Published in final edited form as:
Curr Opin Gastroenterol. 2006 March ; 22(2): 165–170. doi:10.1097/01.mog.0000208463.69266.8c.

Polyphenols and gastrointestinal diseases

Gerald W. Dryden, **Ming Song**, and **Craig McClain**
Departments of Medicine, University of Louisville, Kentucky and The Ohio State University, Columbus, Ohio, USA

Abstract

Purpose of review—This article will review the role of polyphenols in gastrointestinal diseases. Ingested polyphenols are concentrated in the gastrointestinal tract and are not well absorbed into the rest of the body. Thus, the high luminal concentrations achieved support a potential for therapeutic uses in the gastrointestinal tract. Additionally, there is great interest from the general public in complementary and alternative medicine.

Recent findings—Dietary polyphenols are a major source of antioxidants consumed by humans. Polyphenols possess not only antioxidant properties but also antiviral, antibacterial, antiinflammatory and anticarcinogenic effects, as well as the ability to modulate certain signaling pathways such as nuclear factor-κB activation. Green tea polyphenols have been shown to have efficacy in various models of inflammatory bowel disease. Silymarin, or milk thistle, is hepatoprotective against many forms of experimental liver injury and is widely used in human liver diseases, such as hepatitis C and alcoholic cirrhosis, with an excellent safety profile (but with unclear efficacy).

Summary—Substantial in-vitro and animal studies support the beneficial effects of polyphenols in many gastrointestinal diseases. Well designed multicenter trials in humans, such as those called for in the 2005 National Institutes of Health Requests for Applications for Silymarin Centers, will be critical for defining the safety, appropriate dosing and therapeutic efficacy of such agents.

Keywords

cancer; gastrointestinal diseases; inflammatory bowel disease; liver injury; polyphenols

Introduction

The term ‘dietary polyphenols’ refers to members of a large family of related organic plant molecules. Several hundred of these compounds are found in higher plants, generally functioning as defenses against pathogens and ultraviolet radiation [1]. Abundant interest exists in using these compounds to maintain human health and to prevent or treat disease. Polyphenols are the most abundant antioxidants consumed by humans, with a total intake as high as 1 g/day [2•]. Plant polyphenols can be divided into several classes, generally depending on the number of phenol rings contained in the structure. The general backbone

Correspondence to Gerald Dryden MD, Division of Gastroenterology, 550 S. Jackson Street, 3rd Floor ACB, Louisville, KY 40202, USA Tel: +1 502 852 7963; fax: +1 502 852 0846; gwdryd02@gwise.louisville.edu.

for the largest class of polyphenolic compounds, the flavonoids, consists of the diphenylpropane ($C_6C_3C_6$) skeleton. This group of compounds is divided into six major subclasses: flavonols, flavones, isoflavones, flavanones, anthocyanidins, and flavanols (catcechins and proanthocyanidins) (see Table 1 for examples) [1]. Other major nonflavanoid polyphenols include the stilbenes (resveratrol), hydroxybenzoic acids, hydroxycinnamic acids, and lignans and tannins. This article will present an overview of polyphenols, the fate of ingested polyphenols, the effects of polyphenols on the liver and digestive tract, and lastly, safety issues.

Plant polyphenols frequently impart flavor and color to fruits and other plant products. Flavanols, the most prevalent flavanoids in food, generally accumulate in skin and leaves as a result of sun exposure. The site of production in the plant explains the fact that flavanols are commonly found in brewed or fermented beverages, particularly catechins (found in tea), and quercetin and kaempferol (found in red wine). Quercetin is also a predominant component of onions and apples, while myricetin is found in berries. Flavanones are mainly found in combination with flavones in citrus fruits, whereas flavanols and flavones are generally mutually exclusive [3]. Other dietary sources of polyphenols include vegetables, cereal grains, chocolate and dry legumes.

After recognizing the protective effects conferred by flavanoids to higher plants in nature, considerable interest developed in evaluating their potential for protecting humans against oxidative stress related diseases, such as cancer, inflammatory disorders, cardiovascular diseases and neurological disorders such as Alzheimer's disease. A large body of literature implicates oxidative stress as a major component in age-related human diseases. Investigators hypothesize that polyphenol compounds can combat oxidative stress, by acting as reducing agents, hydrogen-donating antioxidants, and singlet oxygen quenchers [3]. Translating this hypothesis into clinically applicable solutions, however, has been difficult. Although research into antioxidant therapy has flourished for several decades (vitamin E, in particular), flavanoids received limited attention in textbooks on antioxidants prior to 1995 [2•]. The results of recent research demonstrate that polyphenols do act as antioxidants, according to the definition that antioxidant compounds must delay, retard or prevent the auto-oxidation or free radical-mediated oxidation of a substrate in relatively low concentrations, while the resulting radical formed by the scavenging must be stable. Preliminary epidemiological studies quantifying dietary polyphenol ingestion demonstrated protection from coronary heart disease, and cancer prevention. Epidemiological studies of plant polyphenol ingestion, however, have been plagued by the fact that extensive alterations occur in polyphenols after harvest, processing, and during digestive metabolism. Most polyphenol compounds undergo some form of conjugation; unfortunately, it appears that it is the unconjugated polyphenol metabolites which are biologically active [2•]. Recent reports confirm free radical scavenging as a mechanism of action, while also demonstrating that cells respond to polyphenols through direct interactions with receptors or enzymes involved in signal transduction, either resulting in modification of the redox status of the cell, or triggering a series of redox-dependent reactions [4–6]. As antioxidants, polyphenols may improve cell survival; as prooxidants, they may induce apoptosis and prevent tumor growth [7]. Substantial research indicates a variety of other bioactive roles, including vasodilatory, anticarcinogenic, antiinflammatory, antibacterial and antiviral properties.

Polyphenol derivatives have also demonstrated the ability to inhibit a variety of biochemical pathways, including phospholipase A_2, cyclooxygenase, lipoxygenase and nuclear factor-κB (NF-κB) activation. These findings and others suggest that the scope of polyphenol effects likely encompasses more than simple antioxidant activity.

Although powerful effects from polyphenol administration have been observed *in vivo*, corresponding clinical benefits have been much more difficult to achieve. One major reason for these divergent findings stems from the fact that poor polyphenol absorption from the gastrointestinal tract typically leads to low maximal plasma concentrations. This fact has led some to hypothesize that the potential for therapeutic benefit from polyphenols would be more dramatic for gastrointestinal disease. The balance of this review will focus on the effects dietary polyphenols exert on the gastrointestinal tract and liver.

Fate of ingested polyphenols

Although many in-vitro studies demonstrate robust biological effects from plant polyphenols, actual in-vivo systemic effects may likely be modest. Some investigators have questioned the ability of ingested dietary polyphenols to affect systemic antioxidant capacity. Given a total antioxidant value in plasma of over 10^3 μmol/l, a minimum concentration of 20–50 μmol/l additional antioxidant from dietary sources would be required to make a significant contribution to systemic antioxidant capacity [4]. This is unlikely to occur, as even high intakes of dietary polyphenols typically result in unconjugated serum levels of up to 1 μmol/l [4]. Direct contact between dietary phenols and the digestive tract mucosa, however, may elicit more dramatic results. A wealth of evidence suggests that luminal concentrations of polyphenols might be much higher than serum concentration [4]. Because of poor intestinal absorption, large quantities of polyphenol compounds are delivered to the colon, where many undergo extensive metabolism via colonic flora. High levels of dietary polyphenols actually alter colonic flora [8]. Unaltered flavanoids and microbial metabolic products of dietary polyphenols might directly affect the colonic mucosa, providing antioxidant effects against dietary sources of reactive oxygen species. Along that line, concentrations of phenolic compounds have been measured in human fecal water [4]. Fecal water is the component of stool that is more likely to interact with the colonic mucosa than stool solids; thus, fecal water polyphenol levels are likely more important indicators of potential bioactivity. Stool water accounts for an average of 70–75% of total fecal weight [4]. Analysis of fecal water polyphenols demonstrates relatively low levels of flavonoids, but significantly higher levels of lower molecular weight phenolic compounds, suggestive of extensive bacterial metabolism [4]. In light of this evidence, we will now evaluate evidence examining the effects of dietary polyphenols on mucosal-based digestive disorders.

Disease processes of the gastrointestinal mucosa

Lined by both squamous and columnar epithelial cells, the digestive tract is susceptible to a variety of diseases arising from this cell layer, including infections, primary inflammatory disorders (such as Crohn’s disease or ulcerative colitis), peptic ulcer disease, and neoplastic conditions.

Inflammatory bowel disease

Preclinical evaluations of green tea polyphenols in animal models of inflammatory bowel disease have demonstrated promising results. Oxidative stress plays a significant role in the pathogenesis of inflammatory bowel disease (IBD). Both peripheral and mucosal-based mononuclear cells as well as activated neutrophils provide a major source of free radicals [9••]. In a recent evaluation of a polyphenol-rich extract of green tea leaves (GTE) [10], investigators examined the effect of GTE on a 2,4, 6-dinitrobenzene sulphonic acid induced model of colitis in Sprague-Dawley rats. GTE was administered via intraperitoneal bolus for 4 days after induction of colitis; the animals were sacrificed, and their colons examined. GTE decreased colonic inflammation and tumor necrosis factor (TNF)-α levels, reduced intercellular adhesion molecule-1 expression, and increased levels of hemeoxygenase-1, an inducible enzyme important in protecting against oxidative stress. Another important potential mechanism for treating IBD, independent of antioxidant properties, relates to the effects of green tea polyphenol fraction on NF-κB. As demonstrated in a fetal intestinal epithelial cell line (IEC-6), the green tea polyphenol (−)-epigallocatechin-3-gallate (EGCG) inhibits the activation of NF-κB by inflammatory mediators in a dosedependent fashion by inhibiting the phosphorylation of inhibitor-κB by inhibitor κ kinase, thus blocking NF-κB from migrating to the nucleus and binding to cytokine promoter sequences [11]. Green tea polyphenols were also evaluated along with two other powerful antioxidants, S-adenosylmethionine and 2(R,S)-n-propylthiazolidine-4(R)-carboxylic acid in the dextran sodium sulfate (DSS) murine model of non-T-cell mediated colitis [12]. All three antioxidants demonstrated improvement in diarrhea, colon histology, body weight, hematocrit, and colon length compared with untreated animals receiving DSS. In addition, serum markers of inflammation (serum amyloid A and TNF-α) were significantly lower in antioxidant-treated animals, suggesting that orally ingested antioxidants can benefit inflammatory conditions of the gastrointestinal mucosa in preclinical models.

Acute diarrhea

Polyphenols may also play a role in controlling noninflammatory diarrheal states. A polyphenol extract from apples was found to have an inhibitory effect on cholera toxin induced diarrhea, in a dose-dependent fashion [13]. This effect could be seen as long as 10 min after toxin injection. The fraction containing highly polymerized cathechins most effectively inhibited the toxin-mediated fluid secretion. A clinical trial in a pediatric population with acute diarrhea evaluated the effects of a tannin-rich carob pod powder, which contained 21.2% polyphenols [14]. The carob pod powder recipients experienced cessation of diarrheal symptoms approximately 1.5 days earlier than controls. A variety of other compounds used as antidiarrheals in traditional medicine have been screened for their active ingredient, and polyphenol components have been identified as the bioactive molecules [15,16].

Peptic ulcer disease

Helicobacter pylori is a common infectious agent which can cause significant injury to the digestive tract, precipitating ulcers, chronic gastritis, and rarely cancer of the stomach. Much of the mucosal damage results from the significant oxidative stress produced during *H.*

pylohri infection [17]. Treatment of *H. pylori* generally consists of administration of proton pump inhibitors along with a variety of antibiotics. Treatment failures and possible adverse outcomes from standard therapy, however, prompted investigators to research potential alternatives. Because of the antioxidant and antiinflammatory properties of green tea polyphenol compounds, Lee *et al.* [17] examined the effects of one particular compound from green tea, EGCG, due to its ability to inhibit lipopolysaccharide-induced inflammation and its antibacterial activity. Human gastric cancer cells (AGS cells) were cultured with a pathogenic strain of *H. pylori*. Pretreatment with low doses of EGCG prevented/attenuated bacterial induced cytotoxicity, DNA damage, toll-like receptor-4 activation of mitogen-activated protein kinase signaling pathway, and apoptosis [17]. Pretreatment with high doses of EGCG (< 250 μmol/l), however, resulted in apoptosis.

Digestive tract cancers

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the US. Dietary factors are implicated in the majority of cases, particularly the high-fat Western diet. Although incompletely understood, one possible mechanism for dietary fat contribution to CRC lies in alterations in arachadonic acid metabolism [18]. Other risk factors include inheritable genetic mutations and IBD involving the colon. Colitis likely increases the risk for CRC via oxidative stress. Therefore, dietary antioxidant therapy has been heralded as a potential chemo-preventative agent for colon and other digestive tract cancers. Catechins have been a major focus of both basic and clinical research in recent years, due to the high level of ingestion, particularly in Asian societies. Epidemiological studies provided the first evidence of a protective benefit from dietary polyphenols. With a cohort of tea-drinking Chinese individuals, Ji *et al.* [19] performed a large population-based case–control study on the effects of green tea consumption on pancreatic enzymes and CRC. After adjusting for age, income, education and cigarette usage, green tea consumption was inversely associated with cancer incidence, particularly pancreatic cancer and CRC. Consumption of green tea by men and women at the highest levels resulted in a significantly lower odds ratio (OR) than in controls (colon cancer 0.82 for males, 0.67 for females, rectal cancer 0.72 for males, 0.57 for females, and pancreatic cancer 0.63 for males, 0.53 for females). Additional evidence for the benefit of green tea polyphenols comes from animal models of colon carcinogenesis based on a high-fat diet. Using the azoxymethane-induced colon carcinogenesis model, responses of phospholipase A_2 activity, cycloxygenase-2 expression, lipoxygenase activity and lipoxygenase metabolite formation, leukotriene B_4 and aberrant colonic crypt formation (ACF) to green tea administration were measured in the colonic mucosa and tumors of rats fed high and low-fat corn oil diets [18]. A low-fat diet resulted in significantly better results in all parameters tested than the high-fat diet. Administration of green tea reduced protein levels of phospholipase A_2 and 5-lipoxygenase, with a corresponding decrease of 90% in leukotriene B_4 levels. Green tea also decreased the incidence of ACF in rats fed a high-fat, but not a low-fat diet [18]. These studies suggest that the antioxidant properties of green tea polyphenols alone might benefit patients at risk for colon cancer.

Polyphenols and liver disease

Silymarin (a hepatoprotective flavonoid) is the active ingredient extracted from *Silybium marianum* (‘milk thistle’), a member of the daisy family whose leaves have prominent white ‘milky’ veins [20•]. This agent protects animals against multiple types of experimental liver injury, such as carbon tetrachloride, acetaminophen, iron overload, bile duct obstruction and, very importantly, amanita mushroom poisoning [20•,21,22]. In several animal species, the drug was effective in both pretreatment phases as well as following ingestion [20•,21,22]. Claims for use as an antidote for acute Amanita poisoning in humans have been made, but its efficacy is less clear. The proposed beneficial mechanisms of action of silymarin in liver disease are multiple, including direct antioxidant effects, inhibition of proinflammatory cytokines, inhibition of fibrosis, effects on lipid metabolism and positive effects on liver regeneration [20•,21–24,25•,26–29].

In the United States, silymarin is probably the most widely used form of complementary and alternative medicine (CAM) in the treatment of liver disease. Claims have been made for its hepatoprotective effects in various forms of toxic hepatitis, fatty liver, cirrhosis, ischemic injury and viral-induced liver disease [20•,21,22] due to its antioxidant activities, antiinflammatory and antifibrotic effects. Controlled trials of silymarin have been performed in Europe, with variable results. A beneficial effect was apparent in patients with alcoholic cirrhosis, especially in those with milder disease (Child’s A category), during a treatment program administering 140 mg three times daily for a mean duration of 41 months [30]. No beneficial effects were found, however, using 150 mg silymarin three times daily in a study of 200 patients with alcoholic cirrhosis, some of which were coinfected with hepatitis C [31]. Both trials had major shortcomings, including high drop-out rates and compliance issues. Silymarin has been shown to improve insulin resistance in alcoholic cirrhotics in at least two major trials [32,33]. By contrast, a retrospective analysis of three different dosing regimens of silymarin failed to demonstrate improvements in liver enzymes with any dose in hepatitis C [34]. Silymarin is likely to remain one of the most popular forms of CAM therapy for liver disease because it has a good safety profile, it has been extensively investigated in multiple forms of experimental liver injury in animals, and some positive results have been reported in humans. The National Institutes of Health (NIH) will be funding large clinical trials in the near future to further define the mechanism(s) of action and efficacy in diseases such as hepatitis C and nonalcoholic steatohepatitis [25•].

Green tea polyphenols have been used extensively in experimental models of liver injury. Our laboratory showed that the green tea polyphenols protected against endotoxin-induced hepatotoxicity and lethality [35]. In this study, green tea also decreased endotoxin-induced NF-κB activation and TNF production. Similarly, green tea polyphenols have been shown to protect against experimental alcohol-induced hepatic fibrosis in rats and to concomitantly decrease endotoxin levels [36].

Green tea (EGCG) protected against the hepatotoxin, carbon tetrachloride [37]. EGCG improved liver histology and liver enzymes and decreased inducible nitric oxide synthase, nitric oxide-generated radicals and immunohistochemical and staining for nitrotyrosine. Green tea from *Camellia sinensis* has attenuated primary graft failure after liver

transplantation of fatty livers in rats [38]. These same investigators showed that *Camellia sinensis* attenuated experimental hepatic fibrosis in rats following bile duct ligation [39]. This green tea polyphenol decreased stellate cell activation, production of the lipid peroxidation product 4-hydroxynoneal and decreased production of the cytokines TNF-α and transforming growth factor (TGF)-β, mediators of liver injury and fibrosis, respectively.

While these recent animal studies provide a strong rationale for the use of green tea polyphenols in liver disease, to our knowledge no major human trials have been performed with these agents in liver disease.

Safety concerns

Because of the relative youth of polyphenol research, many safety questions remain unanswered. Polyphenol contents of all foods have not been adequately characterized, and thorough observational and epidemiological studies have not been carried out. Carefully conducted clinical trials are rare for dietary supplements, due in part to current regulatory requirements. Therefore, suggested dosages of various marketed supplements often have no scientific basis, with some recommendations exceeding the common daily intake from a typical Western diet by around 100 times [40••]. Other safety concerns with plant polyphenols include direct toxicity, inhibiting beneficial effects of other nutrients, and interactions with pharmaceuticals [40••]. Direct toxicity from polyphenol use, as assessed by preclinical and clinical investigations, includes concerns for carcinogenicity, thyroid toxicity, hormonal effects, and other clinical symptoms, such as nausea, vomiting, and diarrhea. Another scenario in which unexpected polyphenol toxicity might arise stems from using a compound that might appear safe when ingested in its native form, but causes toxicity due to contamination during commercial production methods [40••].

Conclusion

This review highlights the current optimism surrounding the use of polyphenols to improve digestive health. Claims for both health promotion and disease treatment using polyphenol compounds abound in the media and lay literature. Unfortunately, scientific knowledge has not kept pace with the popular culture. Therefore, clinicians should make a careful assessment of the validity of any health-related claims behind polyphenol use and balance those potential benefits against the possibility of adverse effects before making recommendations to patients regarding polyphenol supplementation. Several important studies are currently being performed under the sponsorship of the NIH which should provide new insights into the therapeutic efficacy of polyphenols in humans.

Abbreviations

CRC	colorectal cancer
EGCG	(−)-epigallocatechin-3-gallate
IBD	inflammatory bowel disease
NF-κB	nuclear factor-κB

TNF tumor necrosis factor

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 183–184).

1. Manach C, Scalbert A, Morand C, et al. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004; 79:727–747. [PubMed: 15113710]
2. Scalbert A, Johnson IT, Saltmarsh M. Polyphenols: antioxidants and beyond. Am J Clin Nutr. 2005; 81:215S–217S. [PubMed: 15640483] Excellent overview of polyphenols and antioxidants.
3. Rice-Evans CA, Miller NJ, Paganga G. Structure– antioxidant activity relationships of flavonoids and phenolic acids. Free Radical Biol Med. 1996; 20:933–956. [PubMed: 8743980]
4. Halliwell B, Rafter J, Jenner A. Health promotion by flavonoids, tocopherols, tocotrienols, and other phenols: direct or indirect effects? Antioxidant or not? Am J Clin Nutr. 2005; 81:268S–276S. [PubMed: 15640490]
5. Moskaug JO, Carlsen H, Myhrstad MC, Blomhoff R. Polyphenols and glutathione synthesis regulation. Am J Clin Nutr. 2005; 81:277S–283S. [PubMed: 15640491]
6. Forman HJ, Torres M, Fukuto J. Redox signaling. Mol Cell Biochem. 2002:234–235. 49–62.
7. Lambert JD, Hong J, Yang G-Y, et al. Inhibition of carcinogenesis by polyphenols: evidence from laboratory investigations. Am J Clin Nutr. 2005; 81:284S–291S. [PubMed: 15640492]
8. Gee JM, Johnson IT. Polyphenolic compounds: interactions with the gut and implications for human health. Curr Med Chem. 2001; 8:1245–1255. [PubMed: 11562264]
9. Dryden GW, Deaciuc I, Arteel G, McClain CJ. Clinical implications of oxidative stress and antioxidant therapy. Curr Gastroenterol Rep. 2005; 7:308–316. [PubMed: 16042916] Review of assessment of oxidative stress and antioxidant therapies, including green tea polyphenols.
10. Mazzon E, Muia C, Di Paola R, et al. Green tea polyphenol extract attenuates colon injury induced by experimental colitis. Free Radic Res. 2005; 39:1017–1025. [PubMed: 16087483]
11. Yang F, Oz HS, Barve S, et al. The green tea polyphenol (−)-epigallocatechin-3-gallate blocks nuclear factor-kappa B activation by inhibiting I kappa B kinase activity in the intestinal epithelial cell line IEC-6. Mol Pharmacol. 2001; 60:528–533. [PubMed: 11502884]
12. Oz HS, Chen TS, McClain CJ, de Villiers WJ. Antioxidants as novel therapy in a murine model of colitis. J Nutr Biochem. 2005; 16:297–304. [PubMed: 15866230]
13. Saito T, Miyake M, Toba M, et al. Inhibition by apple polyphenols of ADP-ribosyltransferase activity of cholera toxin and toxin-induced fluid accumulation in mice. Microbiol Immunol. 2002; 46:249–255. [PubMed: 12061627]
14. Loeb H, Vandenplas Y, Wursch P, Guesry P. Tannin-rich carob pod for the treatment of acute-onset diarrhea. J Pediatr Gastroenterol Nutr. 1989; 8:480–485. [PubMed: 2723939]
15. Agbor GA, Leopold T, Jeanne NY. The antidiarrhoeal activity of Alchornea cordifolia leaf extract. Phytother Res. 2004; 18:873–876. [PubMed: 15597302]
16. Abdulrahman F, UInyang IS, Abbah J, et al. Gamaniel, effect of aqueous leaf extract of Irvingia gabonensis on gastrointestinal tract in rodents. Ind J Exp Biol. 2004; 42:787–791.
17. Lee K-M, Yeo M, Choue J-J, et al. Protective mechanism of epigallocatechin-3-gallate against Helicobacter pylori-induced gastric epithelial cytotoxicity via the blockage of TLR-4 signaling. Helicobacter. 2004; 9:632–642. [PubMed: 15610077]

18. Ju J, Liu Y, Hong J, et al. Effects of green tea and high-fat diet on arachidonic acid metabolism and aberrant crypt foci formation in an azoxymethane-induced colon carcinogenesis mouse model. Nutr Cancer. 2003; 46:172–178. [PubMed: 14690793]
19. Ji B-U, Chow W-H, Hsing AW, et al. Green tea consumption and the risk of pancreatic and colorectal cancers. Int J Cancer. 1997; 70:255–258. [PubMed: 9033623]
20. Mennen LI, Walker R, Bennetau-Pelissero C, Scalbert A. Risks and safety of polyphenol consumption. Am J Clin Nutr. 2005; 81:326S–329S. [PubMed: 15640498] Review of safety issues and polyphenols.
21. Flora K, Hahn M, Rosen H, Benner K. Milk thistle (Silybum marianum) for the therapy of liver disease. Am J Gastroenterol. 1998; 93:139–143. [PubMed: 9468229]
22. Vogel G, Tuchweber B, Trost W, Mengs U. Protection by silibinin against Amanita phalloides intoxication in beagles. Toxicol Appl Pharmacol. 1984; 73:355–362. [PubMed: 6719456]
23. Mira L, Silva M, Manso CF. Scavenging of reactive oxygen species by silibinin dihemisuccinate. Biochem Pharmacol. 1994; 48:753–759. [PubMed: 8080448]
24. Schumann N, Prockl J, Kiemer AK, et al. Silibinin protects mice from T-cell dependent liver injury. J Hepatol. 2003; 39:333–340. [PubMed: 12927918]
25. Hoofnagle JH. Milk thistle and chronic liver disease. Hepatology. 2005; 42:4. [PubMed: 15962321] A synopsis of silymarin and NIH initiatives.
26. Krueger KJ, McClain CJ, McClave SA, Dryden GW. Nutritional supplements and alternative medicine. Curr Opin Gastroenterol. 2004; 20:130–138. [PubMed: 15703634]
27. Jeong DH, Lee GP, Jeong WI, et al. Alterations of mast cells and TGF-beta1 on the silymarin treatment for Cl(4)-induced hepatic fibrosis. World J Gastroenterol. 2005; 11:1141–1148. [PubMed: 15754394]
28. Saliou C, Rihn B, Cillard J, et al. Selective inhibition of NF-kappaB activation by the flavonoid hepatoprotector silymarin in HepG2: evidence for different activating pathways. FEBS Lett. 1998; 440:8–12. [PubMed: 9862414]
29. Lieber CS, Leo MA, Cao Q, DeCarli LM. Silymarin retards the progression of alcohol-induced hepatic fibrosis in baboons. J Clin Gastroenterol. 2003; 37:336–339. [PubMed: 14506392]
30. Ferenci P, Dragosies B, Dittrich H, et al. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. J Hepatol. 1989; 9:105–113. [PubMed: 2671116]
31. Pares A, Planas R, Torres M, et al. Effects of silymarin in alcoholic patients with cirrhosis of the liver: results of a controlled, double-blind, randomized and multicenter trial. J Hepatol. 1998; 28:615–621. [PubMed: 9566830]
32. Lirussi F, Beccarello A, Zanette G, et al. Silybin-beta-cyclodextrin in the treatment of patients with diabetes mellitus and alcoholic liver disease: efficacy study of a new preparation of an anti-oxidant agent. Diabetes Nutr Metab. 2002; 15:222–231. [PubMed: 12416659]
33. Velussi M, Cernigoi AM, De Monte A, et al. Long-term (12 months) treatment with an anti-oxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients. J Hepatol. 1997; 26:871–879. [PubMed: 9126802]
34. Huber R, Futter I, Ludtke R. Oral silymarin for chronic hepatitis C: a retrospective analysis comparing three dose regimens. Eur J Med Res. 2005; 10:68–70. [PubMed: 15817425]
35. Yang F, de Villiers WJS, McClain CJ, Varilek GW. Green tea polyphenols block endotoxin-induced tumor necrosis factor-alpha production and lethality in a murine model. J Nutr. 1998; 128:2334–2340. [PubMed: 9868178]
36. Li YM, Zhang XG, Zhou HL, et al. Effects of tea polyphenols on hepatic fibrosis in rats with alcoholic liver disease. Hepatobiliary Pancreat Dis Int. 2004; 3:577–579. [PubMed: 15567748]
37. Chen JH, Tipoe GL, Liong EC, et al. Green tea polyphenols prevent toxin-induced hepatotoxicity in mice by down-regulating inducible nitric oxide-derived prooxidants. Am J Clin Nutr. 2004; 80:742–751. [PubMed: 15321817]
38. Zhong Z, Connor HD, Froh M, et al. Polyphenols from Camellia sinenesis prevent primary graft failure after transplantation of ethanol-induced fatty livers from rats. Free Radic Biol Med. 2004; 36:1248–1258. [PubMed: 15110390]

39. Zhong Z, Froh M, Lehnert M, et al. Polyphenols from Camellia sinenesis attenuate experimental cholestasis-induced liver fibrosis in rats. Am J Physiol Gastrointest Liver Physiol. 2003; 285:G1004–G1013. [PubMed: 12791596]

40. Mennen LI, Walker R, Bennetau-Pelissero C, Scalbert A. Risks and safety of polyphenol consumption. Am J Clin Nutr. 2005; 81:326S–329S. [PubMed: 15640498] An overview of polyphenols and safety issues.

Table 1

Flavanoid subclasses with examples

Flavanols	quercetin, kaempferol, myricetin, cathechins
Monomeric flavanols	catechin, epicatechin
Anthocyanidins	cyanidin, pelargonidin, peonidin, delphinidin, malvidin
Flavones	apigenin, luteolin
Flavanones	hesperetin, naringenin, eriodictyol
Isoflavones	daidsein, genistein, glycitein