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The Classification of Medicinal Plants used in Traditional Persian Medicine for the Treatment of Liver Disease based on Phytochemical Properties

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ABSTRACT

Chronic and acute liver diseases are considered a global issue and their medical treatments are commonly challenging to manage. Traditional medicines have used natural products for thousands of years to prevent and treat various diseases. Recent studies have revealed that the pharmacological impacts of herbs are primarily determined by their phytochemical constituents. Therefore, understanding plant chemistry is crucial for the therapeutic use of medicinal plants. In this review, we first introduced some medicinal plants that have the potential to be beneficial for treating liver diseases and disorders, based on Traditional Persian Medicine (TPM) textbooks. Subsequently, we investigated the secondary metabolites of these medicinal plants by analyzing pharmacological research collected from electronic databases. We also discussed their scientific and family names. According to TPM textbooks, 77 medical plants have been identified for the treatment of liver defects, belonging to 43 different families. Their secondary metabolites were studied through data obtained from electronic databases such as Google Scholar, PubMed, Science Direct, and Web of Science. These findings suggest that natural plant extracts hold promise for the prevention and treatment of liver diseases.

Keyword: Liver, Medicinal plants, Phytochemicals, Secondary metabolites, Traditional Persian medicine

INTRODUCTION

Since ancient times, natural products such as plants, microorganisms, animals, and marine organisms have been used in medicines to attenuate injuries and treat diseases [1]. Early humans had an enormous challenge using natural products as medicines due to the consumption of poisonous plants, which resulted in diarrhea, vomiting, coma, or even death. This way made early humans expand their knowledge of edible plants and natural medicines. Traditional medicines have used natural products for the prevention and treatment of diseases for thousands of years [2].

The application of medicinal plant extracts for medical purposes originated and continues in traditional Indian, Egyptian, and Chinese medicine [3]. Several medicinal plants have been commercialized for their beneficial impacts on health, which are linked to various biological functions associated with their traditional applications [4]. Massage therapy and aromatherapy with herbal oils have been shown to have beneficial results and promote immunological and physiological conditions in many ancient communities [3].

Recent studies have shown that the tremendous pharmacological impacts of herbs are fundamentally dependent on their phytochemical constituents, so that the study of plant chemistry is the foundation of the therapeutic uses of medicinal plants. Plants produce two large groups of compounds, primary and secondary metabolites. The secondary metabolites are small molecular products obtained from primary metabolites or play a role as intermediates in their biosynthetic pathways. These molecules show no noticeable effect on the essential cellular functions and are non-essential for the growth and reproduction of the organism, but play bio-ecological roles in the process of organism adaption to environmental niche [5]. Moreover, secondary metabolites have several biological effects, including antifungal, antibiotic, and antiviral properties. This makes them effective at protecting plants from pathogens and serving as vital UV-absorbing compounds that prevent severe leaf damage

from light. Secondary metabolites are classified into several large classes based on their chemical structure. Phenolics, terpenes, steroids, alkaloids, glucosides, amines, and flavonoids are some classes.

Recently, research works have shown that the secondary metabolites have positive beneficial effects on human health, agriculture production, and cosmetic products, contributing significantly to the economy [6]. It was proved that the secondary metabolites are responsible for the medicinal effect of plants. The importance of secondary plant metabolites in traditional medicine and folk uses cannot be overstated. These products of medical plants have been shown to alleviate a wide range of diseases. In modern medicine, secondary metabolites have been used as fundamental compounds to produce medications that treat different diseases, including various cancers and migraines.

Currently, there is no approved remedy for some infections, disorders, and diseases and besides, vaccination is limited to some viral infections. Additionally, medicines available on the market are often costly and may cause side effects. As a result, naturally based pharmacotherapy may be a proper alternative to treating diseases.

The liver is a vital organ in the human body that performs various functions such as detoxification, metabolism, and storage of nutrients. However, the liver can be affected by multiple diseases, such as hepatitis, cirrhosis, and liver cancer. Chronic and acute liver diseases are considered a global issue and their medical treatments are commonly challenging to manage and have restricted effectiveness [7]. For example, liver cancer is the most frequently detected form of cancer and has shown a significant rise in mortality rates worldwide. Surgery plays a crucial role in treating liver cancer; however, numerous patients with advanced stages or metastasis are not eligible candidates for surgical procedures [8]. Despite chemotherapy's ability to directly target cancer cells, it often has limitations such as resistance and side effects. Hence, there is a strong need for an effective strategy for liver cancer treatment that is non-toxic. Moreover, diabetes is a metabolic disease caused by reduced biological effects of glucose or insufficient insulin secretion in the body. This disease affects glucose metabolism and can lead to liver abnormalities and insulin resistance [9]. Various factors, including chemicals, drugs, and viruses, have been reported to lead to serious liver necrosis, which can be difficult to manage with medical therapies. Therefore, it is crucial to find compounds that can effectively treat hepatic failure. Then, finding a new remedy that can safely and successfully prevent or treat liver diseases is a top priority. A wide variety of herbs, plant extracts, and plant-isolated compounds have been investigated for their beneficial effects on liver diseases.

Traditional medicine and folk remedies have utilized secondary plant metabolites for centuries to treat liver ailments. Recent studies have shown that these compounds possess biological properties such as antioxidant and anti-inflammatory effects that can protect the liver from damage. Furthermore, some secondary metabolites have been found to have hepatoprotective effects, which can prevent liver diseases. Therefore, understanding the role of secondary metabolites in liver health and the environmental factors that affect their production is crucial for developing effective treatments for liver diseases.

Nowadays, despite different opinions among medical professionals and complementary medicine practitioners, there is a rising trend to use alternative and complementary medicine which is widely permitted by current legal regulations across the world [10]. There are precious medical works by Iranian sages mentioned in traditional Persian medicine (TPM) books that may be useful for alternative treatments of some diseases.

TPM is an entire system of medicine that dates back to ancient Persia. Studies have shown that TPM has a rich history of using medicinal plants and herbs for treating various diseases. A number of these herbs have been proven to possess anti-inflammatory, antioxidant, and anti-cancer properties by laboratory research. Traditional knowledge of natural medicine is recorded in historical manuscripts. Some of the most popular and influential ancient Persian medical references were Razi or Rhazes Continens Liber (Kitab- al-Havi) by Rhazes and Canon of Medicine (Al-Qanun-fi-al-Tibb) by Avicenna.

The present review focused on effective herbs for liver diseases and disorders based on ancient Iranian books and studied bioactive constituents isolated from medicinal plants based on the scientific literature.

METHODS

This review was designed to gather information regarding herbal medications for the liver in TPM. To search for TPM references, Makhzan-ol-Advieh, The Canon of Medicine, and Taghvim al-Abdan fi Tadbir al-Ensan were used. In the next step, the classification of plants has been performed based on their scientific names and

phytochemical compositions. The required data have been collected from electronic databases such as Google Scholar, PubMed, Science Direct, and Web of Science. The main findings are summarized in the table.

RESULTS

In the current review, a total of 77 medical plant species belonging to 42 families have been reported to treat liver diseases in TPM textbooks specifically. Table 1 shows the bioactive metabolites of medicinal plants in the current study with their scientific and family names. Among them, Apiaceae (7 species), Asteraceae (6 species), and Lamiaceae (4 species) were the dominant families (Figure 1). Figure 2 shows the percentage of the present medicinal plants containing bioactive metabolites. Terpenoids were observed in 68% of medicinal plants with considerable effects on treating liver diseases. Almost 52% of the plants studied in the current review contained phenolic components. Moreover, flavonoids and glycosides were observed in 20% and 16% of medicinal plants, respectively.

Table 1 Secondary metabolites of medicinal plants are used to treat kidney diseases according to traditional Persian medicine.

No.	Scientific name	Family name	Organ	Glycoside	Steroids	Tannins	Flavanoids	Phenolic	Terpenoid	Saponins	Alkaloid	References
1	*Ajuga chamaepitys* (L.) Schreb.	Lamiaceae	Aerial parts	(α-1,6-galactosyl sucrose)				Methyl iridoid	Eucalyptol α-Thujone β-Thujone Camphor Endoborneol			[11]
2	*Ajuga iva* L.	Lamiaceae	aerial parts					Linalool salicylate	α-pinene camphene p-cymene 1,8-cineol 1-octen-3-yl acetate			[12]
3	*Aloe vera* L.	Asphodelaceae	Leaf	glucomannan	Squalene			Anthraquinone Phytol				[13]
4	*Althaea sp.*	Malvaceae	Flower and root									[14]
5	*Anacyclus pyrethrum* DC.	Asteraceae	Root		Gamma-Stigmasterol/ Sitosterol			Benzaldehyde, 2-hydroxy-6-methyl	7-Tetradecenal, (Z) Squalene Bicyclo[7.2.0]undec-4-ene, Squalene 4,11,11-trimethyl-8-methylene-,[1R-			[15]

6	*Apium graveolens* L.	Apiaceae	Leaf			Geraniol	[16]
7	*Aquilaria sinensis* Mer.	Thymelaeaceae				γ-caryophyllene oxide	[17]
8	*Aristolochia longa* L.	Aristolochiaceae				α-Thujone Selinene Spathulenol Zonarene Valerena	[18]
9	*Artemisia maritima* L.	Asteraceae	Fresh, authentic essential oil			α-Terpinene γ-Terpinene Santolina alcohol β-Thujone	[19]
10	*Artemisia sieversiana* Eh.&Wi.	Asteraceae	Stems and leaves			b-Myrcene Carene p-Cymene Borneol Terpineol-4 a-Terpineol a-Copaene Caryophyllene E-b-Farnesene Selina-4,11-diene Germacrene D E, E-a-Farnesene d-Cadinene Spathulenol g-Eudesmol T-Cadinol a-Cadinol a-Bisabolol	[20]
11	*Arum italicum* L.	Araceae		guaiacylglycerol-β-coniferyl		Myrcene Nerol β-Pinene Caryophyllene	[21]
12	*Arum maculatum* L.	Araceae	Roots			Carveol p-Cymene α-Pinene Terpinolene	[22]

13	*Asarum europaeum* L.	Aristolochiaceae	Whole plants				Spirosta nosides α-Asarone, β-Asarone	α-pinene camphene β-pinene myrcene δ−3-carene p-cymene limonene (E)-β-ocimene terpinolene linalool borneol terpinen-4-ol methyl thymol α-copaene		[23]
14	*Asparagus adscendens* Roxb.	Asparagaceae	Root							[24]
15	*Asparagus officinalis* L.	Asparagaceae	Aerial parts/ Fruits /Roots			Quercetin Apigenin	Caffeic acid			[25]
16	*Asparagus racemosus* Willd.	Asparagaceae	Aerial parts, Fruits and Roots			kaempferol			Sarsasapogenin	[26]
17	*Brassica juncea* (L.) Czern.	Brassicaceae	Seeds and leaves	α-Methyl-D-mannopyranoside β-D-Glucopyranoside	γ-Sitosterol/Stigmasterol β-Sitosterol/ Stigmastan-					[27]
18	*Calamintha incana* Boiss. & Held.	Lamiaceae	Aerial parts				Thymol	Limonene p-Cymene 2-Hydroxypiperitone		[28]
19	*Capparis decidua* (Forssk.) Edgew.	Capparidaceae	Fruits	butyl isothiocyana	β-Sitosterol					[29]

20	*Capparis spinosa* L.	Capparidaceae	Roots and leaves	capparisine			bis(5-formylfurfury) ether		Alkaloids	[30]
21	*Carica papaya* L.	Caricaceae	Leaf		Campesterol Stigmasterol			Squalene α-Terpineol (E)-Geraniol		[31]
22	*Carum bulbocastanum* L.	Apiaceae	Fruit					α-Pinene Camphene β-Pinene Limonene Sabinene 1,8-Cineole γ -Terpinene Linalool Camphor Borneol Carvone β-Caryophyllene triterpene		[32]
23	*Carum carvi* L.	Apiaceae	Fruit					α-Pinene β-Pinene β-Myrcene p-Cymene D-Limonene 1,8-Cineol Linalool -Terpineol γ-Terpinene p-Cymen-8-ol Dihydrocarvone cis-Carveol Cuminic aldehyde (R)-Carvone Dihydrocarveol α-Terpinene-7-al		[33]
							Eugenol			

24	*Carum copticum* L.	Apiaceae	Fruit				Myrcene Limonene α-Thujene α-Pinene b-Pinene Sabinene α-Phyllanderene p-Cymene b-Phyllanderene γ-terpinen Terpinene- 4 -ol Carvacrol cymene	[34, 35]
25	*Celastrus paniculatus* Willdenow	Celastraceae	Seed	beta. -Sitosterol acetate		Thymol	Maymyrsine Linalool Cubenol trans-beta-Copaene	[36]
26	*Cichorium intybus* L.	Asteraceae	Root		Anthocyanins	lactucin, 8-deoxylactucin	Lactupicrin α-amyrin	[37]
27	*Cichorium pumilum* Jacq.	Asteraceae	Flower and aerial parts				P-Lactucin Lactucopicrin	[38]
28	*Cinnamomum bejolghota* (Buch. - Ham.) Sweet	Lauraceae	leaf				camphene a-pinene pinene	[39]

29	*Cornus mas* L.	Cornaceae	Fruits				2-(4-Methylcyclohex-3-en-1-yl) propan-2-ol α-terpineol 4,7,7-Trimethylbicyclo [2.2.1] heptan-3-ol/ borneol; 0.29 2-[(2R,5S)-5-Ethenyl-5-methyloxolan-2-yl] propan-; 0.51 2-ol/*cis*-Linalool Oxide (furanoid)*f; 2-[(2S,5S)-5-Ethenyl-5-methyloxolan-2-yl] propan-; 0.14 2-ol/*trans*-Linalool oxide(furanoid), (3S,6S)-6-Ethenyl-2,2,6-trimethyloxan-3-ol/; <0.42 *cis*-pyranoid Linalool oxide Limonene	[40]
30	*Cucumis colocynthis* L.	Cucurbitaceae	Fruits			cyanidin 3-O-rutinoside pelargonidin 3-O-rutinoside Isosaponarin pelargonidin 3-O		[41]
31	Cucumis melo L.	Cucurbitaceae	Fruits			Amentoflavone Hydroxytyrosol Gallic acid Protocatechuic acid Chlorogenic acid		[42]
32	*Equisetum arvense* L.	Equisetaceae	Aerial parts			Hexahydrofarnesyl acetone Thymol		[43]

33	*Eugenia Jambolana* Lam.	Myrtaceae	Fruits	Cyanidin Cyanidin-3-glucoside Cyanidin-3,5-diglucoside Cyanidin-3-diglucoside-5-glucoside Malvidin	Galloyl-glucose ester	Dimethyl-dihydromyricetindiglucoside Isorhamnetin	Caffeic acid Gallic acid	a-Pinene β-Pinene a-Phellandrene Terpinolene y-Terpinene Camphene Myrcene o-cymene p-cymene Terpinolene Linalool Nonanal thujone Camphor borneol terpinen-4- terpineol nerol methyl thymol geraniol caryophyllene	[44]
34	*Eupatorium cannabinum* L.	Asteraceae							[45]
35	*Feronia elephantum* Correa	Rutaceae	Leaf /bark				Tryptamine, N-[4-hydroxyhydrocinnam oyl]-		[46]

36	*Foeniculum vulgare* Mill	Apiaceae	Aerial parts				Linalool Fenchol (z)-p-Terpineoi Nerolidol Isophytol Fenchone Camphor Carvone a-thujene a-pinene sabinene 3-pinene Myrcene a-phellandrene limonene isomer Palustrol	[47]
37	*Fumaria officinalis* L.	Fumariaceae				*p*-Coumaric acid Isoquercitrin Ferulic acid		[48]
38	*Fumaria parviflora* Lam.	Fumariaceae		α-D-diglucoside		Salicylic acid		[49]
39	*Gentiana lutea* L.	Gentianaceae	Root and Aerial parts			Vanillin	Hydroxy 2-butanone Linalool n-Menthone Isomenthone 4-Terpineol Carvone Thymol (E)-Caryophyllene (E)-a-Ionone -Gujunene trans-a-Bergamotene Aromadendrene Geranyl acetone y-Himachalene	[50]
40	*Glycryrrhiza glabra* L.	Fabaceae	Root	Pectin		Coumarins	Glycyrrhizin	[51]

41	*Hippophae rhamnoides* L.	Ellaegnaceae				Limonene cis-Ocimene	[52]
42	*Hyacinthus orientalis* L.	Liliaceae	Flowers	Anthocyanin 3,5-diglucosides	Delphinidin		[53]
43	*Hypericum barbatum* L.	Hypericaceae					[54]
44	*Hypericum coris* L.	Hypericaceae	Leaves and flowers			Linalool Geraniol a-copaene b-caryophyllene a-Pinene Camphene b-Pinene Limonene g-Terpinene	[55]
45	*Hypericum perforatum* L.	Hypericaceae				a-Pinene Myrcene *p*-Cymene Selinene Cadinene Bisabolol β-Phellandrene γ-Terpinene Aromadendrene	[56]
46	*Iris florentina* L.	Iridaceae			-	-	[57]
47	*Laurus nobilis* L.	Lauraceous	Leaf			AThujene αPinene Camphene Sabinene BPinene Myrcene α-Phellandrene δ-3-Carene α-Terpinene p-Cymene Limonene Cis-Ocimene γ-Terpinene Terpinolene Linalool	[58]

48	*Lepidium draba* L.	Brassicaceae		Verbascoside			Chlorogenic acid		[59]
49	*Linaria vulgaris* Mill.	Scrophulariaceae				Pectolinarin Linarin	p-Coumaric acid p-Methoxybenzoic acid Chloro-syringic acid Antirrhinoside 6-O-trans-p-Coumaroyleantirrhinoside Procumbide	Vasicine tricyclic quinazoline	[60]
50	*Malus orientalis* Ugl.	Rosaceae		Phloridzin			Gallic acid caffeic acid syringic acid		[61]
51	*Malva parviflora* L.	Malvaceae	leaves	Rutin		Luteolin Quercetine			[62]
52	*Malva sylvestris* L.	Malvaceae					Quercetin		[63]
53	*Mandragora officinarum* L.	Solanaceae						Hyoscyamine Cuscohygine Apoatropine 3a-Tigloyloxytropane Belladonine	[64]

54	*Nymphaea alba* L.	Nymphaeaceae		Rutin Quercetin Caffeic acid Cinnamic acid		[65]
55	*Petroselinum crispum* (Mill.) Fuss	Apiaceae	Fruit and leaves	Carvacrol	cymene α-Thujene α-Pinene β-Pinene β-Myrcene 3-Caren p-Cymene Sabinene γ-Terpinene α-Terpinolene 4-Thujanol Thymol β-carotene p-cymenene	[66]
56	*Pinus cembera* L.	Pinaceae			Limonene Myrcene α-Pinene β-pinene γ-terpinene	[67]
57	*Pinus halepensis* Mill.	Pinaceae			Limonene Myrcene α-β pinene fl-Pinene Terpinene Sabinene α - phellandrene fl-Phellandrene *p*-cymene Pinocarvone β-Pinene α-longipinene	[68]
58	*Pinus pinea* L.	Pinaceae			Limonene +β-phellandrene *p*-cymene Bornyl *acetate* Myrtenol verbenone	[69]
59	*Piper cubeba* L.	Piperaceae			Cadinene Linalool Sabinene	[70]

60	*Pistacia chia* L.	Anacardiaceae	Fresh bark and leaves			α-pinene Camphene Sabinene *β*-pinene *β*-myrcene p-cymene Limonene (Z)-*β*-ocimene E)-*β*-ocimene α-terpinolene linalool perillene cis-verbenol trans-pinocarveol trans-verbenol *β*-pinene epoxide myrtenal α-terpineol verbenone trans-carveoldihydro carveol linalyl acetate	[71, 72]
61	*Pistacia lentiscus* L.	Anacardiaceae	Fresh bark and leaves	Oligomers flavonoids	α-campholene aldehyde	(E)-anethole Limonene β-pinene caryophyllene Terpinene-4-ol	[73]
62	*Pistacia vera* L.	Anacardiaceae	fresh commercial samples of shelled pistachio		Pinocarveol Vanillin Tyrosol	4- vinylphenol- eugenol Thymol Carvacrol Squalene	[74]
63	*Portulaca oleracea* subsp. sativa DC.	Purtolacaceae	Seed				[75]
64	*Prunus avium* L.	Rosaceous	Fruit				[76]

65	*Rumex acetosa* L.	Polygonaceae	Leaf				Quercetin 3-O-rutinoside Quercetin 3-β-D-glucoside *Quercetin derivative* Kaempferol 3-O-glucoside Luteolin 7-O-glucoside	Catechin Gallic acid Caftaric acid			[77]
66	*Salix acmophylla* Boiss.	Salicaceae			Styrene	Salicin		Coumarin			[78]
67	*Salix aegyptiaca* Fors. .	Salicaceae							Terpineol Cedrol	Alkaloid	[79]
68	*Salix excelsa* S.G.	Salicaceae							tetramethyl-2-hexadecene-1-ol		[80]
69	*Sempervivum arboreum* L.	Crassulaceae	Leaf				3,3',4',5,7-pentahydroxy-6-				[81]

70	*Seseli tortuosum* L. *(Seseli libanotis)*	Apiaceae	Fruit				coumarin	Myrcene α-pinene β-pinene limonene			[82]
	Solanum melongena L.									Hexanal (Dimethylamino)acetone Methoxyethylamine Boscalid	
71		Solanaceae	Fruit	Ethyl iso-allocholate	2-Hydroxyethylphosphine			Neophytadiene Farnesyl acetone 4-Oxononanedioic acid Clionasterol Citronellyl formate			[83]
72	*Stachys officinalis* (L.) Trevis	Lamiaceae	Leaf and flower					Thujene Pinene Sabinene Myrcene Limonene Linalool trans-pinocarveol myrtenal verbenone cubebene copaene phytol			[84]
73	*Syzygium aromaticum* (L.)	Myrtaceae					Eugenol	Thymol Limonene α-Pinene *p*-cymene Cadinene Linalool			[85]
74	*Viola odorata* L.	Violaceae					Methyl eugenol	Pinocarvone Camphor Benzaldehyde Geranylacetone Bornyl *acetate* Borneol Limonene β-Pinene γ-Terpinene myrcene *p*-Cymene β-Farnesene			[86]

75	*Vitis vinifera* L.	Vitaceae				[87]
76	*Zingiber officinale* Rosc.	Zingiberaceae	Root/ Rhizome	4-(4-hydroxy-3-methoxyphenyl)-2-Butanone, ç-Elemene/1H-Cyclopenta [1,3] cyclopropa[1,2]/Copaene benzene, octahydro-7-methyl-3-methylene-4-(1-methylethyl)-,[3aS- Farnesene	Eugenol Isoeugenol Carvacrol Cadinene	[88]
77	*Zizyphus jujuba* Mill.	Rhamnaceae				[89]

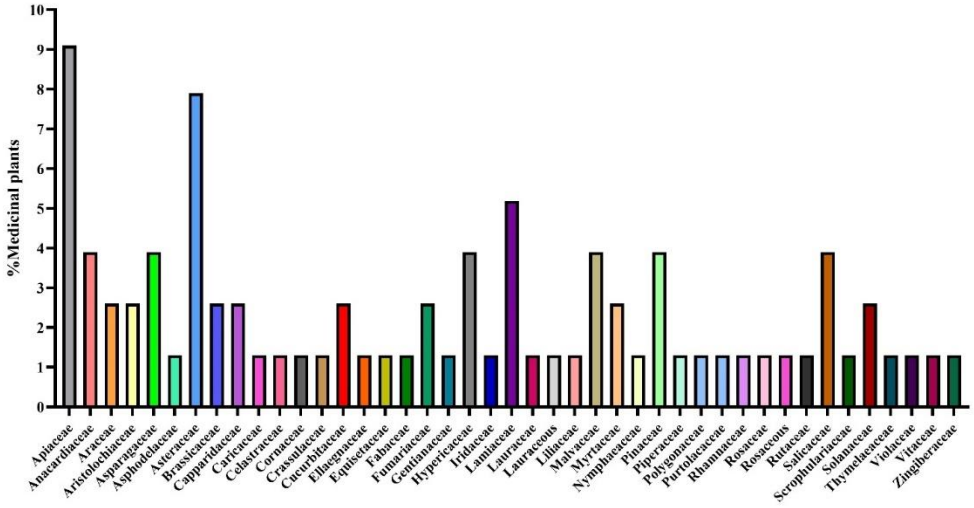

Fig. 1 Percentage of the medicinal plant species from various families studied in the current review.

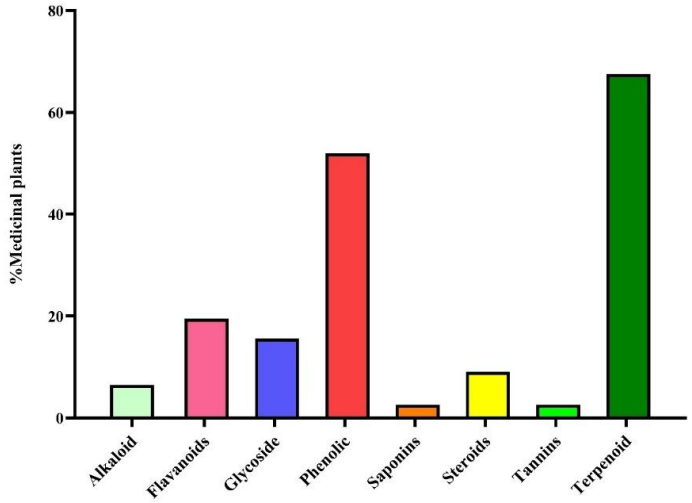

Fig. 2 Percentage of medicinal plants containing secondary metabolites studied in the current review.

DISCUSSION

These days, there has been a rising trend in the usage of alternative medicine. Accumulating evidence has illustrated that early treatment with traditional medicine has proven effective in preventing the progression of mild and moderate diseases into severe and critical conditions [90]. Moreover, alternative medicine has also been successful in providing an effective therapeutic strategy for patients with extreme illnesses and enhancing the ability of the body's resistance to remove pathogenic factors [91]. The biggest challenge in traditional medicine is finding proper remedies from those which are unsafe or ineffective. It is necessary to assess and standardize all traditional drugs and methods for use in modern medicine according to contemporary pharmaceutical and medical standards. Over the past years, the properties of some medicinal plants mentioned in this study were investigated for liver dysfunction or diseases *in vitro* or *in vivo*. For this purpose, there is a need to have a clear view of traditional knowledge compared to current concepts.

The current review discusses the phytochemicals of medicinal plants of TPM that have been proven to be robustly effective in treating patients suffering from liver diseases. Several studies have investigated the potential hepatoprotective effects of plant extracts against acute liver injuries induced by carbon tetrachloride (CCl_4), oxymetholone and thioacetamide, which activate hepatocyte damage in key markers. The effect of medicinal

plants has been studied through evaluation of liver function markers such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin were performed, along with oxidative stress parameters including malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD), and glutathione peroxidase as well as inflammatory mediators such as serum cytokines (IL-1β, IL-10, IL-6), tumor necrosis factor (TNF)-α, and nitric oxide.

The methanol extract from *Ajuga iva* has high concentrations of polyphenolics and flavonoids and has been found to inhibit key digestive enzymes linked to type 2 diabetes. It is particularly effective against α-glucosidase and has a significant inhibition against α-amylase, along with high antioxidant activity, while it is non-toxic. The results suggest that the phenolic compounds in the extract may be responsible for its antioxidant and antidiabetic activities [92]. *Aloe vera*, with various medicinal properties, has been used in ancient medicine to treat fever, burns, and wounds. Previous studies suggest that *A. vera* has anti-diabetic effects with protection against high fat and fructose diet-induced oxidative stress, dyslipidemia, and liver dysfunction. It also improves albumin levels and antioxidant enzyme activities in treated mice. The liver tissues of treated mice showed normal hepatocytes [93]. The ethyl alcohol-water extract of *Ziziphus jujube* leaves, another plant with hepatoprotective properties, was found to have a pharmacological effect and significantly alleviate liver damage induced by CCl_4 in mice. The results have provided evidence that *Z. jujube* not only offers maximum conjugation with dangerous free radicals and diminishes their toxic properties but also suppresses the inflammatory responses of a CCl_4-induced liver injury. Flavonoids were identified as the active ingredients responsible for the biological and pharmacological activities toward hepatoprotection [94, 95]. *Capparis spinosa* L., also known as caper, is a plant traditionally used for medicinal purposes in various parts of the world. The fresh leaf and bud powders of *C. spinosa* contain multiple phytochemicals, including rutin, quercetin, and kaempferol. Daily administration of *C. spinosa* leaf or bud powder normalized biochemical parameters such as blood glucose, insulin, and lipid levels in rats with diabetes mellitus. The hepatoprotective properties of *C. spinosa* may be attributed to flavonoids like quercetin and rutin [4]. Another study found that the administration of *Piper cubeba* ethanolic extract protected against CCl_4-induced hepatic damage in rats by downregulating proinflammatory cytokines and upregulating IL-10. *P. cubeba* ethanolic extract also prevented drug-induced increases in hepatic enzymes, reduced lipid peroxidation, and restored antioxidant enzyme activity along with prevention of CCl_4-induced hepatic damage based on histopathological studies [96]. The potential protective effect of the eugenol-rich fraction of *Syzygium aromaticum* (clove) was investigated on liver cirrhosis induced by thioacetamide. The results showed that *S. aromaticum* had a protective effect on liver cirrhosis, as it inhibited hepatic cell proliferation and decreased oxidative stress. Eugenol, a major component of *S. aromaticum*, may be metabolized to dieugenol, which inhibits lipid peroxidation. This suggests that eugenol may have antioxidant properties that protect against liver cirrhosis [97]. *Anacyclus pyrethrum* L. with potential medicinal properties is commonly used in traditional North African and Indian medicine. The study investigated the anti-diabetic effects of the aqueous extract of *A. pyrethrum* roots in both normal and streptozotocin-induced diabetic rats by administration of a daily dose of 250 mg/kg extract after 21 days. The results showed that the *A. pyrethrum* extract exhibited significant antihyperglycemic activity in diabetic rats. Phytochemical screening of the extract revealed the presence of various compounds, including tannins, saponins, alkaloids, amino acids, steroids, and terpenoids, which may contribute to the potential therapeutic properties of the extract [98]. The neuroprotective and hepatoprotective potentials of *Anagallis arvensis* were evaluated in rat models of interstitial cystitis and hepatotoxicity. The study found that pretreatment with *A. arvensis* significantly decreased the levels of liver markers and lipid profile due to its antioxidant phytochemicals [99]. The study investigated the antioxidant effects of a methanolic extract of *Apium graveolens* in a rat model of arthritis-induced liver oxidative stress. The rats were orally given different doses of *A. graveolens* extract for 24 days after inducing arthritis. The study found that *A. graveolens* treatment significantly reduced the levels of superoxide anion, total peroxide, and oxidative stress index in the liver. Additionally, the activity of glutathione peroxidase and SOD, which are antioxidant enzymes, significantly increased in the liver of arthritic rats treated with *A. graveolens* extract [100].

Furthermore, the hepatoprotective activity of an aqueous extract of *Artemisia absinthium* L. was investigated in a mouse model of liver injury induced by a single CCl_4 administration or injection of endotoxin (lipopolysaccharide). The results of histopathological parameters showed that pretreatment with *A. absinthium*

extract significantly prevented the increase in serum levels of hepatic enzymes in experimental mice-induced liver injury. Additionally, the extract reduced lipid peroxidation in the liver tissue and restored the activities of defense antioxidant enzymes SOD and GPX to normal levels. Histopathological examination showed a reduction in hepatocellular necrosis and reduced inflammatory cell infiltration. Phytochemical analysis revealed the presence of sesquiterpene lactones, flavonoids, phenolic acids, and tannins in *A. absinthium* [101]. In another study, the potential antidiabetic properties of ethanolic extract of *Asparagus adscendens* root were studied *in vivo* and *in vitro* models. They found that *A. adscendens* inhibited the activity of carbohydrate metabolizing enzymes, which are involved in the breakdown and utilization of carbohydrates in the body. The ethanolic extract also stimulated insulin release, suggesting that it may enhance the body's ability to regulate glucose metabolism and enhance glucose uptake, potentially aiding in the management of diabetes. Additionally, in an animal model of diabetes, *A. adscendens* decreased fasting blood glucose levels and increased serum insulin and α-amylase levels [102]. This study investigated the potential protective effects of *Carica Papaya Linn.* Seed extract against liver damage induced by CCl_4 in rats. The study found that *C. Papaya* contained various antioxidants and minerals. The results showed that *C. papaya* extract treatment reduced oxidative stress, inflammation, fibrosis, and apoptosis induced by CCl_4. Liver and kidney function was also improved with *C. Papaya* seed extract treatment [103]. The impact of *Cornus mas* L. fruit extract was studied on liver function in nona-lcoholic fatty liver disease. Fifty patients were randomly assigned to receive either fruit extract for 12 weeks and levels of certain liver function markers were measured before and after the intervention. They found that cytokeratin 18 levels decreased significantly in the group treated with fruit extract compared to the control group [104]. Another study aimed to investigate the hepatoprotective effects of *Citrullus colocynthis* fruit extract on rats with hepatotoxicity induced by paracetamol. The results showed that rats treated with paracetamol had significantly elevated levels of liver function markers, but pretreatment with *C. colocynthis* fruit extract decreased these levels. The histopathological analysis also showed that fruit extract preserved the normal cellular architecture of the liver, suggesting that *C. colocynthis* has significant hepatoprotective and antioxidant activity [105]. The hepatoprotective effects of *Feronia elephantum correa* were evaluated against thioacetamide-induced liver necrosis in diabetic rats. The results showed that *F. elephantum* significantly reduced mortality and improved liver function parameters without affecting liver weight, volume, or serum glucose levels. The results concluded that *F. elephantum* could be useful for preventing liver complications in diabetes. The protective effects of *F. elephantum* against liver necrosis were attributed to its antioxidant activity, particularly from the flavonoids orientin and vitexin present in the extract [106]. Research work has been performed on the antidiabetic potential of *Fumaria officinalis*, a plant traditionally used to treat hypertension, hepatitis, and diabetes. Administration of the aqueous and methanolic extracts exhibited a significant hypoglycemic effect in alloxan-induced diabetic rats compared to normo-glycaemic rats. The extract also improved liver and kidney function tests and reduced damage to cells in the kidney and liver of diabetic rats [107]. The potential hepatoprotective effects of methanol extracts from the aerial parts and roots of *Gentiana cruciata* L. were studied against liver injury induced by CCl_4 in rats. The extracts were found to contain high concentrations of sweroside, swertiamarin, and gentiopicrin. Pretreatment with *G. cruciata* dose-dependently and significantly reduced the levels of serum transaminases, ALP, and total bilirubin, while increasing the total protein level compared to the group treated with CCl_4 alone. Microscopic examination of the liver showed minimal CCl_4-induced lesions and toxic manifestations in rats pretreated with extracts at 400 mg per kg body weight [108]. The effect of *Glycyrrhiza glabra* extracts was investigated on acute liver injuries induced by CCl_4. Aqueous and ethanol extracts of *G. glabra* were used to administer orally to rats that were intraperitoneally injected with CCl_4. The extracts significantly inhibited the activities of AST and ALT and increased the activity of SOD in both serum and liver tissue. Phytochemical analysis showed the presence of flavonoids and polysaccharides in the extracts, which may be responsible for their hepatoprotective activity [109]. In another study, the hepatoprotective effect of an aqueous extract of *Glycyrrhiza glabra* roots was evaluated in rabbit models with acute liver injury induced by CCl_4. The results showed a significant reduction in hepatic enzyme levels, serum bilirubin, and improvement in serum protein levels in animals treated with the extract. The liver tissue also showed restoration of its architecture, absence of necrosis, and mild fatty infiltration [110]. Another study evaluated the hepatoprotective activity of *Hippophae rhamnoides* L. leaf extract on CCl_4-induced liver injury in male albino rats. The extract significantly protected

the animals from liver injury and enhanced antioxidant activity, suggesting it could be developed as a nutraceutical or food supplement against liver diseases [111].

Another study investigated the hepatoprotective potential of *Iris florentina* L. methanolic extract with flavonoids and phenols on paracetamol-induced liver injury in rats. The extract significantly improved serum biomarkers and restored hepatic injury, indicating hepatoprotective potential [112]. A study found that laurel leaf extract *Laurus nobilis* has potential as a natural remedy for managing liver damage induced by CCl_4 in male Wistar rats. Rats treated with the extract had significantly lower liver damage indicators and less severe liver damage. The extract also increased levels of antioxidant enzymes, suggesting a protective effect against oxidative stress [113]. Another research investigated the protective effects of *Lepidium draba* extract on oxymetholone-induced hepato-renal toxicity in rats. The extract improved hepatic and renal biochemical parameters, reduced inflammatory cytokines and nitric oxide levels, and increased antioxidant enzyme activity. The high antioxidant and anti-inflammatory properties of *L. draba* are attributed to its phenolic and flavonoid components [114]. The antidiabetic activity of *Malva parviflora* L. leaf extract and its nano-formulation was measured in rats. The extract and its nano-formulation improved biochemical parameters, decreased glucose levels, increased insulin production, and improved the lipid profile of liver and kidney functions in diabetic rats, showing high antioxidant action and antimicrobial activity [115]. The aqueous methanolic extract of *M. parviflora* was studied to evaluate hepatoprotective activity in mice intoxicated with paracetamol. The extract significantly reduced liver enzymes and total bilirubin levels and was supported by histopathological investigation and detection of hepatoprotective constituents, suggesting that *M. parviflora* could be used as a natural remedy for liver damage. [116] *Nardostachys jatamansi*, an herb used in traditional Indian medicine, has been found to have hepatoprotective activity in rats. A 50% ethanolic extract of the herb's rhizomes significantly reduced liver damage caused by the toxic compound thioacetamide, as evidenced by lowered levels of serum enzymes and increased survival rates. This study supports the traditional use of *N. jatamansi* as a component of some hepatotoxic preparations used in Unani medicine. [117]. The potential hepatoprotective effects of *Nymphaea alba* L. leaf extract were measured on CCL_4-induced hepatotoxicity in rats. The extract was found to significantly improve liver function, oxidative stress parameters, and TNF-α, as well as ameliorating histopathological features of the liver and decreasing caspase-3 expression, implying that *N. alba* leaf extract may be a therapeutic alternative for hepatic disorders. [118]. The study investigated the hepatoprotective effects of three plant extracts, *Pistacia lentiscus*, *Phillyrea latifolia*, and *Nicotiana glauca*, which are used in Jordanian folk medicine for the treatment of jaundice. The extract effects were tested on liver function and serum bilirubin levels of rats with CCl_4-induced hepatotoxicity. The non-boiled aqueous extract of *N. glauca* leaves reduced total serum bilirubin levels, while the boiled aqueous extract of *P. latifolia* reduced bilirubin and ALP levels without affecting ALT and AST activities. Both boiled and non-boiled aqueous extracts of *P. lentiscus* showed significant antihepatotoxic activity by reducing the activity of all three enzymes and bilirubin levels. The non-boiled extract was more effective than the boiled extract and may be a potential treatment for hepatic jaundice in humans [119]. The study aimed to investigate the potential hepatoprotective effects of *Pinus eldarica* extract on acetaminophen-induced liver injury in rats. The administration of *P. eldarica* extract significantly attenuated the increase in serum levels of ALT, AST, and ALP caused by acetaminophen. Additionally, *P. eldarica* administration prevented extensive necrosis and lymphocytic inflammation caused by acetaminophen, suggesting that *P. eldarica* has potential therapeutic effects on acetaminophen-induced liver toxicity in rats [120]. The potential protective effects of *Pistacia lentiscus* var. chia extracts were measured on CCl_4-induced liver damage in rats. The results showed that *P. lentiscus* var. chia extracts have a strong inhibitory effect against lipid peroxidation in rat livers, with a decrease in levels of AST, ALT, and MDA. The pre-treatment *P. lentiscus* var. chia extracts reduced GSH depletion caused by CCl_4, yielding GSH levels comparable to that observed in untreated rats, showing that *P. lentiscus* var. extracts protect liver cells from CCl_4-induced oxidative damage [120]. The effects of *Portulaca oleracea* extract were investigated on acute alcoholic liver injury in 60 male Wistar rats. Results showed that *Portulaca oleracea* extract reduced serum levels of certain enzymes and triglycerides, increased antioxidant capacity, decreased inflammation, and improved lipid metabolism disorder induced by ethanol after seven days [122]. Another study evaluated the effect of feeding *Rumex patientia* seeds on serum glucose and lipid profile in streptozotocin-diabetic rats. Diabetic rats treated with *R. patientia* showed a significant reduction in serum glucose levels at the 2nd and

4th weeks compared to untreated diabetics. *R. patientia* also reduced lipid peroxidation in hepatic tissue, suggesting that this extract could improve glucose and lipid profiles, partly due to its attenuation of lipid peroxidation in hepatic tissue [123]. The effects of *Saccharum officinarum* juice were studied on liver injury caused by the tuberculosis drug Isoniazid in mice. The group treated with Isoniazid and *S. officinarum* juice had decreased levels of liver enzymes. The group treated with juice also showed significant recovery in liver structure [124]. Another study investigated the protective effects of *S. officinarum* juice on paracetamol-induced liver damage in rats. Paracetamol caused liver damage in rats, as evidenced by increased enzyme levels, decreased antioxidant levels, and increased liver weight and volume. Treatment with *S. officinarum* juice reduced serum ALT, AST, ALP, and bilirubin, along with an increase in the antioxidant parameter MDA level [125]. The aqueous methanolic extract of *Viola odorata* was tested in mice with paracetamol-induced liver injury, which caused necrosis and inflammation. *V. odorata* restored elevated levels of serum hepatic enzymes and total bilirubin, and histopathological studies showed attenuation of hepatocellular necrosis and inflammation. High-performance liquid chromatography analysis revealed the presence of hepatoprotective flavonoids isorhamnetin and luteolin in the extract [126]. Another study examined the effects of aqueous and hydro-alcoholic extracts of *V. odorata* on liver function in diabetic rats. Results showed that the extracts reduced Kupffer cells, inflammation, and congestion in the liver tissue. Additionally, the extracts decreased the level of liver enzymes and serum glucose levels in diabetic rats [127]. The study evaluated the effects of total triterpenoids and total flavonoids from *Vitis vinifera* L on immunological liver injury induced by Bacille-Calmette-Guerin (BCG) and lipopolysaccharide (LPS) mice and found that various doses of triterpenoids and flavonoids reduced liver injury, decreased BCG/LPS-induced elevated liver index and spleen index, decreased hepatic nitric oxide and MDA content, increased liver homogenate ALT and AST levels, and restored hepatic SOD activity. The results suggest that the presence of triterpenoids and flavonoids in *V. vinifera* may have properties for the treatment of liver injury [128].

The wide variety of the medical plants of the current study have been used in traditional North African, Indian, Unani, and Uighur medicine as well as in Turkish and Jordanian folk medicine. Overall, these findings suggest that natural plant extracts have potential therapeutic applications in the prevention and treatment of liver diseases. Further research is needed to understand the mechanisms underlying their hepatoprotective effects fully and to develop effective therapies based on these natural compounds.

Declarations

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors. The authors declare no conflicts of interest.

Consent for Publication

All authors consent for publication of this article.

Competing Interests

The authors declare no competing interests.

Availability of Data and Material

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Authors' Contributions

The authors have contributed equally to the parts of the article.

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Abbreviations:

TPM	Traditional Persian Medicine