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A systematic review on hepatoprotective herbal plants

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ABSTRACT

Liver problems are a worldwide concern, and conventional medicinal therapies are ineffective. Hence, safeguarding the healthy liver is vital for good health and well-being. Infections due to virus, immune problems, cancer, alcohol abuse, and an overdose of drugs are some of the causes of liver diseases. Antioxidants derived from medicinal plants and conventional dietary sources can protect the liver from damages caused by oxidative stress system and various chemicals. Plants and plant-derived phytochemicals are appealing hepatoprotective agents since they have less side effects and still there is a lot of interest shown in using herbal tonics for treating liver disorders. The plant kingdom plays a major role in the life of human beings and animals. The plant, as one of the important sources, still maintains its original place in the treatment of various diseases, including liver disorders, with no ill effects. Considerable studies have been carried out on ethnomedicinal plants; however, only few medicinal plants have attracted the interest of scientists, to investigate them for a remedy for hepatoprotective. 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. Clinical research in this century has confirmed the efficacy of several plants in the treatment of liver disease. Hence, this review article contributes to the knowledge of reported indigenous plants, which are prevalent for prevention and treatment of liver disorders. The present review is focused on different herbal plants that have potential to cure the hepatotoxicity. Comprehensive scientific studies on safety and efficacy of these plants can revitalise the treatment of liver diseases.

Keywords: Liver diseases, herbal drugs, traditional medicine, hepatitis, hepatoprotective activity.

INTRODUCTION

Liver diseases which are still a global health problem may be classified as acute or chronic hepatitis (inflammatory liver diseases), hepatosis (non-inflammatory diseases) and cirrhosis (degenerative disorder resulting in liver fibrosis). Unfortunately, treatments of choice for liver diseases are controversial because conventional or synthetic drugs for the treatment of these diseases are insufficient and sometimes cause serious side effects. Since ancient times, mankind has made use of plants in the treatment of various ailments because their toxicity factors appear to have lower side effects. Many of the currently available drugs were derived either directly or indirectly from medicinal plants. Recent interest in natural therapies and alternative medicines has made researchers pay attention to traditional herbal medicine. In the past decade, attention has been centered on scientific evaluation of traditional drugs with plant origin for the treatment of various diseases. Due to their effectiveness, with presumably minimal side effects in terms of treatment as well as relatively low costs, herbal drugs are widely prescribed,

even when their biologically active constituents are not fully identified.

The utility of natural therapies for liver diseases has a long history. Despite the fact that most recommendations are not based on documented evidence, some of these combinations do have active constituents with confirmed antioxidant, anti-inflammatory, anticarcinogenic, antifibrotic, or antiviral properties. Although a large number of these plants and formulations have been investigated, the studies were mostly unsatisfactory. For instance, the therapeutic values, in most of these studies, were assessed against a few chemicals-induced subclinical levels of liver damages in rodents. The reasons that make us arrive at such a conclusion are lack of standardization of the herbal drugs, limited number of randomized placebos controlled clinical trials, and paucity of traditional toxicologic evaluations. Hundreds of plants have been so far examined to be taken for a wide spectrum of liver diseases. Natural products, including herbal extracts, could significantly contribute to recovery processes of the intoxicated liver. According to reliable scientific information obtained from the research on medicinal plants, plants such as *Silybum marianum, Glycyrrhiza glabra*, Phyllanthus species (Amarus, Niruri, Emblica), and *Picrorhiza kurroa* have been widely and most of the time fruitfully applied for the treatment of liver disorders, exerting their effects via antioxidant-related properties. 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.

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. 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.

Medicinal plants play an important role in the lives of rural people particularly in remote parts of developing countries with few health facilities. It is estimated that around 70,000 plants species from lichens to towering trees has been used for medicinal purpose. The present review provides the importance of the plants with hepatoprotective activity. There are many plants with this activity and some of them are mentioned in the review. In this review article, an attempt has been made to compile the reported hepatoprotective plants from India and abroad and may be useful to the health professionals, scientists and scholars working the field of pharmacology and therapeutics to develop evidence based alternative medicine to cure different kinds of liver diseases in man and animals.

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 indicaxanthin); (3) the anthocyanins (cranberries); and (4) and resveratrol; all of these have generally been analyzed based on their chemoprotective properties against cancer. 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, anti-pyretic, cardioprotective, anti-bacterial, anti-viral, anti-protozoal, and anti-carcinogenic capacities.

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 xanthines.

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. 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.

In the present work, we reviewed hepatoprotective activity of the medicinal plants and has arranged them in the systemic order as constructed in Table 1.

Andrographis paniculata

Andrographolide active constituent of *Andrographis paniculata* (Family of Acanthaceae) antagonized the toxic effects of paracetamol on certain enzymes (SGOT, SGPT and ALP) in serum as well as in isolated hepatic cells as tested by trypan blue exclusion and oxygen uptake tests, in a significant dose dependent (0.75-12 mg/kg p.o. x 7days) manner. Neoandrographolide increase GSH, glutathione 5-transferase, glutathione peroxidase, SOD and LPO level.

Anoectochilus formosanus

Aqueous Extracts of fresh whole plant of *Anoectochilus formosanus* (Family of Orchidaceae) at dose 130 mg/kg showed inhibition of chronic hepatitis (induced by CCl_4) in mice by reducing SGPT and hepatic hydroxyproline level. It also diminished the hypoalbuminemia and splenomegaly. In an in vitro study, the LD_{50} values for H_2O_2 induced cytotoxicity in normal liver cells were significantly higher after kinsenoside (isolated from AFEW-2) pre-treatment at the dose 20-40 ug/ml.

Azadirachta indica

Effect of *Azadirachta indica* leaf (Family of Meliaceae) extract on serum enzyme levels (glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, acid phosphatase and alkaline phosphatase) elevated by paracetamol in rats was studied with a view to observe any possible hepatoprotective effect of this plant. It is stipulated that the extract treated group was protected from hepatic cell damage caused by paracetamol induction. The findings were further confirmed by histopathological study of liver. The anti-hepatotoxic action of picroliv seems likely due to an

alteration in the biotransformation of the toxic substances resulting in decreased formation of reactive metabolites.

Fig 1: Hepatoprotective plants
A) *Asparagus racemosus* B) *Amaranthus spinosus* C) *Apium graveolens* D) *Arachniodes exilis*

Table 1: List of hepatoprotective activity plants

S. No.	Biological Name	Family	Part used
1	*Acacia mellifera*	Fabaceae	Leaves
2	*Adansonia digitata*	Malvaceae	Fruit's pulp
3	*Acanthus ilicifolius*	Acanthaceae	Leaves
4	*Andrographis lineata*	Acanthaceae	Leaves
5	*Asteracantha longifolia*	Acanthaceae	Whole plant
6	*Asparagus racemosus*	Liliaceae	Whole plant
7	*Amaranthus spinosus*	Amaranthaceae	Whole plant
8	*Apium graveolens*	Apiaceae	Seeds
9	*Arachniodes exilis*	Dryopteridaceae	Rhizomes
10	*Aloe barbadensis*	Liliaceae	Aerial parts
11	*Artemisia absinthium*	Asteraceae	Aerial parts
12	*Azadirachta indica*	Meliaceae	Leaf
13	*Aerva lanata*	Amaranthaceae	Whole plant
14	*Acacia confuse*	Leguminosae	Bark
15	*Alocasia indica*	Araceae	Leaves
16	*Acacia catechu*	Leguminosae	Whole plant
17	*Aegle marmelos*	Rutaceae	Pulp/seeds
18	*Alchemilla mollis*	Rosaceae	Aerial parts and root
19	*Anoectochilus formosanus*	Orchidaceae	Whole plant

20	*Amaranthus tricolor*	Amaranthaceae	Leaves
21	*Allium hirtifolium*	Alliaceae	Corn and flower
22	*Artemisia scoparia*	Compositae	Aerial parts
23	*Allium sativum*	Alliaceae	Bulb
24	*Ammi majus*	Apiaceae	Whole plant
25	*Agrimonia eupatoria*	Rosaceae	Leaf
26	*Alchornea cordifolia*	Euphorbiaceae	Leaves
27	*Argemone Mexicana*	Papaveraceae	Whole plant
28	*Angelica sinensis*	Apiaceae	Root
29	*Astragalus membranaceus*	Fabaceae	Roots
30	*Annona squamosa*	Annonaceae	Leaf
31	*Actinidia deliciosa*	Actinidiaceae	Fruit
32	*Abelmoschus esculentus*	Malvaceae	Roots
33	*Andrographis paniculate*	Acanthaceae	Whole plant
34	*Amaranthus caudatus*	Amaranthaceae	Whole plant
35	*Asparagus racemosus*	Asparagaceae	Roots
36	*Azima tetracantha*	Salvadoracaeae	Leaves
37	*Anisochilus carnosus*	Lamiaceae	Stem
38	*Achyrocline satureioides*	Asteraceae	Aerial parts
39	*Adoxaceae Viburnum tinus*	Acanthaceae	Leaves
40	*Bixa Orellana*	Bixaceae	Whole plant
41	*Berberis vulgaris*	Berberidaceae	Fruit
42	*Bupleurum kaoi*	Umbelliferae	Dried roots
43	*Baliospermum montanum*	Euphorbiaceae	Roots
44	*Boerhaavia diffusa*	Nyctaginaceae	Roots
45	*Bacopa monnieri*	Plantaginaceae	Whole plant
46	*Balanites aegyptiaca*	Zygophyllaceae	Bark, unripe fruits, leaf
47	*Bauhinia variegate*	Fabaceae	Bark
48	*Boerhaavia diffusa*	Nyctaginaceae	Roots
49	*Byrsocarpus coccineus*	Connaraceae	Leaf
50	*Butea monosperma*	Fabaceae	Bark
51	*Beta vulgaris*	Amaranthaceae	Roots
52	*Calotropis procera*	Apocynaceae	Leaf, flowers, root, bark
53	*Cochlospermum planchoni*	Coclospermaceae	Rhizomes
54	*Combretum hartmannianum*	Combretaceae	Leaves
55	*Clutia abyssinica*	Euphorbiaceae	Leaves
56	*Cynara scolymus*	Apiaceae	Leaf
57	*Calendula officinalis*	Asteraceae	Flower heads
58	*Citrullus lanatus*	Cucurbitaceae	Fruits
59	*Cannabis sativa*	Cannaceae	Seeds
60	*Canna indica*	Cannaceae	Aerial parts
61	*Cassia fistula*	Fabaceae	Leaves
62	*Curcuma longa*	Zingiberaceae	Rhizome
63	*Cordia macleodii*	Boraginaceae	Leaves
64	*Cassia fistula*	Leguminosae	Leaves
65	*Clerodendrum inerme*	Verbenaceae	Leaf
66	*Cassia occidentalis*	Caesalpiniaceae	Leaves
67	*Careya arborea*	Lecythidaceae	Bark
68	*Croton oblongifolius*	Euphorbiaceae	Aerial parts
69	*Ceriops decandra*	Rhizophoraceae	Bark, leaf
70	*Cochlospermum vitifolium*	Cochlospermaceae	Bark
71	*Cassia tora*	Caesalpiniaceae	Leaves
72	*Carum copticum*	Apiaceae	Seed
73	*Chamomile capitula*	Asteraceae	Fresh natural mature capitula
74	*Caesalpinia bonduc*	Fabaceae	Plant materials
75	*Capparis spinosa*	*Capparaceae*	Root bark
76	*Cleome viscose*	Capparidaceae	Leaf
77	*Cichorium intybus*	Asteraceae	Leaves
78	*Casuarina equisetifolia*	Casuarinaceae	Plant materials
79	*Cajanus scarabaeoides*	Fabaeceae	Whole plant

80	*Cydonia oblonga*	Rosaceae	Leaf
81	*Chloroxylon swietenia*	Rutaceae	Whole plant
82	*Cajanus cajan*	Leguminosae	Leaf
83	*Carissa carindas*	Apocyanaceae	Root
84	*Clitoria ternatea*	Fabaceae	Leaves
85	*Cucumis trigonus*	Cucurbitaceae	Fruit
86	*Camellia sinensis*	Theaceae	Leaves and buds
87	*Commiphora opobalsamum*	Burseraceae	Aerial parts
88	*Capparis decidua*	Capparaceae	Stem, branches, root
89	*Daucus carota*	Apiaceae	Roots
90	*Decalepis hamiltonii*	Asclepiadaceae	Root
91	*Dobera glabra*	Salvadoraceae	Leaves
92	*Elephantopus scaber*	Asteraceae	Whole plant
93	*Enicostemma Axillare*	Gentianaceae	Whole plant
94	*Euphorbia fusiformis*	Euphorbiaceae	Tubers
95	*Embelia ribes*	Myrsinaceae	Fruits
96	*Eruca sativa*	Cruciferae	Seeds
97	*Ficus carica*	Moraceae	Leaves
98	*Fructus Schisandrae chinensis*	Magnoliaceae	Dried fructus
99	*Fumaria indica*	Papaveraceae	Whole plant
100	*Ficus religiosa*	Moraceae	Stem bark
101	*Garcinia indica*	Clusiaceae	Fruit rind
102	*Grewia mollis*	Malvaceae	Leaves
103	*Grewia tenax*	Malvaceae	Leaves
104	*Glycyrrhiza glabra*	Fabaceae	Roots
105	*Gentiana olivieri*	Gentianaceae	Aerial parts
106	*Gundelia tourenfortii*	Asteraceae	Fresh edible stalk
107	*Ganoderma lucidum*	Polyporaceae	Winter mushrooms
108	*Glycosmis pentaphylla*	Rutaceae	Plant materials
109	*Ginkgo Biloba*	Ginkgoaceae	Leaf
110	*Gmelina asiatica*	Verbenaceae	Aerial parts
111	*Hypericum perforatum*	Hypericaceae	Aerial parts
112	*Haloxylon salicornicum*	Chenopodiaceae	Aerial parts
113	*Hyptis suaveolens*	Lamiaceae	Leaves
114	*Hygrophila auriculata*	Acanthaceae	Root, seeds
115	*Halenia elliptica*	Gentianaceae	Whole plant
116	*Hypericum japonicum*	Clusiaceae	Whole plant
117	*Hibiscus sabdariffa*	Malvaceae	Calyces
118	*Hibiscus esculentus*	Malvaceae	Root
119	*Ipomoea carnea*	Convolvulaceae	Leaves
120	*Juncus subulatus*	Juncaceae	Powdered tuber
121	*Juniperus procera*	Cupressaceae	Aerial parts
122	*Kalanchoe pinnata*	Crassulaceae	Leaves
123	*Kigelia Africana*	Bignoniaceae	Leaves, seeds
124	*Khaya senegalensis*	Meliaceae	Bark
125	*Lactuca indica*	Compositae	Aerial parts
126	*Laggera pterodonta*	Asteraceae	Whole herb
127	*Lawsonia inermis*	Lythraceae	Leaves
128	*Leucas aspera*	Lamiaceae	Whole plant
129	*Leucas cilita*	Lamiaceae	Whole plant
130	*Luffa echinate*	Cucurbitaceae	Fruits
131	*Lepidium sativum*	Cruciferae	Seeds
132	*Mallotus japonicas*	Euphorbiaceae	Cortex
133	*Marrubium vulgare*	Lamiaceae	Whole plant
134	*Melia azhadirecta*	Piperaceae	Leaves
135	*Morinda citrifolia*	Rubiaceae	Fruit
136	*Myoporum lactum*	Myoporaceae	Leaves
137	*Myrtus communis*	Myrtaceae	Leaves
138	*Momordica subangulata*	Cucurbitaceae	Whole plant
139	*Moringo Oleifera*	Moringaceae	Leaves

140	*Mangifera horsefieldii*	Anacardiaceae	Pulp
141	*Momordica dioica*	Cucurbitaceae	Leaves
142	*Naregamia alata*	Meliaceae	Whole plant
143	*Nelumbo nucifera*	Nelumbonaceae	Leaves
144	*Nigella sativa*	Ranunculaceae	Seed
145	*Ocimum sanctum*	Lamiaceae	Leaf
146	*Occimum basilicum*	Lamiaceae	Whole plant
147	*Orthosiphon stamineus*	Lamiaceae	Leaves
148	*Peganum harmala*	Nitrariaceae	Seed
149	*Phyllanthus amarus*	Euphorbiaceae	Whole plant except root
150	*Phyllanthus niruri*	Euphorbiaceae	Leaves and fruits

DISCUSSION

Popularity of herbal remedies is increasing globally and at least one quarter of patients with liver diseases use ethnobotanicals. More efforts need to be directed towards methodological scientific evaluation for their safety and efficacy by subjecting to vigorous preclinical studies followed by clinical trials to unravel the mysteries hidden in the plants. This approach will help exploring the real therapeutic value of these natural pharmacotherapeutic agents and standardized the dosage regimen on evidence-based findings to become more than a fashionable trend. Many herbals are on the market to support health, relieve symptoms and cure diseases. However, most of these products lack scientific pharmacological validation. In experimental hepatotoxicity models in laboratory or higher animals, several herbals exerted hepatoprotective/curative effects that warrants their clinical testing. Due to lack of scientific based pharmacological data, most of the herbal formulations cannot be recommended for the treatment of liver diseases.

A phyto-therapeutic approach to modern drug development can provide many invaluable drugs from traditional medicinal plants. Search for pure phytochemicals as drugs is time consuming and expensive. Numerous plants and polyherbal formulations are used for the treatment of liver diseases. However, in most of the severe cases, the treatments are not satisfactory. Although experimental evaluations were carried out on a good number of these plants and formulations, the studies were mostly incomplete and insufficient. The therapeutic values were tested against a few chemicals-induced subclinical levels of liver damages in rodents. Development of such medicines with standards of safety and efficacy can revitalise treatment of liver disorders and hepatoprotective activity.

It is estimated that about 7,500 plants are used in local health traditions in, mostly, rural and tribal villages of India. Out of these, the real medicinal value of over 4,000 plants is either little known or hitherto unknown to the mainstream population. The classical systems of medicine such as Ayurveda, Siddha, Amchi, Unani and Tibetan use about 1,200 plants. A detailed investigation and documentation of plants used in local health traditions and pharmacological evaluation of these plants and their taxonomical relatives can lead to the development of invaluable plant drugs for many dreaded diseases. Random screening of plants has not proved economically effective. Liver is a vital organ play a major role in metabolism and excretion of xenobiotics from the body.

Due to extensive exposure to hazardous chemicals, sometimes the free radicals generated are so high that they overpower the natural defensive system leading to hepatic damage. The drugs/chemicals with anti-oxidant properties such as Vitamin E and silymarin have been shown to protect against toxin induced hepatotoxicity. On the other hand, inflammation is a key event in hepatotoxin induced liver damage. The toxins directly or through oxidative stress mechanism may trigger inflammatory response in the liver, which is evident from a significant increase in the proinflammatory cytokines including TNF-α and IL-6 and hepatocyte inflammation. Majority of hepatoprotective herbs have been shown to suppress oxidative stress and inflammation. Our survey and published reports clearly suggest that medical plants used in traditional medicine are rich sources of medicinally active chemical constituents such as phenols, coumarins, lignans, terpenoids, carotenoids, glycosides, flavonoids, organic acids, alkaloids, and xanthene. Some of the purified phyto-molecules isolated from these plants have also been shown to possess potent hepatoprotective activity. Further investigation into the lead molecules that may produce better, safe, and effective therapeutic effects is warranted to overcome the pharmaceutical imbalance between remedies that protect the liver and drugs that induce hepatotoxicity. Moreover, quality control of herbal drugs and randomized controlled clinical trials will further validate the evidenced based herbal therapy for the treatment of liver diseases.

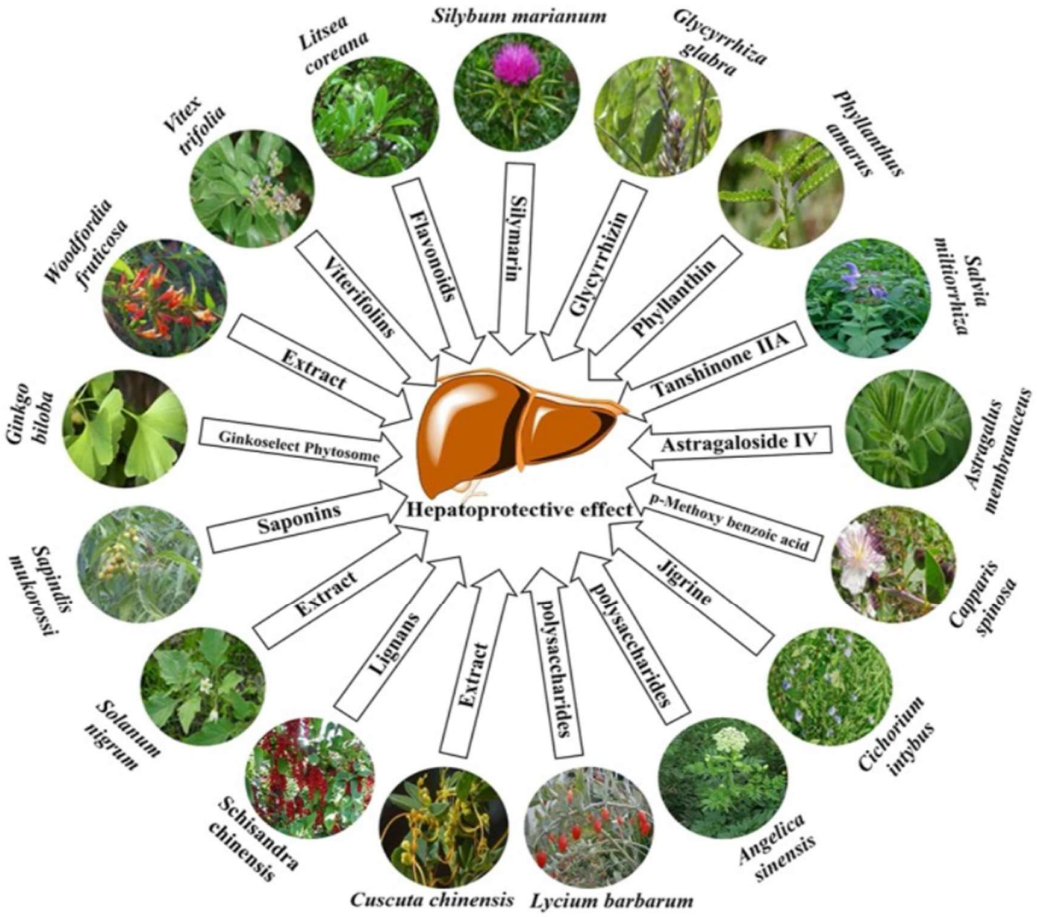

Fig 2: Some important medicinal hepatoprotective plants

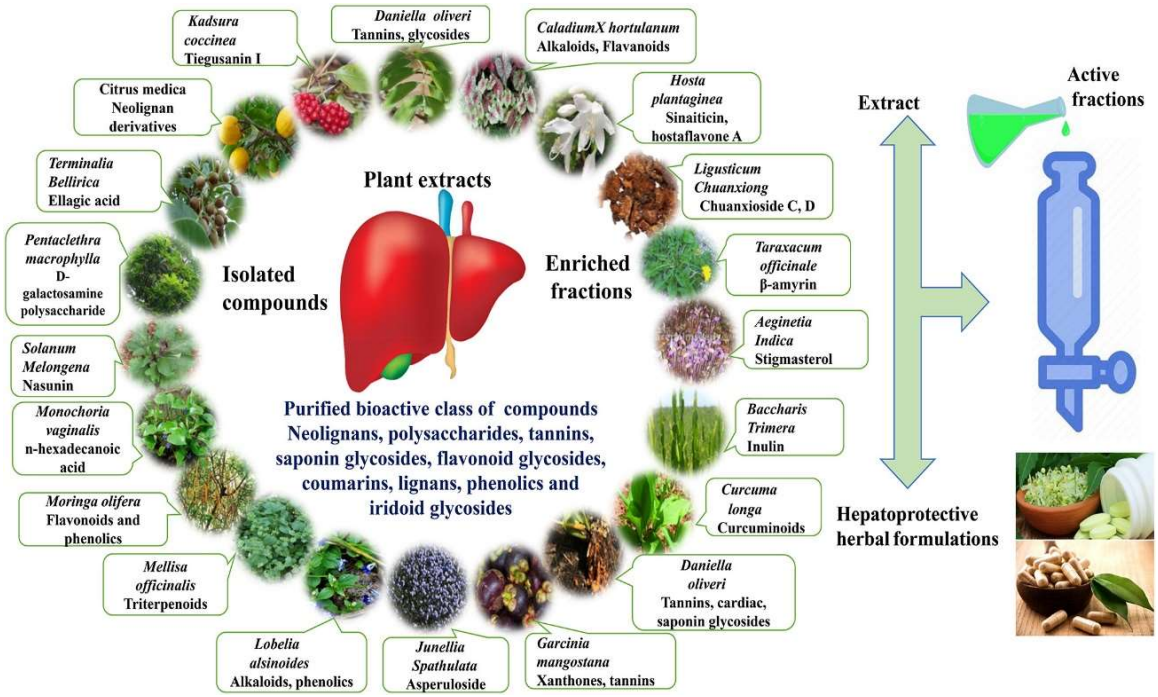

Fig 3: Hepatoprotective plants

CONCLUSION

Therapies developed along the principles of Western medicine are often limited in efficacy, carry the risk of adverse effects, and are often too costly, especially for the developing world. Therefore, treating liver diseases with plant-derived compounds, which are accessible and do not require laborious pharmaceutical synthesis seems highly attractive. Therefore, treating liver diseases with plant derived compounds which are accessible and do not require laborious pharmaceutical synthesis seems highly attractive. Effective formulations should be advanced the use of indigenous medicinal plant life, with proper pharmacological experiments and clinical trials. The manufacture of plant products needs to be ruled by using standards of protection and efficacy.

The importance of medicinal plants can be determined from World Health Organization's estimates, which states that up to 80% of the world's population fulfill their healthcare needs from medicinal plants. There has been a significant rise in using over-the-counter medicinal plant products containing powerful medicinal drugs and are believed to have to produce progressive effects with reduced side effects. However, therapeutic failures or adverse effects have been observed in many cases as pharmacological mechanisms of the herbal mixtures/preparations are not well-studied. The most important concern involving the use of medicinal plants is to identify and standardize the exact method of preparation of an extract, identification of active ingredients and details of administration. In this relationship, the screening and characterization of other undiscovered herbal products in traditional medicine is needed. The integration of the therapeutic use of traditional Chinese medicinal knowledge with the synthetic and traditional oriental medicinal knowledge is a key area of research.

Author contributions

All authors contributed to data collection, drafting or revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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