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REVIEW

A quest for staunch effects of flavonoids: Utopian protection against hepatic ailments

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Abstract The role of flavonoids as the major red, blue and purple pigments in plants has gained these secondary products a great deal of attention over the years. Flavonoids are polyphenols and occur as aglycones, glycosides and methylated derivatives. Flavonoids are the main components of a healthy diet containing fruits and vegetables and are concentrated especially in tea, apples and onions. Till date, more than 6000 flavonoids have been discovered, out of which 500 are found in free state. They are abundant in polygonaceae, rutaceae, leguminosae, umbelliferae and compositae. Flavonoids are powerful antioxidants. In addition to their role in nutrition, flavonoids possess many types of pharmacological activities, including anti-inflammatory, antioxidative, hepatoprotective, vasorelaxant, antiviral and anticarcinogenic effects. The present review is focused on flavonoids derived from natural products that have shown a wise way to get a true and potentially rich source of drug candidates against liver ailments. The present review initially highlights the current status of flavonoids and their pharmaceutical significance, role of flavonoids in hepatoprotection, therapeutic options available in herbal medicines and in later section, summarizes flavonoids as lead molecules, which have shown significant hepatoprotective activities.

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Contents

1. Introduction

The flavonoids are a diverse group of polyphenolic compounds widely distributed in the plant kingdom (Harborne and Williams, 2000). Flavonoids are nearly ubiquitous in plants and are recognized as the pigments responsible for the colors of leaves, especially in autumn (Saraf et al., 2007). Flavonoids contribute to the flavor and pigmentation of the fruits and vegetables in the human diet (Timberlake and Henry, 1986). More than 6000 plant flavonoids have been described, and they have been classified into at least 10 chemical groups according to their structural patterns. However, laboratory and epidemiologic studies have focused on six flavonoid subgroups: flavones, flavonols, flavan-3-ols (catechins), procyanidins, flavanones, and isoflavones (Theodoratou et al., 2007). They also have important roles in plant growth, reproduction, and pathogen and predator resistance (Harborne and Williams, 2000). These are formed in plants and participate in the light-dependent phase of photosynthesis during which they catalyze electron transport (Middleton et al., 2000).

Flavonoids are present in plants either as aglycones or as glycoside conjugates. Attached sugar moieties include D-glucose,

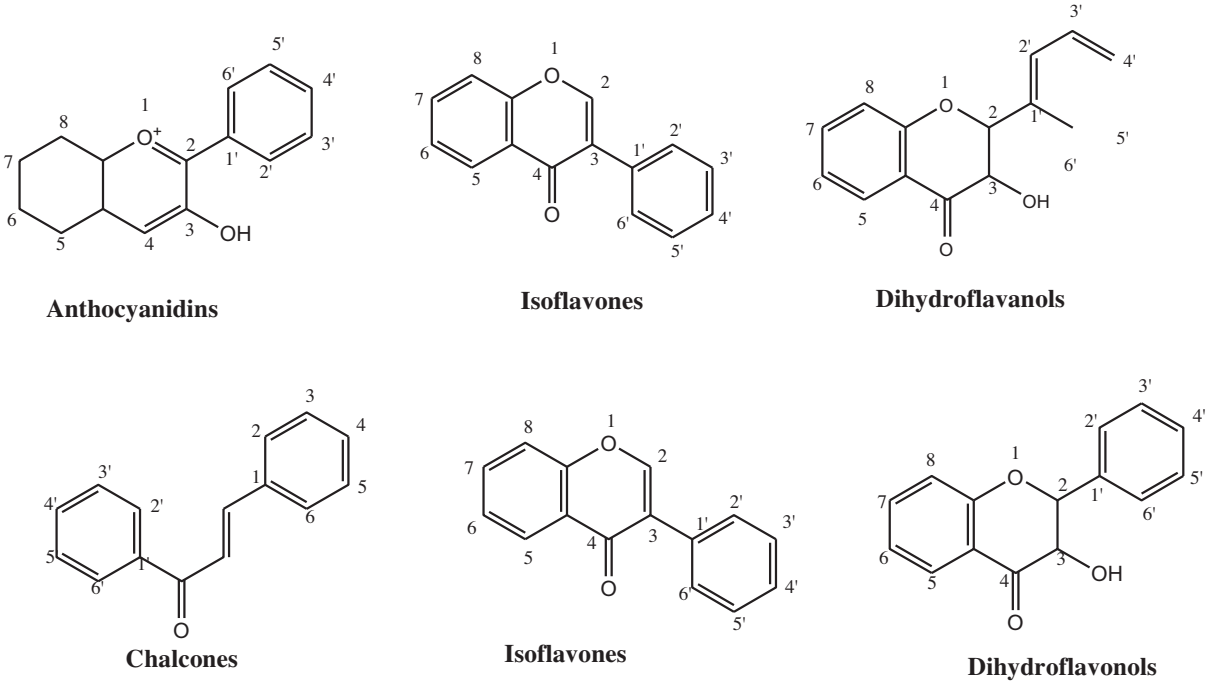

Figure 1 Basic structure of various flavonoids and related compounds.

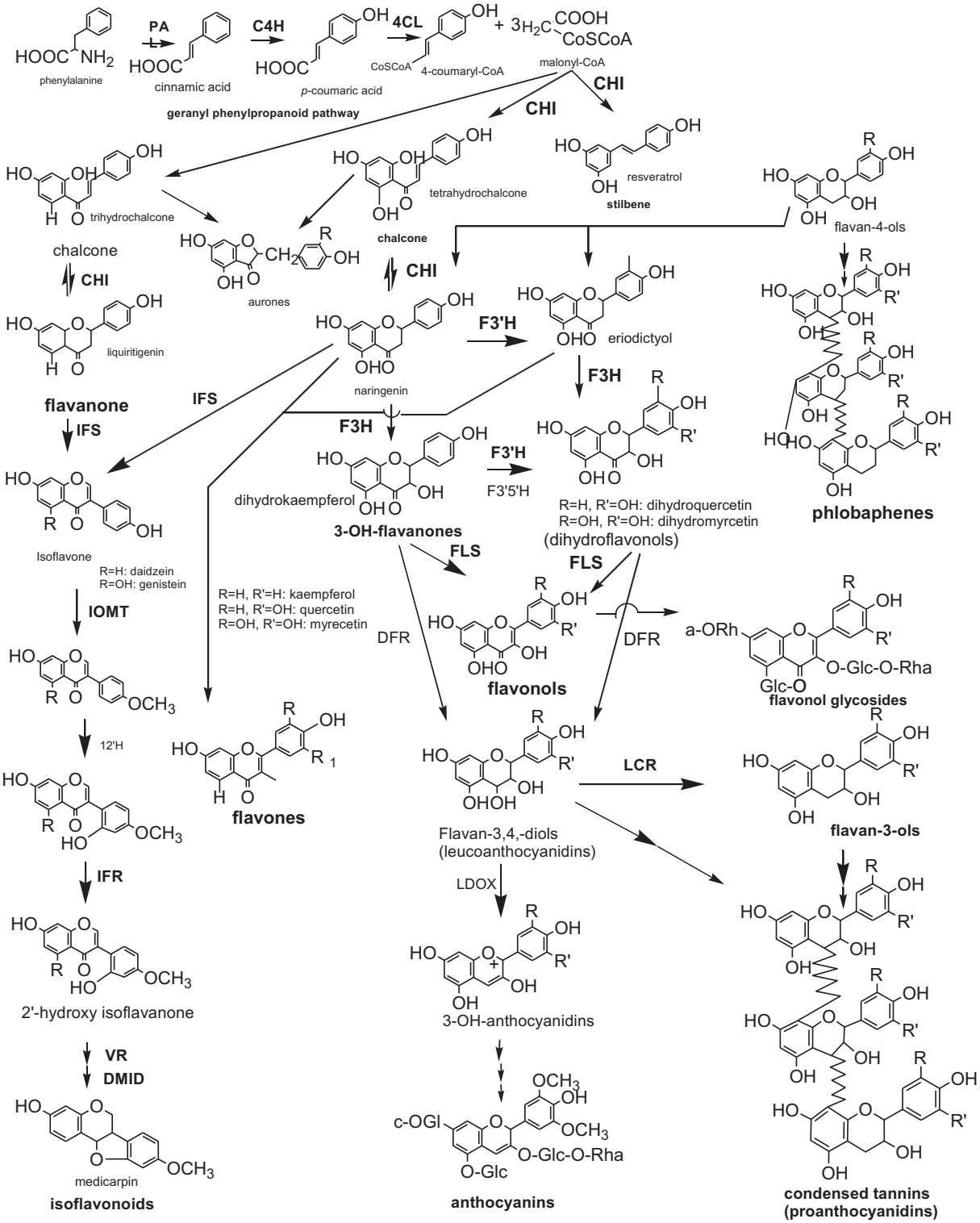

Figure 2 The major branch pathways of flavonoid biosynthesis.

L-rhamnose, glucorhamnose, galactose, lignin, and arabinose (Ross and Kasum, 2002). The basic structure of various flavonoids and their related compounds are given in Fig. 1. They are prominent components of citrus fruits (Kefford and Chandler, 1970) and other food sources (Herrmann, 1976) and are consumed regularly with the human diet. It is generally recognized that an increased consumption of vegetables and fruits protects against cancer and cardiovascular diseases (Hollman, 2004). In addition to their role in nutrition, flavonoids possess many types of pharmacological activities, including anti-inflammatory, antioxidative, hepatoprotective, antiviral and anticarcinogenic effects (Chen et al., 2007). This class of compounds has become increasingly popular in terms of health protection because they possess a remarkable spectrum of biochemical

and pharmacologic activities (Watjen et al., 2005). Perhaps the most active area of flavonoid research at the present time is the possible medicinal contribution that flavonoids make to human health (Stipcevic et al., 2006). The present review is focused to cover the current status of flavonoids and their pharmaceutical significance, role of flavonoids in hepatoprotection, therapeutic options available in herbal medicines containing flavonoids and phenolic compounds and chemically defined flavonoid molecules reported for hepatoprotection.

2. Biochemical pathway for flavonoid biosynthesis

Flavonoids constitute a relatively diverse family of aromatic molecules that are derived from phenyl and malonyl-coenzyme A, CoA; via the fatty acid pathway (Shirley, 2001).

In the early steps of flavonoid biosynthesis elucidated by Woo et al. (2005) with slight modifications, in Fig. 2, phenylalanine derived from the shikimic acid pathway is converted to coumaroyl-CoA by phenylalanine ammonia-lyase, cinnamate 4-hydroxylase, and 4-coumarate: CoA ligase. Chalcone synthase, the first committed enzyme for flavonoid synthesis, results in the condensation of coumaroyl-CoA with three molecules of malonyl-CoA from acetyl-CoA to form naringenin. Naringenin chalcone then is converted to naringenin by chalcone isomerase. Naringenin is further converted by glycosylation, acylation, and methylation of its three rings. The end result of all these enzymatic steps is the synthesis of substituted flavones, flavonols, catechins, deoxyflavonoids, and anthocyanins. Isoflavonoids are formed from naringenin or deoxyflavonoids by an aryl migration of the B-ring to the 3-position, followed by hydroxylation at the 2-position, which is catalyzed by isoflavone synthase (IFS), a cytochrome P450 enzyme. The 2-hydroxyisoflavone intermediate is unstable and is dehydrated to yield isoflavone (Woo et al., 2005).

Enzyme names are abbreviated as: cinnamate-4-hydroxylase (C4H), chalcone isomerase (CHI), chalcone synthase (CHS), 7,29-dihydroxy, 49-methoxyisoflavanol dehydratase (DMID), flavanone 3-hydroxylase (F3H), flavone synthase (FSI and FSII), isoflavone *O*-methyltransferase (IOMT), isoflavone reductase (IFR), isoflavone synthase (IFS), leucoanthocyanidin dioxygenase (LDOX), leucoanthocyanidin reductase (LCR), *O*-methyltransferase (OMT), phe ammonia-lyase (PAL), rhamnosyl transferase (RT), stilbene synthase (STS), UDPG flavonoid glucosyl transferase (UFGT) and vestitone reductase (VR).

3. Flavonoids in pharmaceuticals

Epidemiological studies have shown that a diet rich in plant-derived food is consistently associated with a reduced risk of developing chronic diseases. Flavonoids are also common constituents of plants used in traditional medicine to treat a wide range of diseases (Lazaro, 2009). Flavonoids are postulated to play pivotal roles in the adaptation to their biological environments both as defensive compounds (phytoalexins) and as chemical signals (Li and Jiang, 2007). Quercetin, the most abundant flavonoid in nature, present in large amounts in vegetable, fruits, tea, and olive oil, and because it contains a number of phenolic hydroxyl groups, it exhibits its therapeutic potential against many diseases, including ischemic heart diseases, atherosclerosis, liver fibrosis, renal injury, and chronically biliary obstruction (Mandal et al., 2007). Green tea, especially its major polyphenolic constituent, epigallocatechin-3-gallate, has received much attention as a potential cancer chemopreventive agent (Phosrithong and Ungwitayatorn, 2009). Medicinally important flavonoids, along with their pharmaceutical significance are discussed as follows:

3.1. Flavonoids as anticancer agents

Flavonoid and its derivatives possessing *p*-glycoprotein inhibitory effects may become candidates of effective agents in cancer chemotherapy. The important mechanism by which flavonoids exert their *in vivo* chemoprotective effects is through their inhibition of efflux transporters and metabolizing enzymes, such as CYP i.e., cytochrome P-450 (Bansal et al., 2009). Detailed studies have revealed that quercetin exerted a dose-dependent inhibition of growth and colony formation. The flavonoids like kaempferol, catechin, toxifolin and fisetin are also reported to suppress cell growth (Tapas et al., 2008).

3.2. Flavonoids as antibacterial agents

Flavonoids like rutin, naringin and baicalin possess antibacterial activity (Sharma, 2006). Flavonoids are hydroxylated phenolic substances but occur as a C6–C3 unit linked to an aromatic ring (Cowan, 1999). Since they are known to be synthesized by plants in response to microbial infection, it should not be surprising that they have been found *in vitro* to be effective antimicrobial substances against a wide array of microorganisms. Their activity is probably due to their ability to complex with extracellular and soluble proteins and to complex with bacterial cell walls, as in case of quinones. More lipophilic flavonoids may also disrupt microbial membranes (Firas and Hassan, 2008). Flavonoid compounds also exhibit inhibitory effects against multiple viruses. Numerous studies have documented the effectiveness of flavonoids such as swertifrancheside, glycyrrhizin and chrysin against human immunodeficiency virus (HIV) (Cowan, 1999).

3.3. Flavonoids as antiprotozoans

Flavonoids, especially those isolated from plants, have been demonstrating promising antileishmanial and antitrypanosomal activities. *Baccharis* species have been the source of antileishmanial and antimalarial compounds, with active phenolics and triterpenoids. The methanolic extracts of *B. trimera* have also been shown to be effective against cutaneous species of leishmania, including significant activity against pathogenic yeasts (Grecco et al., 2010). The antioxidant, antiprotozoal and suppressive effects of flavonoids on CYP enzymes and *p*-glycoproteins indicate that they can be synergistically combined with currently used antiparasitic drugs, instead of in substitution to those drugs, to extend their life span, to increase their bioavailability and to delay the development of drug resistance by parasites and microorganisms (Ferreira and Luthria, 2010).

3.4. Flavonoids as anti ulcer and gastroprotective agents

Peptic ulcer is a chronic and appalling disease. Today, it is dominant among the diseases that affect the world's population. The

principal factors causing this disease are inadequate dietetic habits, prolonged use of non-steroidal anti-inflammatory drugs, stress and infection by *Helicobacter pylori*, in addition to other factors of genetic origin (Falcao et al., 2008). Several mechanisms have been proposed to explain the gastroprotective effect of flavonoids; these include increase of mucosal prostaglandin content, decrease of histamine secretion from mast cells by inhibition of histidine decarboxylase and inhibition of *H. pylori* growth (Borrelli and Izzo, 2000). Most of these effects have been attributed to the influence of flavonoids on arachidonic acid metabolism, their vasoprotective action and their ability to interfere with the formation of histamine in the gastric mucosa (Nwafor, 2004).

3.5. Flavonoids as hepatoprotective

Flavonoids represent a beneficial group of naturally occurring compounds with hepatoprotective potentials. Hepatoprotective potential of some flavonoids may be owing to their antioxidant activity and capability of normalization of impaired membrane function activity (Mukherjee et al., 2009). Silymarin is a natural extract with hepatoprotective properties composed mainly of flavonolignans, with silibinin being its principal constituent (Khabiya and Joshi, 2010). The aqueous extract of *Psidium guajava* Linn. leaves showed good hepatoprotective activity in carbon tetrachloride induced acute and chronic liver damage, paracetamol induced liver damage and thioacetamide induced liver necrosis (Roy et al., 2006). The flavonoid rich alcoholic extract of *Thuja occidentalis* was found to possess good hepatoprotective property against carbon tetrachloride induced liver damage (Dubey and Batra, 2008).

3.6. Flavonoids on cardiovascular system: vasorelaxing effect

To date, a substantial number of studies have reported the efficacy of dietary flavonoids or plant foods or extracts in reducing biomarkers of cardiovascular disease risk in acute and short-term interventions with healthy volunteers and at-risk population groups (Hooper et al., 2008). Flavonoids have strong antioxidant properties *in vitro*, and investigators hypothesized that reduced cardiovascular risk might reflect an antioxidant effect, including an ability to scavenge reactive oxygen species and prevent oxidative modification of low density lipoprotein, a critical step in atherogenesis (Shenouda and Vita, 2007). Animal studies as well as human studies, although limited in number, have shown beneficial changes in biological phenomena related to cardiovascular health after the consumption of polyphenol rich foods such as cocoa, red wine, and tea (Erlund et al., 2008).

3.7. Flavonoids as neuroprotective agents

Synthetic flavonoids, such as 6-bromoflavone and 6-bromo-3′-nitroflavones, were shown to displace [3H] flumazenil binding to membranes from rat cerebellum but not from spinal cord, indicating selectivity for the BZ-Omega receptor subtype, but the latter was more potent than 6-bromoflavone. Results from tail conflict tests in rats showed that these synthetic flavonoids possess anxiolytic like properties similar or superior to that of diazepam (Tapas et al., 2008).

3.8. Flavonoids as anti-inflammatory

Plant flavonoids show anti-inflammatory activity *in vitro* and *in vivo* (Kim et al., 2004). Effects of flavonoids on a variety of inflammatory processes have been object of diverse reviews and it has been demonstrated that they are able to inhibit a series of enzymes which are activated in the course of the inflammatory process. Prostaglandins and nitric oxide biosynthesis is involved in inflammation, and isoforms of inducible nitric oxide synthase (iNOS) and of cyclooxygenase (COX-2) are responsible for the production of a great amount of these mediators. *In vitro* studies have confirmed that the flavonoid quercetin inhibits nitric oxide production and the expression of iNOS. Although the inhibition of iNOS can contribute to the anti-inflammatory effect of flavonoids, the mechanism responsible for such effect is not known in depth (Gallego et al., 2007).

3.9. Flavonoids as anti-diabetic agents

So far, many anti-diabetic flavonoids have been reported, such as myricetin with insulinomimetic effects, quercetin with anti-diabetic effects in streptozotocin induced diabetic rats, and kaempferol-3,7-*O*-(α) dirhamnoside with hypoglycemic and antioxidant effects (Zhu et al., 2010). Some flavonoids and polyphenols, as well as sugar derivatives, are found to be effective against the inhibitory activities of α-glucosidase and aldose reductase or other treatment approaches to diabetes (Jung et al., 2006). Long term effects of diabetes include progressive development of specific complements such as retinopathy, which affects eyes and lead to blindness; nephropathy in which the renal functions are altered or disturbed and neuropathy which is associated with the risks of amputations, foot ulcers and features of autonomic disturbance including sexual dysfunctions. Numerous studies report the anti-diabetic effects of polyphenols. Tea catechins have been investigated for their anti-diabetic potential (Pandey and Rizvi, 2009). Hesperetin has the potential to treat multiple ocular diseases like diabetic retinopathy, diabetic macular edema and cataract, by virtue of its wide-ranging pharmacological activities (Srirangam and Majumdar, 2010). *Trigonella foenum graecum* seeds are also known to possess a hypolipidemic effect and also offer antilithogenic potential due to its encouraging effect on cholesterol metabolism. Its seed has also been shown to be effective in the prevention of retinopathy and other diabetic complications when used alone or in combination with sodium orthovandate (Pandey and Rizvi, 2009).

3.10. Flavonoids as antioxidants

The best described property of phenolics is the antioxidant capability toward free radicals normally produced by cells metabolism or in response to external factors (Leopolsdini et al., 2011). Flavonoids, a group of naturally occurring benzo γ-pyrone derivatives, have been shown to possess several biological properties (including hepatoprotective, anti-thrambotic, anti-inflammatory, and antiviral activities), many of which may be related, partially at least, to their antioxidant and free-radical-scavenging ability (Theodoratou et al., 2007; Middleton et al., 2000). Antioxidants are radical scavengers, which protect the human body against free radicals (Qureshi et al., 2010).

These are the compounds, that protect cells against the damaging effects of reactive oxygen species, such as singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals and peroxynitrite. An imbalance between antioxidants and reactive oxygen species results in oxidative stress, leading to cellular damage. Oxidative stress has been linked to cancer, aging, atherosclerosis, ischemic injury, inflammation and neurodegenerative diseases (Parkinson's and Alzheimer's). Many flavonoids may help to provide protection against these diseases by contributing, along with antioxidant vitamins and enzymes, to the total antioxidant defense system of the human body. Epidemiological studies have shown that flavonoid intake is inversely related to mortality from coronary heart disease and to the incidence of heart attacks. A variety of flavonoids control the oxidation at the cellular level as antioxidants by interfering with enzyme activity, chelating of redox-active metals and by scavenging free radicals (Saraf et al., 2007).

4. Role of flavonoids in hepatoprotection

Chronic liver diseases represent a major health burden worldwide, with liver cirrhosis being the ninth leading cause of death in Western countries (Kim et al., 2002). Many ayurvedic medicines are used for treating liver disorders. Thus search for crude drugs of plant origin with antioxidant activity has become a central focus of study of hepatoprotection (Usha et al., 2007). The antiradical property of flavonoids is directed mostly toward HO; and O_2 as well as peroxyl and alkoxyl radicals (Saija et al., 1995). Because of the high reactivity of the hydroxyl group of the flavonoids, radicals are made inactive, according to the following equation:

$$\text{Flavonoid(OH)} + R^{\cdot} \rightarrow \text{Flavonoid}(O^{\cdot}) + RH \quad (1)$$

where R• is a free radical and O• is an oxygen free radical. Selected flavonoids can directly scavenge superoxides, whereas other flavonoids can scavenge the highly reactive oxygen derived radical called peroxynitrite (Nijveld et al., 2001). Due to their low redox potentials ($0.23 < E7 < 0.75$ V), flavonoids (Fl–OH) are thermodynamically able to reduce highly oxidizing free radicals with redox potentials in the range 2.13–1.0 V, by hydrogen atom donation:

$$Fl - OH + R^{\cdot} \rightarrow Fl - O^{\cdot} + RH \quad (2)$$

where R• represents superoxide anion, peroxyl, alkoxyl, and hydroxyl radicals.

The aroxyl radical (Fl–O•) may react with a second radical, acquiring a stable quinine structure. (Meng et al., 2010).

In natural conditions, most of the flavonoids occur as glucosides bound to the sugar moiety and are highly stable and water soluble (Srivastava and Gupta, 2009). Many of the flavonoids are widely described as antioxidants and have many types of pharmacological actions (Cheng and Breen, 2000). Diverse medical applications for tea flavonoids e.g., as chemiprotectors against cancer and cardiovascular disease, hepatoprotectors and antioxidants are reported (Alvarez et al., 2008). Among the many hepatoprotective herbs/compounds, milk thistle (*Silybum marianum*), glycyrrhizin, *Bupleurum chinense* (Saiko), *Schisandra chinensis* (Wuweizi) and *Phyllanthus amarus* used in traditional Chinese medicine have been most extensively studied and documented (Wang et al., 2007a). Silybum extracts are being used from centuries for the treatment of liver diseases (hepatitis, cyrosis, and icterus), against the intoxication with *Amanita* species, and also in the case of peoples with alcoholic problems. The hepatoprotective effect of these extracts (against hepatotoxicity of carbon tetrachloride, paracetamole, or Dgalactosamine) are due to the antioxidant properties of flavonoids, to the inhibition of the synthesis of phosphatidylcholine, and stimulating of hepatic synthesis of RNA proteins; silybin also stimulate the RNA polymerase I, and further the ribosomal RNA and the protein synthesis (Hadaruga and Hadaruga, 2009). A variety of substances which might contribute to hepatoprotective activity have also been identified in extracts of *Anogeissus latifolia* including tannins, gallic acid, ellagic acid and flavonoids such as lutin and quercetin, which are potential antioxidants (Pradeep, 2009).

Naringin is reported to inhibit nitrite induced methhemoglobin formation by scavenging superoxide, hydroxyl & other radicals (Kumar et al., 2003). Naringin exhibited antioxidant capacity based on increasing the gene expression of superoxide dismutase and catalase activities, & glutathione peroxidase and thereby increasing the hepatic superoxide dismutase and catalase activities, protecting the plasme vitamin E, and decreasing the hepatic mitochondrial H_2O_2 content (Jeon et al., 2001). Naringin is also shown to have hepatoprotective action (Choe et al., 2001).

Phenolic compounds acting as antioxidants may function as terminators of free radical chains and as chelators of redox-active metal ions that are capable of catalyzing lipid peroxidation (Flora, 2009). The flavonoids, such as apigenin-7-glucoside, luteolin-7-glucoside and quercitin prevented the glutathione depletion and lipid peroxidation induced by an acute intoxication with carbon tetrachloride, ethanol, acetominophen and bromobenzene in the liver and in the rats with biliary obstruction (Babenko and Shakhova, 2008). Genistein is an isoflavone found primarily in the soy protein. Administration of oral genistein was established to reduce lipid peroxidation in the liver and to increase total antioxidant capacity in hamsters (Kuzu, 2007).

The flavonoids are typical phenolic compounds that act as potent metal chelators and free radical scavengers, and which modulate intracellular signaling caused by upstream binding partners, such as, regulatory kinases and receptors (Min, 2009). The capacity of flavonoids to act as antioxidants depends upon their molecular structure ((Wang et al., 2007b). Characteristics of flavonoid structure for most effective radical-scavenging activity are:

1. The catechol (*o*-dihydroxy) group in the ring confers great scavenging ability.
2. A pyrogallol (trihydroxy) group in ring B of a catechol, as in myricetin, produces even higher activity. The C2–C3 double bond of the C-ring appears to increase scavenger activity because it confers stability to the phenoxy radical produced.
3. The 4-oxo (keto double bond at position 4 of the C-ring), especially in association with the C2–C3 double bond, increases scavenger activity by delocalizing electrons from B-ring.
4. The 3-OH group on the C-ring generates an extremely active scavenger; in fact, the combination of C2–C3 double bond and 4-oxo group appears to be the best combination on the top of the catechol group.
5. The 5-OH and 7-OH groups may also add scavenging potential in certain cases (Tapas et al., 2008).

Table 1 List of medicinal plants used as hepatoprotective in Ayurveda (Sharma et al., 1993).

S. No.	Scientific name (parts used)	Family	Common name	Chemical constituents	Use in TSM
1.	*Acorus calamus* (rhizome)	Araceae	Vashambu	Volatile oil, sesquiterpenes, asarone, acorone	Nervine tonic, anti-spasmodic, wound healing, skin diseases, bonefracture
2.	*Aegel marmelos* Corr.(leaves)	Rutaceae	Vilvam	Marmelosin, coumarin, umbelliferone	Febrifuge, anti-diabetic, catarrh
3.	*Allium sativum* Linn.(bulb)	Liliaceae	Lasan	Allicin, allisatin I&II, essential oil	Indigestion, skin diseases, earache. Bulb fried with mushroom act as antidote on snake bite, antiviral activity, inhibit cellular proliferation of virally infected cells
4.	*Aloe barbadensis* Mill.(plant)	Ranunculaceae	Gheekunvar	Aloin, isobarneloin, emodin, phenolic compounds	Seborrheic dermatitis, psoriasis vulgaris, genital herpes, skin burns, diabetes (type II), HIV infection, anticancer, ulcerative colitis wound healing, mucositis, radiation dermatitis, acne vulgaris, frostbite, stomatitis, constipation
5.	*Artemesia cappillaris* (plant)	Asteraceae	Sweet worm wood	Coumarins, flavonol glycosides, aglycones	Liver ailments
6.	*Azadirachta indica* A. Juss (plant)	Meliaceae	Vembu	Flavones, lactones	Liver tonic, fever, skin diseases
7.	*Anethum graveolens* (fruit)	Umbelliferae	Dilla, Shubit	Flavonoids, coumarins, phenolic acids	Gastralgia, colic pain
8.	*Bergenia ligulata* (root & leaves)	Saxifragaceae	Pasanabheda	Berganine, flavonols, catechins	Antiviral edema, anti-inflammatory
9.	*Curcuma longa* (rhizome)	Zingiberaceae	Haridra	Curcumin	Antiinflammatory
10.	*Cheiranthus cheiri*	Cruciferae	Tudri	Flavonoids, cardiac glycosides, alkaloids	Anti-spasmodic, purgative
11.	*Carthamus tinctorius* Linn (flower)	Compositae	Safflower	Carthamin	Cardiac and cerebral vascular diseases, high blood pressure, diabetes
12.	*Colchicum luteum* (corms)	Liliaceae	Suranjan	Colchicin	Rheumatoid arthritis, analgesic, anti-inflammatory
13.	*Capparis spinosa* (root)	Capparaceae	Himsra, Capers	Glucocapparin flavonoids, sterols, terpenes	Hepatic stimulant
14.	*Citullus lanatus* (root, seeds)	Cucurbitaceae	Matira	Triterpenoid glucoside	Demulcent, diuretic, pectoral, tonic
15.	*Corylus avellana* (fruit)	Betulaceae	Hazel	Flavonoids, spermidine	Diuretic, astringent, diaphoretic, febrifuge, nutritive
16.	*Cyphomandra betacea* (plant)	Solanaceae	Manipuri	Flavonoids, lycopene	Skin, diabetic patients, acidosis, eye diseases, obesity, liver, diarrhea
17.	*Glycyrrhiza glabra* (root)	Leguminosae	Yashti-madhu	Glycyrrhizin, glycyrrhetic acid, flavonoids, flavanones, chalcones, isoflavones	Laxative, antioxidant, cancer protecting, stimulates interferon production
18.	*Heydichium spicatum* (rhizome)	Zingiberaceae	Sutti	Diterpenes	Vasodilatory, hypotensive, anti-spasmodic, tonic, carminative, stimulant
19.	*Lithospermum officinale* (plant)	Boraginaceae	Gomwell	Naphthoquinones	Antipyretic, anti gout, kidney stones, diarrhea
20.	*Myrtus communis* (fruit)	Myrtaceae	Myrtle	Volatile oil	Hair growth, respiratory disorders
21.	*Nelumbo mucifera* (flowers)	Nymphaceae	Kamala	Nelumbin, nupharine	Astringent
22.	*Ocimum tenuiflorum* (seeds, leaves)	Labiatae	Nagathein	Volatile oil	Expectorant, catarrh, bronchitis, gastric disorders, carminative, refrigerant, febrifuge
23.	*Picrorhiza kurroa* (rhizome)	Scrophulariaceae	Kutki	Acetophenones, androsin, iridoid, acetosyringenin	Jaundice, dyspepsia
24.	*Phyllanthus niruri* Linn (plant)	Euphorbiaceae	Jar amla, Jangali amla	Flavonoids like quercetin, rutin, isoquercetin, astralgin, phyllanthin, hypophyllathin	Hepatitis, jaundice, antiviral, gonorrhea, diabetes
25.	*Pinus roxburghii* (volatile oil)	Pinaceae	Chir pine	Beta-carotene, α & β pinene	Diuretic
26.	*Pistacia vera* (seed)	Anacardiaceae	Pistachio	Polyphenols	Antimicrobial
27.	*Rheum emodi* Wall (rhizome)	Polygonaceae	Rewandchini	Rhaponticin, emodin, chrysophanic acid	Astringent, laxative, antibacterial
28.	*Pterocarpus marsupium* (wood)	Leguminosae	Uthiravenkai	Pigments	Stomachache

(*continued on next page*)

Table 1 List of medicinal plants used as hepatoprotective in Ayurveda (Sharma et al., 1993).

S. No.	Scientific name (parts used)	Family	Common name	Chemical constituents	Use in TSM
29.	*Strychnos nux-vomica* (bark, seeds)	Loganiaceae	Poison nut	Strychnine, brucine	Tonic, digestive stimulant, respiratory and circulatory stimulant
30.	*Terminalia chebula* Retz. (fruit)	Combretaceae	Haritaki, Chebulic myrobalan	Tannins	Purgative, expectorant, onic. anti-mutagenic
31.	*Terminalia bellirica* (fruit)	Combretaceae	Bahera	Flavonoids, tannins	Antisecretory, analgesic, hepatoprotective, cardioprotective, hypoglycemic, hypotensive, anti-spasmodic, bronchidilatory
32.	*Vitex agnus-castus* (fruit)	Verbenaceae	Chaste tree	Flavonols	Hyperprolactenemia
33.	*Vitex negundo* Linn. (plant)	Verbenaceae	Notchi	Flavonoids, iridoid glycosides	Liver complaints, cholera

5. List of different medicinal plants containing flavonoids reported for hepatoprotection

Since the flavonoids are well tolerated, widely studied and least toxic (Vijayaraghavan et al., 2008), estimated dietary flavonoid intake can reach 50–800 mg per day, or higher, if dietary supplements are consumed (Tsuji and Walle, 2008). Among the herbal drugs, silymarin has been used as a dietary supplement for hepatoprotection for over 2000 years (Eminzade et al., 2008). Hesperidin is a flavanone glycoside abundantly found in sweet orange and lemon and is an inexpensive by-product of citrus cultivation (Tirkey et al., 2005). Hesperidin flavanoglycone protects against gamma-irradiation induced hepatocellular damage and oxidative stress in Sprague–Dawley rats (Kannampalli et al., 2008). Some of the polymethoxylated citrus flavonoids have also in preliminary studies demonstrated antiproliferative properties (Walle, 2007). Chinese green tea (*Camellia sinensis*) contains high levels of antioxidant polyphenols, including catechin, epicatechin, gallocatechin, epigallocatechin, epicatechin gallate and gallocatechin gallate (Lehnert et al., 2010). Examples of some medicinal plants used as hepatoprotective in ayurveda along with their active principles are enlisted in Table 1.

As seen from Table 1 above, flavonoids and phenolic compounds are the metabolites being rapidly found in medicinal plants, basically used for hepatoprotection. Also, i*n vitro* experimental systems also showed that flavonoids possess anti-inflammatory, antiallergic, antiviral, and anticarcinogenic properties (Nijveld et al., 2001). So, a chemically defined component (i.e., a flavonoid) of a herbal product, that can serve as hepatotropic drug may be explored to get a true and potentially rich source of drug candidates against liver ailments.

6. Important flavonoids reported for hepatoprotection

The main dietary groups of flavonoids are flavonols (e.g., kaempferol, quercetin), which are found in onions, leeks, broccoli, flavones (e.g., apigenin, luteolin), which are found in parsley and celery, isoflavones (e.g., daidzein, genistein), which are mainly found in soy and soy products, flavanones (e.g., hesperetin, naringenin), which are mainly found in citrus fruit and tomatoes, flavanols (e.g., catechin, epicatechin, epigallocatechin, epigallocatechin gallate), which are abundant in green tea, red wine, chocolate, and anthocyanidins (e.g., pelargonidin, cyanidin, malvidin), whose sources include red wine and berry fruits (Spencer, 2007).

A large number of flavonoids and phenolic compounds have been isolated from crude plant extracts with proven hepatoprotective potential. Some chemically defined organic molecules containing flavonoids and phenolic compounds as major class/category along with their botanical source and part of the plant which is being used in therapeutics, for hepatoprotective potential (Adewusi and Afolayan, 2010) are listed in Table 2.

7. Conclusion

The need for new and useful compounds to provide assistance and relief in all aspects of the human condition is ever growing. In developing countries the availability of modern medicines is limited. So traditional medicine is still the mainstay of health

Table 2 List of some chemically defined organic molecules containing flavonoids having hepatoprotective potential.

S. No.	Chemical substance	Plant	Plant part	Category	References
1.	Anastatin A	*Anastatica hierochuntica* L	Whole plant	Flavonoids	Yoshikawa et al. (2003)
2.	Anastatin B	*Anastatica hierochuntica* L	Whole plant	Flavonoid	Yoshikawa et al. (2003)
3.	5,7,4′-Trihydroxy-3′-methoxyisoflavone	*Erycibe expansa* Wall	Stem	Isoflavone	Matsuda et al. (2004)
4.	Genistein	*Erycibe expansa* Wall.	Stem	Isoflavone	McCarty et al. (2009)
5.	Rubiadin	*Rubia cordifolia* Linn	Roots	Dihydroxy anthraquinone	Rao et al. (2006)
6.	Mangiferin	*Salacia reticulata*	Roots	Phenolic compound	Chakraborty and Chakraborty (2010)
7.	(−)-4′-*O*-Methylepigallocatechin	*Salacia reticulata*	Roots	Phenolic compound	Yoshikawa et al. (2002)
8.	Onitin	*Equisetum arvense* L	Aerial parts	Phenolic compound	Oh et al. (2004)
9.	Luteolin	*Equisetum arvense* L	Aerial parts	Flavonoid	Domitrovic et al. (2009)
10.	Phyllanthin	*Phyllanthus amarus* Schum	Leaves, roots, seed	Flavonoids	Pramyothin et al. (2007)
11.	Agathisflavone	*Canarium manii* King	Whole	Biflavonoid	Lin et al. (1997)
12.	Wighteone	*Cudrania cochinchinensis* (Lour.)	Roots	Flavonoid	Lin et al. (1996)
13.	Naringenin	*Cudrania cochinchinensis* (Lour.)	Roots	Flavonoid	Lee et al. (2004)
14.	Kaempferol	*Rhodiola sachalinensi*	Roots	Phenolic compound	Song et al. (2003)
15.	Salidroside	*Rhodiola sachalinensi*	Roots	Phenolic compound	Wu et al. (2009)
16.	Rutin	*Artemisia scoparia*	Stem	Flavonoid	Janbaz et al. (2002)
17.	Troxerutin	*Artemisia scoparia*	Leaves	Flavonoid	Adam et al. (2005)
18.	Kolaviron	*Garcinia kola*	Seeds	Biflavonoid	Farombi (2000)
19.	Catechin	*Camellia sinensis*	Whole	Flavonoid	Hesham and Beshbishy (2005)
20.	Glycyrrihizin	*Glycyrrhiza glabra* Linn	Root/stolon	Flavonoid	Shiota et al. (1999)
21.	3,5-Di-*O*-caffeoyl quinic acid	*Suaeda glauca*	Seeds	Phenoic compounds	An et al. (2008)
22.	Curcumin	*Curcuma longa*	Rhizomes	Curcumin, carotene, pigment	Somchit et al. (2002)
23.	Galangin	*Alpinia galangal* Linn	Rhizomes	Flavonoid, flavonol	Zhang et al. (2010)
24.	Scopoletin	*Solanum lyratum*	Aerial parts	Coumarin	Kang et al. (1998)
25.	Vitexin 7-*O*-β-L-glucopyranoside & vitexin 2″-*O*-β-glucopyranoside	*Vitis vinifera*	Seeds	Flavones	Kim et al. (2004)
26.	Arjunolic acid	*Terminalia arjuna*	Bark	Triterpenoid saponins	Hemlatha et al. (2010)
27.	Andrographolide	*Andrographis paniculata*	Leaves	Diterpenoid lactone	Handa and Sharma (1990)
28.	Gossypin	*Hibiscus vitifolius*	Whole	Glucosyl flavone	Ralhan et al. (2009)
29.	Plumbagin	*Plumbago zeylanica*	Root	Pigment	Ralhan et al. (2009)
30.	Epicatechin	*Nelumbo nucifera*	Leaves	Flavanols	Raj et al. (2010)
31.	Isoquercitrin	*Phyllanthus amarus* Schum	Whole plant	Flavonoid	Huang et al. (2010)
32.	Wedelolactone	*Phyllanthus amarus* Schum	Aerial parts	Polyphenolics	Dalal et al. (2010)
33.	Silybin, isosilybin, silychristin, silydianin	*Silybum marianum*	Seeds	Flavonoids and phenolic compounds	Thorat et al. (2010)
34.	Eclipta alba	Green tea (*Camellia sinensis*)	Whole	Flavonoid	Strobel and Daisy (2003)
35.	Halichrysin A and B	*Helichrysum arenarium* (L.) Moench	Whole	Isoflavonoid	Thorat et al. (2010)

care and most drugs come from plants (Rajbhandari, 2009). The plants may offer new alternatives to the limited therapeutic options that exist at present in the treatment of liver and other diseases or their symptoms, and they should be considered for future studies. In view of the need for safe and effective treatment, a study of the role of silymarin in the management of non-B acute viral hepatitis was investigated, which showed significantly earlier recovery from hepatomegaly and enlarged spleen in patients receiving silymarin. Both meciadiol and sofalcone have been studied for anticancer effectiveness and found to be effective in clinical trials. Sofalcone has been used clinically in Japan for treatment of gastroduodenal ulcers (Narayana et al., 2001). The present study identified flavonoids, triterpenes and phenolic compounds as classes of compounds with hepatoprotective potential. The potent hepatoprotective activities of the chemically defined molecules isolated from natural products represent an exciting advance in the search for effective liver protective agents, especially now, when there is an urgent need for new innovative drug leads. Further studies including clinical trials need to be carried out to ascertain the safety of these compounds as a good alternative to conventional drugs in the treatment of liver diseases.

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