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REVIEW ARTICLE

Flavonoids: A Potent Substance in Anti-ulcer and Hepatoprotective Agents

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Abstract

Herbs have been used to treat various diseases in one form or another for the betterment of mankind since the ancient ages. As a result of this usage, the situation gradually deteriorated due to overexploitation, resulting in a decrease in natural resource production. Looking in to the benefits, the flora and fauna were rehabilitees through tissue culture, conservation, plantation and other means to ensure their availability in their natural form. Nature is the best chemist, as it aids in the treatment of ailments and provides the results of them. It is impossible to find any plant that has no medical use. Ulcer and liver diseases are at an alarming rate in the developing countries. A number of drugs, which are in the existing medications for peptic ulcer and hepatic diseases, are on the comeback list due to their adverse effects and drug interactions. Drugs, which are derived from the flora, have an important role in treatment and show a higher rate of acceptance. Flavonoids are the naturally occurring, low-molecular-weight molecules seen mostly distributed in the vegetable kingdom and hold an utmost thurst in declining the generation of reactive oxygen species. Secondary compounds like apigenin, sylimarin, genesis, quercetin, kaempherol and catechins have a significant role in these diseases. This article focuses on the importance of flavonoids, which can serve as potent anti-ulcer and hepatoprotective agents.

Keywords: Flavonoids, Herbs, Liver, Secondary Metabolites, Ulcer

1. Introduction

Ulcers and diseases concerning the liver are now considered serious health problems. The liver is the vital organ for metabolism, secretion and storage. Nearly a thousand deaths are found to be due to hepatic failure and they become more severe if neglected. The observations from peptic ulcer groups are almost the same count as both are the silent processes of damaging the cells and tissues in our body system. The phenomenon of developing hepatocellular carcinoma are the general form, which correlates with the disease pattern[1-3]. They are due to the production of reactive species occurring which are with the damaged cells and further these cells form carbon-carbon bond with the lipids, which are in tissues and gives the major strength[4].

The formation of ulcers is an outbreak in the inflamed skin or in the mucus lining, making a path in the digestive canal. The majority of ulcers are due to imbalance, which occurs in the normal systematic process, and they are associated witha higher rate of aggression in the mucosal resistance[5]. Both the forms of ulcers namely gastric and duodenal ulcers form the corrosive action of pepsin and hydrochloric acid present in the mucosa linked to the upper gastrointestinal tract. Ulcers generally vary in the range of about 0.3cm to 0.5 cm or even bigger in size in diameter[6]. The most common cause of duodenal ulcers in adult males is due to lifestyle habits. The occurrence of gastric ulcers

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occurs in the mid-age to older age to imbalance food habits and socio-economic class of pupils[7].

On the other hand, the liver, being the largest organ in the system, holds a fundamental function that serves in the regulation of various processes involving carbohydrates, proteins, fatty substances, the removal of toxins present in the body, the secretion of fluids from gastric juice, and finally, vitamins. These elements make up a healthy liver in the body[8,9].

- Owing to these functions hepatic ailments become a threat in the community and hold their position to date in the world[10]. The following factors are associated with liver diseases:Generation of higher quantities of free radicals, which fails its own defensive mechanism and damages the process of liver metabolism, leading to diseases such as fatty liver, jaundice, cirrhosis, etc.
- Poisoning with chemicals related to carbon tetrachloride, which in turn leads to the accumulation of lipid particles and eventually necrosis.
- Solvents such as ethanol, have a capacity to generate free radicals, which decrease the potential benefits of the enzymatic studies.

The classification of liver diseases is in three different sections, like[11-14]:

- Inflammatory cause of the liver
- Non-inflammatory, like hepatitis
- Degenerative, like cirrhosis.

The application of primitive methods was to be viewed as the best relief from aliments by having a mechanism based on the traditional system and usage of herbs by ancient people[15]. The available options in the treatment of these diseases were still limited and lacking because the root causes were different for different group of pupils[16]. For the search for newer drugs, the screening models were thoroughly assessed and are listed in Table 1.

There are a number of medicinal plants used commonly in the profile of dosing for liver disorders. This article aims to provide a complete list of plants and herbs that are beneficial in eradicating liver disorders (Table 2).

The need and importance of herbal drugs are generally growing due to their better acceptability and compatibility with mankind. Various medicinal plants

Table 1. Comparison between models[17]

Anti-ulcer activity	Hepatoprotective activity
• Histamine induced ulcers • Hydrochloric acid induced ulcers • Acetic acid induced ulcers • Ethanol induced ulcers[18] • Aspirin induced ulcers[19] • Water immersion stress induced ulcers[20] • Pylorus ligation induced ulcers[21] • Reserpine induced ulcers[22] • Indomethacin induced ulcers[23] • Serotonin induced ulcer[24]	• Paracetamol (acetaminophen) induced hepatotoxicity • CCl_4 induced hepatotoxicity • Alcohol and Carbon tetrachlorideinduced hepatotoxicity • Carbon tetrachloride and paraffin induced hepatotoxicity • d-galactosamine/ lipopolysachharide (GalN/LPS) induces hepatotoxicity • Thioacetamide induced hepatotoxicity • Antitubercular drugs hepatotoxicity

Table 2. Herbs comprising the potential use of hepatoprotective activity

Sr. No.	Name of the plant	Part used	Extraction solvent	Chemical constituent	Animal model	Hepatotoxic agent	References
1	*Aerva lanata* (Amaranthaceae)	Leaf, Root	Aqueous alcoholic extract	Sitosteryl plamitate, hentriaconten,	Rat	Paracetamol	25, 26
2	*Artemisia capillaris* (Asteraceae)	Whole plants	Aqueous ethanol extract	Eupatolin, Capillartemisin A	Rat	*Carbon tetrachloride*	27
3	*Aphanamixis polystachya* (Meliaceae)	Leaf	Extract of Ethanol	Polyprenol, lutein	Rat	Carbon tetrachloride	28
4	*Allium hirtifoli*um (Alliaceae)	Leaf	Aqueous alcoholic extract	Shallomin, Quercetin and Kaempferol	Rat	Alloxan induced	29, 30
5	*Amorphophallus paeoniifolius* Linn (Araceae)	Tubers	Methanol and aqueous extract	Steroids and Flavonoids	Rat	Paracetamol	31
6	*Allium sativum* (Alliaceae)	Bulbs	Ethanolicextract	Sapogenins, Saponins, Allicin	Rat	Cadmium	32, 33
7	*Berberi vulgaris* (Berberidaceae)	Fruit	Methanolic extract	Berberine, oxyacanthine, and flavonoids	Rat	Carbon tetrachloride	34, 35
8	*Calendula officinalis* (Asteraceae)	Flower	Methanolic extract	α-thujene and T-muurolol, flavonol glycosides, flavonoids	Albino Rat	Carbon tetrachloride	36, 37
9	*Cercissili quastrum* (Leguminoseae)	Whole plants	Hydro alcoholic extract	Myricitoside, diterpenoids, triterpenoids	Rat	Carbon tetrachloride	37
10	*Citrullus lanatus* (Cucurbitaceae)	Fruits	Methanolic extract	Triterpenes, flavanoids, saponins	Rat	Carbon tetrachloride	38, 39
12	*Daucus carota* (Apiaceae)	Seeds	Methanolic Extract	Triterpenes, flavonoids	Wister rat	Lindane	40, 41
13	*Decalepis hamiltonii* (Asclepiadaceae)	Roots	Aqueous extract	2-Hydroxy-4-methoxybenzaldehyde Vanillin, Borneol	Rat	Ethanol	42, 43
14	*Eclipta alba* (Asteraceae)	Leaves	Alcoholic extract	Terpenes, flavonoids	Rat and mice	Carbon tetrachloride	44
15	*Epaltes divaricata* (Compositae)	Whole Plants	Aqueous Extract	Flavonoids, Ascorbic acid, carotenoids, tannis and lignins	Mice	Carbon tetrachloride	45, 46
16	*Emblica officinalis* (Euphorbiaceae)	Fruit	Hydroalcoholic Extract	kaempferol-3-Rhamnogluscoside Quercetin-3-Rhamnoglucoside, Stepposide	Rats	Rifampicin, Isoniazide and pyrazinamide	47
17	*Hypericum perforatum* (Clusiaceae)	Dried aerial parts	Alcoholic Extract	Flamin, kaempferol, narringenin and isohelichrysin	Male albino Mice	Carbon tetrachloride	48

18	*Lactuca indica* (Asteraceae)	Aerial parts	95% Methanolic Extract	Sterols and flavonoids	Rat	Carbon tetrachloride	49
19	*Mentha pieperata* (Labiatae)	Leaves	Aqueous Extract	Myrcene, pipiritone, eugenol, menthone.	Albino Wistar Rats	Carbon tetrachloride	50
20	*Silybum marianum* (Asteraceae)	Whole plants	Ethanolic extract	Isoflavonoid and Silymarin	Rats	Carbon tetrachloride induced liver toxicity	51, 52
21	*Taraxacum officinale* (Asteraceae)	Roots	Aqueous extract	carotenoids, lutein, flavonoids	Rats	Carbon tetrachloride induced liver toxicity	53, 54

Table 3. Herbs and shrubs with anti-ulcer activity

Sl No	Name of the plant	Part used	Extraction solvent	Chemical constituent	Animal Model	Ulcer creating agent	References
1	*Cynodon dactylon* (Poaceae)	Aerial parts	Alcoholic extract	Flavonoids	Albino Rats	Pylorus ligation	55
2	*Cucarbita pepo* (Cucurbitaceae)	Seed	Methanolic extract	Terpenoids, cucurbitacian	Rat	Stress induced	56
3	*Boswellia serrata* (Burseraceae)	Bark	Petroleum ether	squalene, polyprenol, lutein	Male albino rat	Aspirin	57
4	*Pycnanthus angolensis* (Myristicaceae)	Bark	Ethanolic extract	Flavonones, epicatechin and (+)-catechin	Male Albino Wistar rat	Ethanol	58
5	*Alstonia scholaris* (Apocyanaceae)	Bark	Ethanolic Extract	Coumarins, flavonoids, phlobatannin, saponins and tannins	Male albino rat	Pylorus ligation	59
6	*Asparagus racemosus* (Asparagaceae)	Roots	Methanolic extract	Shatavarin, flavonoid	Male albino rats	Indomethacin	60
7	*Azadirachta indica* (Meliaceae)	Leaf	Aqueous extract	Flavonoids, proteins	Rat	Indomethacin treated, ethanol and histamine	61, 62
8	*Butea foandosa* (Fabaceae)	Leaves	Chloroform and ethanolic extract	Butrin, flavonoids	Rat	Hydrochloric acid	63
9	*Bauhinia variegata* (Fabaceae)	Leaves	Aqueous extract, ethanolic extract	Flavonoids	Rat	Aspirin	64
10	*Hibiscus Rosa* (*Malvaceae*)	Leaves	Methanol extract	Flavonoids, anthocyanins, quercetin	Rat	Pyloric ligation	65
11	*Murrya koenigii* (Rutaceae)	Root Stem and Leave	Methanol extract	Monoterpenes	Albino Rat	Hydrochloric acid, indomethacin	66

12	*Ocimum Sanctum* (Lamiaceae)	Leaves	Alcoholic extra	Alkaloids, saponins,apigenin	Rat	Aspirin and ethanol	67
13	*Moringa oleifera* (Moringaceae)	Leaves	Alcoholic extract	Alkaloids, flavonoids, zeatin, kaempferom, and terpenoid	Rat	Aspirin and ethanol induced	68
14	*Sophorasub prostrata* (Fabaceae)	Whole plants	Alcoholic extract	Sophoradin	Rat	Pylorus ligated	69
15	*Glicyrriza glabra* (Fabaceae)	dried roots and rhizomes	Ethanol extract	Flavonoids, Glabra	Swiss mice	Water immersion and acetic acid induced ulcer	70
16	*Sylibinmarium* (Asteraceae)	Whole plants	Methanolic extract	Sylimarin	Rat	Ethanol, cold resistance, pylorous ligation	71
17	*Genistar umelica* (Fabaceae)	Whole plant	Methanolic extract	Genistin, luteoline-7-glycoside	Rat	Pylorus ligation	72, 73
18	*Eucalypus maculate* (Myrtaceae)	Leaves	Methanolic extract	Quercetin	Rat	Cold resistance and pylorus ligation	74
19	*Rhammus procubens* (Rhamnaceae)	Whole plants	Aqueous and Ethanolic extracts	Kaempherol	Rat	Pylorous ligation	75
20	*Anacardium accidentate* **(**Anacardiaceae)	leaves	Hydroalcoholic Extract	Catechins	Rat	Pylorous ligation HCl ethanol	76, 77

are used traditionally in the treatment of peptic ulcers (Table 3).

2. Some Important Flavonoids

2.1 Luteolin

It belongs to the flavonoid group of the plant kingdom and is isolated from Reseda *luteola*. A yellow microcrystalline powder. Combination is used in traditional herbal remedies as potent scavenging properties[78] (Figure 1).

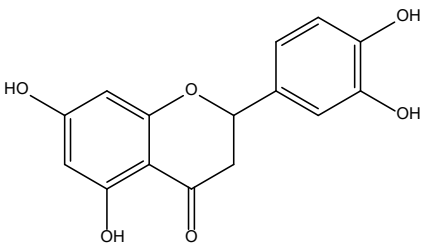

Figure 1. Luteolin.

2.2 Acacetin

This compound belongs to an O-methylated flavone found in *Robinia pseudoacacia.* Shows potential benefits in curing liver against chemical induced moiety[79] (Figure 2).

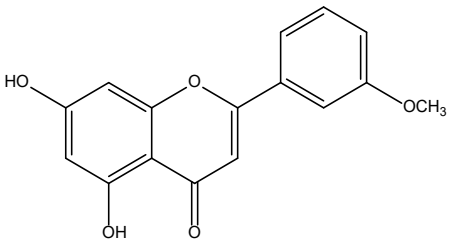

Figure 2. Acacetin.

2.3 Apigenin

Scientifically belonging to the flavone class. It combines the sugar portion with the non-sugar moiety. A yellow crystalline solid, which shows potential effects on ulcer activity[80] (Figure 3).

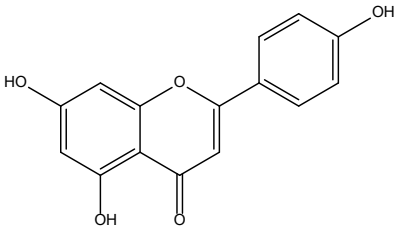

Figure 3. Apigenin.

2.4 Silymarine

A derived complex with a combination of silybin, silydianin, and silychris derived from the milk thistle plant[81] (Figure 4).

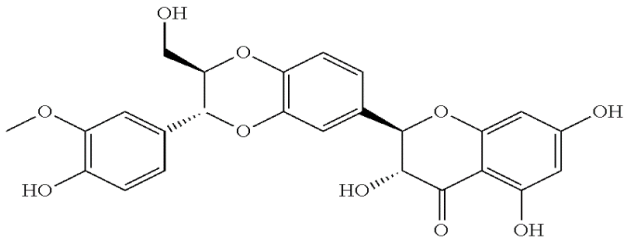

Figure 4. Silymarine.

2.5 Kaempferol

Belongs to the class of flavonols. Tan oily in nature with yellow crystalline solid with solubility in water and organic solvents. Possess a greater extent of antioxidant activity[82] (Figure 5).

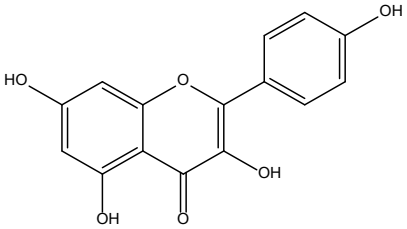

Figure 5. Kaempferol.

2.6 Salvigenin

Obtained from the plant *Dorema glabrum*. Salvigenin is a highly potent free radical scavenging molecule, and apart from that, the synergistic effects are seen as hepatoprotective activity and in tumour cells[80] (Figure 6).

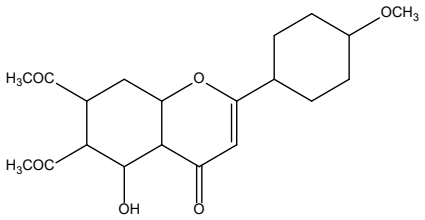

Figure 6. Salvigenin.

2.7 Quercetin

Commonly found fruits, vegetables, leaves, and grains. Possess a broader range in curing various pharmacological effects such as antioxidants, ROS etc.,[83] (Figure 7).

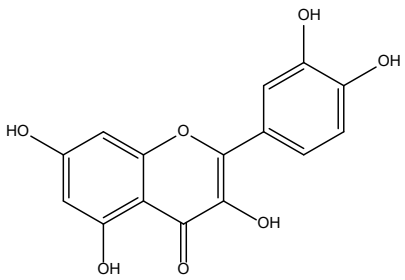

Figure 7. Quercetin.

3. Conclusion

Natural herbs and plants serve as the best remedy for the liver and ulcer healing properties due to their potential benefits, as they have fewer side effects and more beneficial parameters. These are due to the presence of metabolites, which show the potency of the activity. Owing to the importance of flavonoids, they are also useful in the degeneration of cells, as they are significantly involved in the process of oxidation developed by cells on intra- and extra-cellular parameters. Flavonoids are seen potential in the healing process of gastric juice owing to mucoprotective activity. Compounds like silymarin, quercetin, apigenin, salvigenin luteolin etc., have shown its importance in these diseases mainly.

Therefore, the search for newer medications along with these combinations can lead to the eradication of these diseases, which are silent in nature but can be fatal to humankind. Hence, the search is on for these drugs and active moiety to cure the aliments with maximum benefits.

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