promoter agent for human health and an ideal candidate for possessing hepatoprotector capacity.

**Hepatoprotective evidence for propolis:** The hepatoprotective effects of Cuban propolis were first examined González *et al.*<sup>[108]</sup> in a mouse model of acute hepatotoxicity induced by a high oral dose (600 mg/kg) of PCM; 95% ethanol extract of propolis *ip*, at doses of 25, 50, and 100 mg/kg *bw*, was found to decrease significantly both the activity of serum ALAT and the concentration of reduced GSH in the liver, which was raised by PCM alone. Propolis extract also reduced liver damage induced by PCM, as observed by optical, as well as electron microscopic, examination. The ALAT and GSH levels were 65.1 ± 5.36 and 538 ± 0.30, respectively, at a dose of 100 mg/kg *bw* in the propolis-treated group, compared with ALAT (89.0 ± 3.77) and GSH levels (3.44 ± 0.47) in the PCM-treated control group of mice. Later, Ramirez *et al.*<sup>[109]</sup> further reported the hepatoprotective effects of Cuban red propolis against acetaminophen (PCM)-administered liver injury in mice. The ALAT level was found to decrease significantly at *ip* doses of 25, 50, and 100 mg/kg of propolis. Similarly, Czamecki *et al.*<sup>[110]</sup> also found protective effects of lipid flower pollen extract against PCM-induced hepatotoxicity in mice.

González *et al.*<sup>[111]</sup> further examined a 95% ethanol extract of Cuban red propolis on CCl<sub>4</sub>-induced liver injury in rats. Propolis extract at doses of 5, 10, and 25 mg/kg administered *ip* decreased ALAT and MDA levels in blood serum. The ALAT level decreased to 34.1 ± 4.2

**Table 3 Major compounds identified in propolis resin**

Chemical groups	Compounds
Alcohols	Benzene methanol, cinnamyl alcohol, glycerol, $\alpha$ -glycerol phosphate, hydroquinone, isobutenol, phenethyl alcohol
Aldehydes	Benzaldehyde, caproic aldehyde, p-hydroxybenzaldehyde, isovanillin, vanillin
Aliphatic acids and aliphatic esters	Acetic acid, angelic acid, butyric acid, crotonic acid, fumaric acid, isobutyric acid, methylbutyric acid, isopentyl acetate
Amino acids	Alanine, $\beta$ -alanine, $\alpha$ -aminobutyric acid, $\gamma$ -aminobutyric acid, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine
Aromatic acids	Benzoic acid, caffeic acid, cinnamic, coumaric, acid, ferulic acid, gallic acid, gentisic acid, hydroxycinnamic acid, p-hydroxybenzoic acid, isoferulic acid, 4-methoxy cinnamic acid, salicylic acid, vanillic acid
Aromatic esters	Benzyl acetate, benzyl benzoate, benzyl caffeate, benzyl coumarate, benzyl isoferulate, benzyl salicylate, butenyl caffeate, butyl caffeate, cinnamyl benzoate, cinnamyl caffeate, ethyl benzoate
Chalcones	Alpinetin chalcone, naringenin chalcone, pinobanksin chalcone, pinocembrin chalcone, sakuranetin chalcone
Flavanones	Naringenin, pinobanksin, pinobanksin-3-acetate, pinobanksin-3-butyrate, pinobanksin-3-hexanoate, pinobanksin-3-methyl ether, pinobanksin-3-pentanoate
Flavones and flavonols	Acacetin, apigenin, apigenin-7-methyl ether, galagin, galagin-3-methyl ether, izalpinin, isorhamnetin, kaempferol, quercetin, ramnetin, rannocitrin
Waxy acids	Arachid acid, behenic acid, cerotic acid, lauric acid, linoleic acid, lignoceric acid, montanic acid, myristic acid, oleic acid, palmitic acid, stearic acid
Ketones	Acetophenone, dihydroxy-acetophenone, methylacetophenone
Terpenoids and other compounds	$\alpha$ -acetoxybetulenol, $\beta$ -bisabolol, 1,8-cineole, $\alpha$ -copaene, cymene, limonene, styrene, xanthoreol, naphthalene, sesquiterpene alcohol, sesquiterpene diol
Steroids	Calinasterol acetate, b-dihydrofucosterol acetate, ucoesterol acetate, stigmasterol acetate
Sugars	Fructofuranose, $\alpha$ -D-glucopyranose, $\beta$ -D-glucopyranose

U/L in the 10-mg/kg propolis-treated group compared with the CCl<sub>4</sub>-treated control, which had an ALAT level of 117.7 ± 3.6 U/L. The concentration of TG in the liver in the same experiment was also decreased by propolis treatment. With regard to histopathological evaluation of CCl<sub>4</sub>-induced liver injury in rats, González *et al.*<sup>[111]</sup> found a significant reduction in ballooned cells in the livers of propolis-treated rats (25, 50, and 100 mg/kg *bw*), compared with the CCl<sub>4</sub>-treated group.

Similarly, Sharma *et al.*<sup>[112]</sup> also found decreases in ALAT and ASAT, which were raised by alcohol or CCl<sub>4</sub> (68.39 ± 1.89 and 65.89 ± 0.75 IU/L) to physiological levels (39.33 ± 0.90 and 40.66 ± 0.51 IU/L) by co-administration of propolis. Moreover, Basnet *et al.*<sup>[113]</sup> examined the hepatoprotective activity of Brazilian propolis against CCl<sub>4</sub>-induced toxicity in rats; water extract (PWE) showed a stronger protective effect than the corresponding methanol and chloroform extracts when 200-mg/kg propolis extracts were administered orally. The GOT, GPT, and LDH levels in the blood serum of CCl<sub>4</sub>-treated control groups increased to 1132 ± 140, 395 ± 56, and 353 ± 51 U/L, respectively, 24 h after CCl<sub>4</sub> administration. In contrast, in the PWE pre-treated group, GOT (481 ± 88 U/L), GPT (157 ± 19 U/L), and LDH (247 ± 28 U/L) were significantly decreased. The hepatoprotective effect of oral administration of PWE was also evaluated in a D-GalN/LPS-induced liver injury model in mice. In the control group, it was observed that the GPT level rapidly increased to 6901 U/L 8 h after administration of D-GalN/LPS, while the GPT levels with 200- and 100-mg/kg doses administered *po* to PWE-treated groups were 355 and 1204 U/L, respectively. PWE also showed significant hepatoprotective activity against CCl<sub>4</sub>-induced liver cell injury in cultured rat hepatocytes. Fractionation and chemical analysis, guided by

*in vitro* hepatoprotective activity (CCl<sub>4</sub>-induced liver cell injury in cultured rat hepatocytes), led to the isolation of four dicaffeoylquinic acid derivatives from PWE, *i.e.*, (1) methyl 3,4-di-*O*-affeoylquinic acid; (2) 3,4-di-*O*-caffeoylquinic acid; (3) methyl 4,5-di-*O*-caffeoylquinic acid; and (4) 3,5-di-*O*-caffeoylquinic acid. All of these dicaffeoylquinic acid derivatives possessed significant hepatocyte protective activity against CCl<sub>4</sub>-induced cell injury.

In 1999, Sugimoto *et al.*<sup>[114]</sup> studied the hepatoprotective effect of Brazilian propolis on D-GalN-induced hepatic injury in rats. When the 95% ethanol extract was administered orally three times at a dose of 3 or 30 mg/kg at 18 h and 1 h before and 8 h after D-GalN injection, the propolis extract caused increases in serum ASAT and ALAT activities induced by D-GalN injection in a dose-dependent manner. A significant effect was observed in mice treated with a dose of 30 mg/kg propolis extract.

Lin *et al.*<sup>[115]</sup> observed that an ethanol extract of propolis at an oral dose of 10 mg/kg significantly inhibited the elevations of serum GOT, GPT, and TGs levels in an alcohol-induced liver injury model in rats. In contrast, in an *in vivo* model, Mahran *et al.*<sup>[116]</sup> observed a dose-dependent hepatoprotective effect of aqueous propolis extract on isolated rat hepatocytes against CCl<sub>4</sub>-induced toxicity *in vitro*. Later, Barskota *et al.*<sup>[117]</sup> examined the hepatocyte protective effects of nine different propolis samples collected from Brazil, Peru, the Netherlands, and China on D-GalN/TNF- $\alpha$ -induced cell death in primary cultured mouse hepatocytes at 200- and 100- $\mu$ g/mL concentrations. It was observed that nearly all of the methanol extracts possessed stronger hepatocyte protective effects than the corresponding water extracts. Moreover, all of the methanol extracts had significant hepatoprotective activity both at 100- and 200- $\mu$ g/mL concentrations, with the cell survival rate ranging from 49.3% to 117.7%

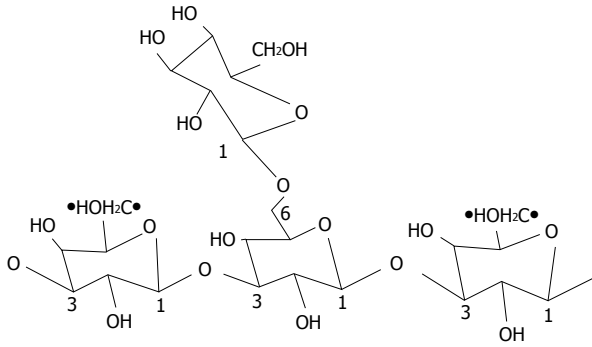


Figure 1 Structure of (1→3) beta-glucans with ramifications for (1→6).

compared with that the controls (35.0%). These findings suggest that the aqueous and alcoholic extracts of propolis possessed hepatoprotective effects against toxic compounds, such as  $\text{CCl}_4$ , paracetamol, and D-GalN, as well as immunologically, in D-GalN/LPS-induced liver injury models. In the most recent study, this capacity was explored against a more modern compound, cypermethrin. A pyrethroid pesticide was used preferably, instead of OC and OP pesticides, due to its high effectiveness, low toxicity to non-target organisms, and easy biodegradability.

Gomaa *et al.*<sup>[118]</sup> evaluated the protective effect of propolis against cypermethrin-provoked hepatic damage utilizing 50 adult male albino rats that were classified into four groups as follows: group I (control), subdivided into (1) a negative control, in which 2.0 mL of saline solution was administered; and (2) a positive control, which received the same amount but of corn oil; group II, which received cypermethrin (14.5 mg/kg); group III, which was administered propolis (200 mg/kg) dissolved in saline solution; and finally, group IV, which received the pyrethroid pesticide combined with propolis. All of the compounds were orally administered daily and over 4 wk. At the end, blood samples were obtained to estimate the hepatic enzyme levels (ALAT, ASAT, and ALP) and to determine total proteins and levels of albumin, TC, TGs, and VLDL-c. Later, the animals were sacrificed to obtain their livers and to quantify the levels of MDA and antioxidant enzymes (CAT, SOD, and GPx), as well as for histopathological examination. Their results indicated that cypermethrin induced an increase in the levels of the hepatic enzymes TC and MDA, while the total proteins albumin, TGs, and VLDL-c and the antioxidant enzymes were reduced in comparison with the controls. Histopathological examination of the livers revealed congestion of the central and portal veins with hydrotrophic degeneration of the hepatocytes. However, in contrast, the combined administration of propolis with cypermethrin induced a significant decrease in the levels of hepatic enzymes, TC, and MDA, as well as an increase in the levels of antioxidant enzymes, total proteins, TGs, and VLDL-c. Moreover, histopathological examination of the liver revealed apparent improvement in the lesions induced by the pyrethroid pesticide. The authors' conclu-

sion was that propolis exerted a beneficial influence via reduction of the hepatotoxic effects of cypermethrin, suggesting that its protective spectrum was quite broad.

## POLYSACCHARIDES

### $\beta$ -glucans

**Overview:** Different foods and natural products have traditionally been accepted as health remedies due to the popular belief that they cause fewer adverse effects. Therefore, it is indispensable to determine the beneficial potentials of these foods and natural products, and well as to understand the mechanism or mechanisms by which they exercise this potential.

The  $\beta$ -glucans belong to a group of polysaccharides that are localized in the intermediate layer of the cell wall of yeasts, algae, fungi, and some bacteria and cereals (such as barley and oatmeal)<sup>[119,120]</sup>. They mainly consist of a linear central backbone of D-glucose linked in the  $\beta$  (1→3) position with glucose side branches (linkage  $\beta$  1→6) of various sizes (Figure 1), which occur at different intervals along the central backbone. Beta glucans are derived from cereals that present residues of glucose with  $\beta$  (1→3) and  $\beta$  (1→4) linkages<sup>[120]</sup>.

In recent years, these polysaccharides have begun to acquire great economic importance due to their immunological activity; thus, they have been classified as biological response modifiers (BRs). However, this is not the sole property that they possess because different studies have shown their antiviral, antiparasitic, antifungal, antimicrobial, antioxidant, antigenotoxic, antitumor, antimutagenic, and anticlastogenic potential<sup>[120]</sup>.

**Hepatoprotective evidence for  $\beta$ -glucans:** Despite  $\beta$ -glucans having shown different therapeutic effects, investigations directed toward providing evidence of its hepatoprotective potential have been insufficient because it is a field of recent study. The first studies were conducted by Neyrinck *et al.*<sup>[121]</sup>, who evaluated a diet supplemented with laminarin (LAM), a fermentable marine  $\beta$  (1→3) glucan, to avoid lipopolysaccharides (LPS)-induced hepatotoxicity (*Escherichia coli* lipopolysaccharides) through the modulation of the immune response in hepatic tissue. Wistar rats were fed a standard diet (control) and/or a diet supplemented with  $\beta$  (1→3) glucan, extracted from brown algae over 25 d (5% for 4 d, followed by 10% for 21 d). At the end of this period, the animals were administered LPS (10 mg/kg) *ip*, and after 24 h, they were sacrificed. The results of these studies showed that hypothermia, hyperglycemia, and hypertriglyceridemia, which occurred soon after the administration of LPS, were less pronounced in rats treated with LAM, compared to the controls. The increases in ALAT, ASAT, and LDH activity were diminished by the action of treatment with LAM, and similarly, the latter reduced the number of serum monocytes, nitrite ( $\text{NO}_2$ ), and TNF-alpha.  $\beta$  (1→3) glucan also modulated intrahepatic immune cells: it lowered the occurrence of peroxidase-positive cells (cor-

responding to monocytes/neutrophils) and, in contrast, increased the number of ED2-positive cells, corresponding to resident hepatic macrophages, *i.e.*, Kupffer cells. In conclusion, the hepatoprotective effect of marine  $\beta$  (1  $\rightarrow$  3) glucan during endotoxic shock could be linked to its immunomodulatory properties, suggesting that lower recruitment of inflammatory cells inside the liver and lower secretion of inflammatory mediators play important roles in the hepatoprotective effects of LAM. Thus, these effects could be attributed to a direct effect of  $\beta$ -glucan on the immune cells or an indirect effect through its dietary fiber properties

In contrast, paramylon [a  $\beta$  (1  $\rightarrow$  3)-D-glucan isolated from *Euglena gracilis* Z] administered orally in three doses (500, 1000, and 2000 mg/kg) to rats with previous hepatic lesions induced by *ip* administration of CCl<sub>4</sub> at 50% (2.0 mL/kg of *bm*) demonstrated that paramylon prevented a rise in the serum levels of hepatic enzyme markers (GPT and GOT) and inhibited fatty degeneration and hepatic necrosis induced by CCl<sub>4</sub>. Pre-administration of paramylon also reduced the index of hepatic apoptosis and the enzymatic activity of SOD, CAT, and GPT. These results demonstrated that paramylon presented protective action through an antioxidant mechanism against the acute hepatic lesions induced by the organochlorine compound<sup>[122]</sup>.

## CONCLUSION

The present study synthesized the most accurate evidence for the hepatoprotective effects of some fruits and plants, of a natural resin, and of one of the main polysaccharides present in the cellular wall of yeasts, algae, and cereals against different toxic compounds that cause hepatic damage. In the same fashion, the investigations presented validated the use of fruits and plants in popular medicine to control hepatic damage, considered within the area of chronic degenerative diseases. The plants, fruits, and compounds described could offer novel alternatives to the limited therapeutic options that exist for the treatment of liver diseases; thus, these foods should be considered in future studies. In general, this article identified and provided evidence of some phytochemicals with hepatoprotective activity, the principal mechanisms of action of which were related to their antioxidant potential, a characteristic that should motivate and promote the search for effective protective agents, which must be evaluated later in pre-clinical and clinical assays to determine their safety and their chemopreventive capacity.

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