Ugwu and Suru *Egyptian Liver Journal* (2021) 11:88
https://doi.org/10.1186/s43066-021-00161-0

Egyptian Liver Journal

REVIEW

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Medicinal plants with hepatoprotective potentials against carbon tetrachloride-induced toxicity: a review

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Abstract

Background: Carbon tetrachloride (CCl_4) is a well-characterized hepatotoxic agent. With rising cases of liver diseases, the identification, assessment, and development of hepatoprotective agents from plants source has become imperative.

Main body: With arrays of literature on plants with hepatoprotective potentials, this review sourced published literatures between 1998 and 2020 and systematically highlighted about 92 medicinal plants that have been reported to protect against CCl_4-induced liver injury in animal models. The results show that herbal plants provide protection for the liver against CCl_4 by downregulation of the liver marker enzymes and activation of antioxidant capacity of the liver cells with the restoration of liver architecture. We also provided the traditional and accompanying pharmacological uses of the plants. A variety of phytochemicals mostly flavonoids and polyphenols compounds were suggested to offer protection against liver injuries.

Conclusion: It can be concluded that there are a variety of phytochemicals in plant products with hepatoprotective activity against CCl_4-induced toxicity in animal models.

Keywords: Carbon tetrachloride, Medicinal plants, Hepatoprotective, Silymarin, Folkloric medicine

Background

The liver being an important organ is often exposed to array of threats [1]. Injury to the liver can lead to deterioration of its functions and may culminate in organ failure [2]. The likely risk factors for the development of the liver diseases have been suggested to include pathogenic microorganisms and viruses, hepatotoxins, overdose and duration of drugs, obesity and malnutrition, alcohol, autoimmune disorders, type-2 diabetes, and genetic factors [1]. The diseases of the liver are of public health concern because orthodox remedies for liver diseases produce limited results with attendant side effects. As such, utilization of complementary and alternative herbal medicine has attracted research interest for novel plausible hepatoprotective agents capable of ameliorating or reversing liver injury with little side effects [3, 4]. Over the years, this search has gained impetus with many studies focusing on hepatoprotective potentials of plant drugs.

Carbon tetrachloride (CCl_4) is a known hepatotoxicant in humans and animal models [5]. It has been successfully used in hepatotoxicity research as a model and to appraise hepatoprotective agents [6, 7]. With reports on the rise of liver diseases and numerous literature reports on plants with potential hepatoprotective activity, this review highlighted the mechanism of CCl_4 toxicity, the significance, effectiveness, and underlying mechanisms of herbal plant extracts on CCl_4-induced toxicity in experimental animal models.

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Main text

Insight on the mechanism of carbon tetrachloride hepatotoxicity

Prior to the Montreal Protocol, CCl_4 was formerly and widely used as a fire suppressant, as a precursor to refrigerants, propellants for aerosol cans, as a cleaning agent, a widely used solvent in organic chemistry, as a pesticide, and anesthetics [8, 9]. However, it is rarely used today because of adverse health effects and environmental safety concerns. Symptoms associated with acute inhalation of low–medium doses include headache, weakness, lethargy/general anesthesia, nausea, vomiting, and respiratory arrest. For medium to high oral exposure, the liver is known to be the primary site of CCl_4-induced toxicity beginning with acute but progressive centrilobular injury that may culminate in cell death [10].

Experimental deductions

Due to the complex nature of CCl_4-induced liver damage, there have emerged several independent mechanisms to explain each of the facets of the associated changes. The interrelationship among diverse mechanisms proposed for each of these associated changes has not been well-established/outlined. This is primarily because early and later changes associated with the hepatotoxic development have been mixed up. As a result, a harmonized understanding of the intricate mechanisms involved in hepatic damage has become partly elusive. However, this has not obscured the following experimental deductions (Fig. 1):

- Changes in endoplasmic reticulum (ER) function due to decrease in glucose-6 phosphatase [11], which may not be unconnected with CCl_4-induced glycogen depletion and attendant protection from carbohydrate-rich diets [12, 13]. Besides, CCl_4-induced disruption and disassociation of polyribosomes from ER alters its anabolic function as manifested in decreased incorporation of amino acids into proteins such as albumin and fibrinogen [14]. Additionally, CCl_4-induced hypomethylation of 2′-O-ribose moieties in rRNA might have resulted from transient increase in cytosolic Ca^{2+}. This increase may activate the selective destruction of rRNA methylases via

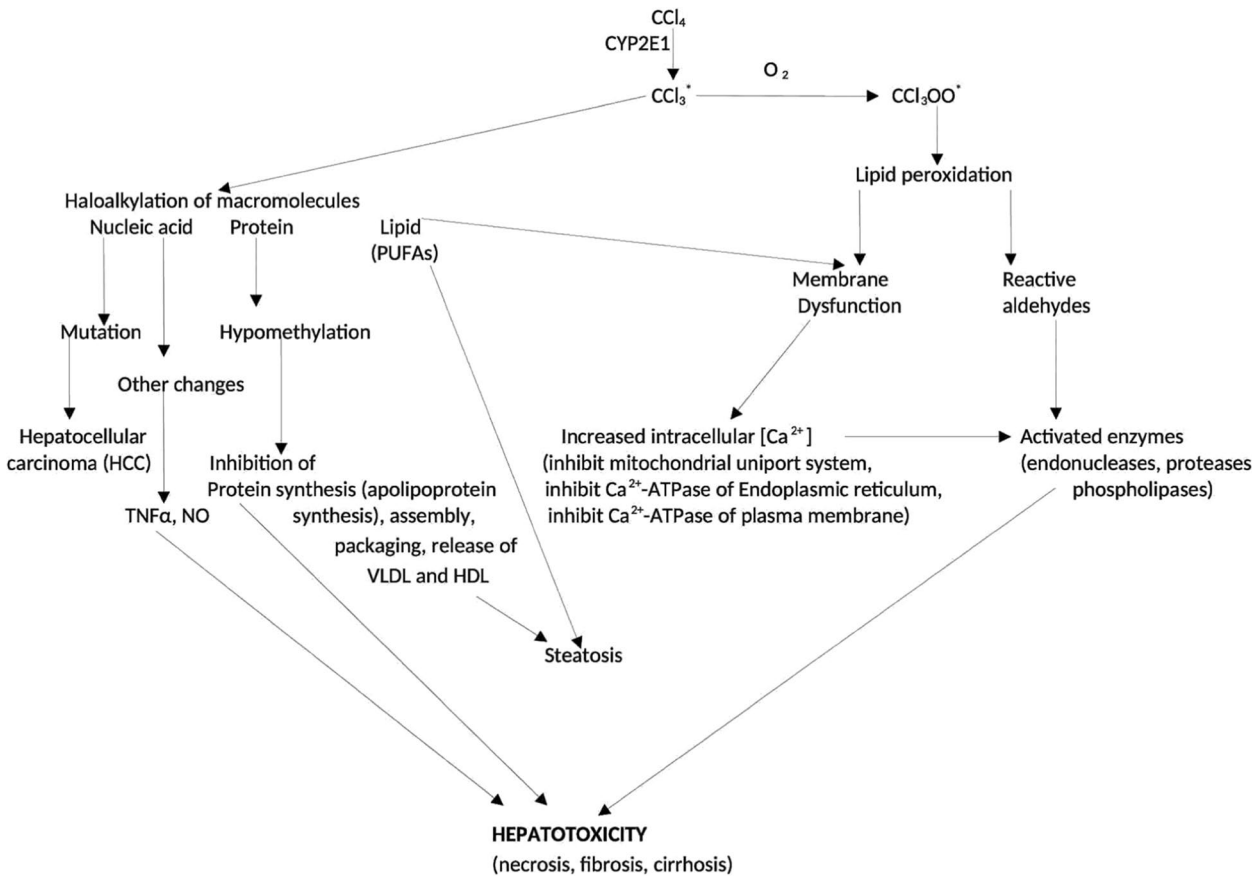

Fig. 1 Hepatotoxic mechanism of CCl_4

the action of demethylases or proteases. Overall, the protein synthetic function of ER in the centrilobular region may be hampered with an attendant defects in the ability of the liver to effectively respond to additional insults [10].

- Calcium homeostasis underlies some aspects of CCl_4 hepatotoxicity (plasma membrane blebbing and fatty accumulation- steatosis); CCl_4 may elicit dramatic redistribution of intracellular Ca^{2+} stores, albeit no total cellular change [10]. Calcium ion (Ca^{2+}) homeostasis is maintained by 3 mechanisms: (i) Ca^{2+} extrusion by plasma membrane ATPase, (ii) Ca^{2+} sequestration by mitochondria, and (iii) Ca^{2+} sequestration by liver ER. So, CCl_4 may cause decreased Ca^{2+} sequestration by ER and mitochondria, decreased extrusion by plasma membrane ATPase, as well as blockage of gap junctional intercellular communication may favor increase cytosolic Ca^{2+}. An ATP-dependent Ca^{2+} sequestration by hepatic ER has been shown to be disrupted by CCl_4 [15]. Endoplasmic reticulum membrane permeability may also be altered, being one indicator of impending cell death [16].
- Rapid destruction/decrease in cytochrome P_{450} in centrilobular regions (suggesting that CCl_4 was metabolized by ER mixed-function oxidase system), which is orchestrated by low levels of reduced glutathione (GSH) and low oxygen tension. In turn, low level oxygen tension may limit competition between O_2 and CCl_4 for cytochrome P_{450} binding (i.e., CCl_4 may readily bind to cytochrome P_{450}).
- Metabolic products [trichloromethyl (CCl_3^*) or peroxytrichloromethyl (CCl_3-OO^*) free radical] elicit damage: lipid peroxidation of vulnerable unsaturated fatty acids in membrane phospholipids and destruction of haem moiety of cytochrome P_{450}.
- Blockage of gap junctional communication by CCl_4 thereby shutting down intercellular communication.
- Changes in mitochondrial function: disruption of oxidative phosphorylation due partly to chelation of calcium [17].

Making sense out of experimental deductions

The hepatic biotransformation of CCl_4 primarily involves metabolic activation to transient reactive intermediates. Under low oxygen partial pressure, cytochrome P_{450} catalyzes the reductive de-halogenation of CCl_4 resulting in predominant formation of CCl_3^* and $CHCl^*$ radicals [18, 19]. These reactive intermediates may bind covalently to cellular components (membranes, microsomes) and impinge on mostly lipid metabolism (increased synthesis, decreased transport out of the hepatocyte) thereby culminating in hepatic steatosis (fatty liver) [20, 21].

Dianzani [22] reported that covalent modification of lipoproteins occurs prior to their decreased transport out of hepatocytes. Intracellular maturation of lipoproteins in the Golgi apparatus is dependent on galactosylation which is catalyzed by glucosyl- and galactosyltransferases [23]. The CCl_4-induced damage of Golgi apparatus and eventual reduction in the activities of these enzymes may explain the observed decrease in lipoprotein secretion associated with CCl_4 intoxication. Thus, CCl_4-induced inhibition of lipoprotein secretion, and its attendant hepatic steatosis mainly result from covalent binding of CCl_4 metabolites to cell constituents, but not due to lipid peroxidation.

Under high oxygen partial pressure, however, CCl_3^* may interact with oxygen to form CCl_3-OO^*. The peroxy radicals may elicit the peroxidation of unsaturated fatty acids especially in membrane phospholipids of intracellular and plasma membranes [24]. Some of the lipid peroxidative products may inflict further damage leading to increased membrane permeability and a comprehensive loss in membrane integrity [25]. Thus, both covalent binding of CCl_4 metabolites and lipid peroxidation work in tandem to elicit the hallmark of damage seen in CCl_4-induced hepatotoxicity.

The consequences of loss of membrane integrity are enormous and may lead to cascade of events culminating in liver necrosis. These events may include disturbed Ca^{2+} homeostasis/dramatic redistribution of Ca^{2+} in hepatocytes, leakage/efflux of K^+, and influx of Na^+ [10, 26].

Beside the peroxidative action, CCl_4-derived free radicals and their attendant oxidative stress have been shown to enhance NF-kB expression, which in turn initiates the synthesis of cytotoxic cytokines, which may be partly responsible for liver injury [27]. Tumor necrosis alpha (TNF-α) has been implicated in CCl_4-induced hepatocellular damage [28]. At lower doses of CCl_4, inflammatory responses prevail. Healthy hepatocytes are insensitive to tissue necrosis factor alpha (TNF-α) action, but become sensitive once protein and RNA synthesis are inhibited [29].

Summarily, CCl_4 hepatotoxicity may be due to a combination of factors such as the thorough inhibition of protein synthesis, the severe derailment of intracellular Ca^{2+} sequestration, and the effect on membrane integrity. These factors may result and progress through a series of steps that contribute to various extents to the ultimate damage: reductive dehalogenation, covalent binding of resulting radicals; inhibition of protein synthesis (in particular, apolipoprotein synthesis), assembly, packaging and release of VLDL and HDL, fat accumulation;

Table 1 List of traditional plants with anti-hepatotoxic potential against acute carbon tetrachloride hepatotoxicity

s/n.	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
1	*Abelmoselius manihot* (L) *medic*	*Malvaceae*	Flower, ethanol	Treatment of jaundice and hepatitis, control of fertility, easing of child birth and stimulation of lactation.	Anti-inflammatory, antioxidant, antibacterial, anticonvulsant, cardioprotective, and neuroprotective actions	[32]
2	*Acacia mellifera*	*Fabaceae*	Leaves, acetate/aqueous/n-butanol	Treatment of cold, malaria, syphilis, and bowel problems.	Antimalarial, antimicrobial, antiviral activity against HIV-1, and herpes simplex virus	[33]
3	*Aegle marmelos correa ex Roxb*	*Rutaceae*	Pulp/seed, aqueous	Treatment of jaundice, hepatitis, piles, tuberculosis and antidiarrheal. Used as stomach tonic.	Antidiarrhoeal, anti-inflammatory, and wound healing effects	[34]
4	*Aegle marmelos correa ex Roxb with piperine*	*Rutaceae*	Leaves, 70% ethanol	Used as astringent, laxative and expectorant. Treatment of inflammation, cataract, diabetes, diarrhea, and asthma.	Antifungal, ulcer healing, anti-inflammatory, antidiabetic, diuretic, anticancer, and antioxidant properties	[35]
5	*Alangium salviifolium* .	*Alangiacea*	Stem bark, methanol.	Treatment of rheumatism, cancer and hemorrhoids. Root used to manage skin diseases, diarrhea, fever, carminative, and purgative expectorant.	Antiarthritic, androgenic, anthelmintic, antidiabetic, hepatoprotective, and anti-inflammatory effects	[36]
6	*Alhagi maurorum (camel thorn)*	*Fabaceae*	Leaves, methanol	As a remedy for rheumatic pains, bilharziasis, liver disorders, and urinary tract infection.	Antioxidant, antidiarrheal, and antiulcerogenic activities.	[37]
7	*Alhagi maurorum Medikus.*	*Fabaceae*	Aerial parts, 90% ethanol	Treatment of liver problems, migrane and cataract. As tonic, digestive, antipyretic, laxative, diuretic, and aphrodisiac	Antiulcer, antibacterial, antioxidant, anti-inflammatory, analgesic, antipyretic, antifungal, and hepatoprotective effects	[38]
8	*Allium sativum (Single clove garlic)*	*Amaryllidace*	Garlic bulbs, 70% ethanol	Used as nutraceuticals	Antidiabetic, anticancer, antioxidant, immune modulation activities, and lowering of blood pressure.	[39]
9	*Amaranthus spinosus*	*Amaranthaceae*	Whole plant, 50% ethanol	Prevent swelling around the stomach. Used in the treatment of jaundice	Anti-inflammatory, antimalarial, antibacterial, antidiuretic, antiviral, immunostimulatory, and antioxidant effects	[40]
10	*Amorphophallus campanulatus (Roxb)*	*Araceae*	Tubers, aqueous	Treatment of piles, abdominal pain, tumors, enlargement of spleen, asthma, and rheumatism	Antibacterial, antifungal, and cytotoxic activities	[41]
11	*Argemone Mexicana L*	*Papaveraceae*	Crude powder leaf	Treatment of malaria, fever, abdominal pains, and jaundice	Antibacterial, anti-inflammatory, wound-healing, antifertility, antistress, anti-allegic, cytotoxic, antidiabetic, and antihepatotoxic activities	[42]
12	*Artemisia iwayomogi*	*Compposita*e	Aqueous	Treatment of hepatic disorders	Antioxidant, cytoprotection, choleretic, hepatoprotection, antimicrobial, anti-inflammatory and antifibrotic effects.	[43]

Table 1 (continued)

s/n.	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
13	*Bauhinia variegate*	*Leguminasea.*	Stem bark, alcohol	Treatment of bronchitis, leprosy, diarrhea, piles, and tumor. Used as astringent	Hypoglycaemic, haemagglutinating, antibacterial, and antifungal effects	[44]
14	*Bougainullra spectabillis*	*Nyctaginaceae.*	Esculetin	Treatment of liver damage, cough, pertussis, and bronchitis	Antimicrobial, anticancer, antidiabetic, anti-inflammatory, antihyperlipidaemic, antioxidant, antiulcer, and antihepatotoxic activities	[45]
15	*Bryonia diocia Jacq*	*Cucurbitaceae*	Leaves, 80% ethanol	Treatment of various inflammatory conditions, brochial complaints, asthma, intestinal ulcer, hypertension, and arthritis. Applied as a rubefacient to muscular pains. Treatment of fever and bronchitis	Antinociceptive, antimicrobial, antioxidant, hepatoprotective, anticancer, hypercholesterolemia, analgesic, anti-inflammatory, cytotoxic, and hepatoprotective	[46]
16	*Brysocarpus coCClneus Schum*	*Connaraceae*	Leaves, aqueous	Mouth and skin sores, swellings, tumors, earache, muscular pain, and jaundice	Antioxidant and hepatoprotection	[47]
17	*Cajanus cajan*	*Leguminosae*.	Aerial, 70% ethanol	Jaundice and stomach disorders	Anthelmintic, antioxidant and protection against alcohol-induced liver damage	[48]
18	*Calotropis gigantean R.Br*	*Asclepiadaceae*	Stem, 50% ethanol.	In tooth ache and ear ache, sprain, anxiety, pain, epilepsy, and in mental disorders	Antidiarrheal, analgesic, CNS activity, and pregnancy interceptive properties	[49]
19	*Camellia ntidissima Chi*	*Theaceae*	Leaves, 10 % ethanol	Treatment of dysentery, hypertension, diarrhea, faucitis, hepatitis, jaundice, liver cirrhosis and sores	Leaves show antioxidative, antitumor, antibacterial, anti-inflammatory, hypoglycaemic, hypolipdemic, antidepressant, antillergic, and immunomodulatory activities	[1]
20	*Canna indica L*	*Cannaceae*	Aerial part, methanol	Treatment of diuresis, fever, dropsy, earaches, and eye disease	Analgesic, antioxidant, and hepatoprotective effects	[50]
21	*Capparis spinosa*	*Capparidaceae*	Root bark, 80% ethanol	Treatment of hepatic diseases. Reducing flatulence, treatment of rheumatism, anemia, and gout. Used as diuretics	Antidiabetic, hypoglycaemic, antioxidant, antiapoptotic, antibacterial, anti-inflammatory, antifungal, and hepatoprotective effects	[51]
22	*Capsella busa-pastoris (L.) Medik*	*Brassicaceae*	Aerial parts, 90% ethanol	Remedy for liver, hemorrhages, respiratory problem, and as diuretic	Antimicrobial, antioxidant, anticancer, anti-inflammatory, and sedative effects	[38]
23	*Carissa opaca*	*Apocynaceae*	Leaves, 95% methanol	Treatment of asthma, cardiac disorder and cough	Antioxidant, membrane stabilization, antipyretic and aperient activities	[52]
24	*Carthamus tinctorius L*	*Asteraceae*	Flower, hydroxysafflor yellow A	Treatment of dysmenorrhea, amenorrhea, postpartum abdominal pains, and pains of the joints. As antidote to poisoning and purgative	Antioxidant, antidiabetic, hepatoprotective, anti-inflammatory, antifungal, antimicrobial, and hepatoprotective effects	[53]

Table 1 (continued)

s/n.	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
25	*Carthamus tinctorius. L*	*Asteraceae*	Flower, Na_2CO_3	Treatment of gynecological diseases, osteoporosis, cardiovascular diseases, and angiitis	Nutraceutical, hepatoprotective, antioxidant, promoting blood circulation, and inhibiting platelet aggregation, anti-inflammatory, antipyretic, antitumor, and antidiabetic activities	[54]
26	*Carum carvil*	*Apiaceae*	Fruit, aqueous	Treatment of jaundice, indigestion and pneumonia. As appetizer, diuretic and gastric stimulant	Anti-inflammatory, spasmolytic, antimicrobial, antioxidant, caminative, antidiabetic, immunomodulatory, anticancer, and hypolipidaemic properties	[55]
27	*Cassia angustifolia Vahl*	*Caecalpiniaceae*	Leaves, ethanol.	Used in jaundice, rheumatoid arthritis, blood disease, diarrhea, ringworm, skin diseases, dysentery and as laxatives	Hepatoprotection and antioxidant activities	[56]
28	*Cassia angustofolia vahl*	*Leguminosea*	Leaves, 90% alcohol	Used as laxative, febrifuge, treatment of anemia, typhoid, cholera, jaundice and tumors	Hepatoprotection and antioxidant activities	[57]
29	*Cassia fistula Linn*	*Caesalpinacea*	Leaves, 90% ethanol	Treatment of Jaundice and rheumatism. Used as a laxative.	Hepatoprotective and antioxidant properties	[58]
30	*Cichorium intybus*	*Asteraceae*	Esculetin	Treatment of acne, inflammation of throat, jaundice, enlargement of spleen, diarrhea, vomiting, and rheumatism	Hepatoprotection, antihelminthic, antimicrobial, antidiabetic, and analgesic effects	[45]
31	*Cichorium intybus*	*Asteraceae*	Seed, ethanol	Treatment of acne, inflammation of throat, jaundice, enlargement of spleen, diarrhea, vomiting, and rheumatism.	Hepatoprotection, antihelminthic, antimicrobial, antidiabetic, and analgesic effects	[59]
32	*Cichorium intybus*	*Asteraceae*	Seed, 0.03% methanol.	Treatment of acne, inflammation of throat, jaundice, enlargement of spleen, diarrhea, vomiting, and rheumatism	Hepatoprotection, antihelminthic, antimicrobial, antidiabetic, and analgesic effects.	[59]
33	*Cichorium intybus*	*Asteraceae*	Leaves, hydroethanol (1:1)	Treatment of acne, inflammation of throat, jaundice, enlargement of spleen, diarrhea, vomiting, and rheumatism	Hepatoprotection, antihelminthic, antimicrobial, antidiabetic and analgesic effects.	[60]
34	*Cinnamomum verum*	*Lauraceae*	Cinnamon powder, 95% ethanol	Treatment of diabetes, respiratory, and gynecological ailments	Enhancement of glycogen synthesis, antioxidant, antidiabetic, hypolidemic, antipyretic, and analgesic activities	[61]

Table 1 (continued)

s/n.	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
35	*Cinnamomum verum*	*Lauraceae*	Bark essential oil, dichloromethane	Preventing heart diseases, reduction in cholesterol and as an antidiabetic	Antioxidant, boosting cognitive activity, antiangiogenesis, anti-inflammatory, antimicrobial, and protection against Parkinson' disease	[62]
36	*Cinnamomum zeylanicum L*	*Lauraceacea*	Bark, 80% ethanol	Flavoring for foods and in traditional medicine to treat variety of health conditions	Antimicrobial, insecticidal, antityrosinease, antioxidant, antimutagenic, anti-inflammatory, hypotensive, and cholesterol-lowering effects.	[63]
37	*Citrus aurantium (essential oil)*	*Rutaceae*	Peel skin, aqueous oil	Diaphoretic and antiseptic	Analgesic, anti-inflammatory, antifungal, and antibacterial activities	[64]
38	*Citrus limon(L.) Burm.F*	*Rutaceae*	Fruit, 70% ethanol	Treatment of liver ailment and jaundice. Treatment of sluggish liver, rheumatism, fever, and febrile diseases	Chemoprevention, lipid peroxidation inhibitor, hypocholesterolemic, and antioxidant effects.	[65]
39	*Clerodendrum volubile*	*Verbenaceae*	Leaves, 50% methanol.	Treatment of diabetes, ulcer, arthritis, and rheumatism	Antidiabetic, antihypertensive, antioxidant, and anticancer effects	[66]
40	*Clitoria ternatea L*	*Fabaceae*	Leaves, ethanol	Treatment of liver diseases, insect bites, asthma, leukoderma, and inflammation	Antihelmintic, antihistaminic, antimicrobial, cytotoxic, anti-inflammatory, wound healing, proteolytic, hypoglycemic, and antioxidant activities	[56]
41	*Corianderum sativum. L*	*Apiaceae*	Leaves, ethanol	Treatment of jaundice	Anxiolytic, antidepressant and sedative-hypnotic effects. Neuroprotective, antibacterial, anti-inflammatory, analgesic, antidiabetic, antifungal, and hypolipidaemic effects	[67]
42	*Corianderum sativum. L. (essential oil)*	*Apiaceae*	Fruits, aqueous	Recommended for spastic condition of the gastro intestinal oral tract, flatulence, fullness and loss of appetite due to their antispasmodic, and antimicrobial activities	Anxiolytic, antidepressant and sedative-hypnotic effects. Neuroprotective, antibacterial, anti-inflammatory, analgesic, antidiabetic, antifungal, and hypolipidaemic effects	[55]
43	*Coriandrum sativum*	*Umbelifera*	Leaves/stem, 70% ethanol	Treatment of ailments like spasm, rheumatism, neuralgia, gastric complaint, bronchitis, diarrhea, carminative and diuretic tonic	Hypoglycemic, antibacterial, antifungal, free radical scavenging, and lipid peroxidation properties	[68]
44	*Cortex dictamni*	*Rutaceae*	Whole plant, aqueous	Treatment of Jaundice, chronic hepatitis, cough rheumatism and some skin diseases. To clear heat, dry dampness, dispel wind, treatment of arthritis, eczema, rubella, and urticarial	Good scavenger of free radicals and inhibition of lipid peroxide	[69]

Table 1 (continued)

s/n.	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
45	*Curcuma longa. L*	*Zingiberacae*	Rhizome(root), 50% ethanol and curcumin	Used for the treatment of chronic diseases like diabetes mellitus, dermatological infection, and depression	Anti-inflammatory, immunoregulatory, and antioxidant effects	[70]
46	*Cytisus scoparius L*	*Leguminosae*	Aerial, 70% ethanol	As a diuretic hypnotic, sedative, and antidiabetic	Used as diuretic, hypnotic, sedative, antidiabetic, and hepatoprotector	[71]
47	*Dicoma anomala Sond*	*Asteraceae*	Root, aqueous	Treatment of cold and cough, fever, ulcer, and dermatosis	Antisplasmodial, antibacterial, anthelmintic, antiviral, antioxidant, and anti-inflammatory effects	[72]
48	*Dioscorea alata peel*	*Dioscoreaceae*	Peel, aqueous	To strengthen stomach function, anorexia, and to eliminate diarrhea	Anti-inflammatory effect	[73]
49	*Eclipta alba(L) Hassk*	*Asteracea*	Leaves, aqueous	Treatment of Jaundice. Juice used in treatment of hair problem, typhoid, dysentery, and skin diseases	Hepatoprotection, antidiabetic, analgesic, antimicrobial, antioxidant, anticancer, anti-inflammatory, and immunoregulatory activities	[74]
50	*Emblica officinalis (Gaertn)*	*Euphorbiaceae*	Fruit, methanol	Relieving cough and skin diseases	Antidiabetic, cytoprotective, anti-ulcerogenic, immunomodulatory, antioxidant, and anticataractogenic effects	[75]
51	*Entada pursaetha DC*	*Fabaceae*	Stem, 85% ethanol	Used as narcotic. Treatment of jaundice. As an anthelmintic, in curing eye diseases, diarrhea, and skin diseases	Hepatoprotective and antioxidant effects	[76]
52	*Ephedra foliate Boiss*	*Ephedraceae*	Aerial parts, 90% ethanol	Treatment of allergies, asthma, lung congestion, chills and cold	Antidiabetic, anticancer, antimicrobial, antioxidant, anti-inflammatory, and hepatoprotective effects	[38]
53	*Euphorbia dracunculoides .L*	*Euphorbiaceae*	Aerial part, 95% methanol	Curing skin disorders and edema. Used as diuretic and laxative and in the treatment of rheumatism, snake bite and edema	Anti-inflammatory, analgesic and antioxidant activities. Hepatoprotection against hepatocyte cell lines	[5]
54	*Fagonia schweinfurthii(Hadidi) Hadidi*	*Zygophyllaceae .*	Whole plant, ethanol.	Treatment of Jaundice, diabetes, joint pains, asthma and dropsy.	Antioxidant, hepatoprotective, anti-inflammatory, wound healing and analgesic activities.	[77]
55	*Fiscus carica Linn*	*Moraceae.*	Leaves, ethyl acetate.	Treatment of vitiligo, diabetes, cough, asthma, constipation and gingivitis.	Cytotoxic, hypoglycemic and anthelmintic activities.	[78]
56	*Flemingia macrophylla*	*Fabaceae/ Leguminosae.*	Root, aqueous.	Treatment of rheumatism, arthropathy, chronic nephritis, menalgia, and menopausal syndrome.	Antioxidative, anti-inflammatory, analgesic, hypotic-sedative and anxiolytic effects.	[79]

Table 1 (continued)

s/n.	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
57	*Ginko biloba*	*Ginkgoaceae* .	Leaves, aqueous.	Treatment of Alzheimer's dementia and other cognitive dysfunctions.	Antioxidant, cardioprotective, antiasthmatic, antidiabetic, management of cerebral insufficiency, and decreased gastric injury caused by ethanol.	[80]
58	*Glyphae brevis*	*Tiliaceae.*	Leaves, 50% methanol.	Treatment of hepatitis, jaundice and impotence.	Carminative, anticonvulsant effects, anti-inflammatory, antioxidant and improvement of lipid metabolism.	[81]
59	*Graptopetalum paraguayense E, Walther*	*Crassulaceae*	Leaves, aqueous	Regulation, alleviation of hepatic disorders, relief of pain, detumescence and carbuncles	Antioxidant, anti-inflammatory, neuroprotective, hypertension regulation, antioxidant activity, and inhibition of cancer cells	[82]
60	*Hibiscus sabdariffa. L*	*Malvaceae.*	Aerial parts, 90% ethanol	Used to prepare herbal drinks and as a flavoring agent. As diuretic and choleretic	Antibacterial, antioxidant, nephroprotective, antidiabetic and antihypertensive effects	[38]
61	*Hippophaerhamnoides L*	*Elaegnaceae*	Seabuckthorn berry polysaccharide, alcohol.	Treatment of asthma and circulatory disorders	Antioxidative, antimicrobial, antiatherogenic, cardioprotective, hepatoprotective, radioprotective, and anti-inflammatory effects	[83]
62	*Indigofera oblongifolia*	*Leguminaceae*	Whole plant, 90% ethanol	Treatment of hepatic diseases and dysentery, enlargements of liver and spleen. An antidote of poison	Antimicrobial, anti-inflammatory and analgesic activities	[84]
63	*Launaea procumbens*	*Asteraceae*	Aerial parts, chloroform	Treatment of kidney disorders, hormonal imbalance, and sexual diseases	Spasmogenic, cardiovascular, anticarcinogenic, anti-inflammatory, hepatoprotective, and antioxidant properties	[85]
64	*Lawson inermis L (Henna)*	*Lythraceae*	Leaves, 99% methanol	Used as astringent, hypotensive, sedative against headache. Treatment of jaundice, leprosy, and nervous disorder	Antimicrobial, anti-tumorigenic, anti-inflammatory, anti-apoptotic, antihyperglycaemic, antilipidaemic, antidiabetic, antiviral, and hepatoprotective effects	[86]
65	*Lawsonia inermis Linn*	*Lythraceae*	Leaves, aqueous	Treatment of liver diseases, jaundice, and burn	Anti-inflammatory, antipyretic, analgesics, antimicrobial, anticancer, and hepatoprotective properties	[87]
66	*Leucas cephalotes Linn.*	*Labiatae*	Whole plant, methanol	Treatment of liver disease, snake bite, and bronchitis, inflammation and jaundice.	Antifilarial and antidiabetic activities.	[88]
67	*Lobularia maritima*	*Brassicaceae*	Leaves, 10% ethanol	Antiscorbutic, diuretic, and as an astringent	Antioxidant and anti-inflammatory effects	[7]

Table 1 (continued)

s/n.	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
68	*Luffa acutangula (Var) amara*	*Cucurbitaceae*	Leaves, ethanol	As a laxative and carminative digestible. Treatment of anemia, jaundice, biliousness bronchitis, asthma, and piles	CNS depressant, antioxidant, and larvicidal activities	[89]
69	*Lygodium flexuosum(L.) Sw*	*Lygodiaceae*	Whole plant, n-hexane	Treatment of jaundice and liver disorders	Hepatoprotection against CCl_4	[90]
70	*Madhuca indica Syn*	*Sapotaceae*	Bark, methanol	Used as stimulants, demulcent, astringents, remedy of itching, and swelling	Anti-inflammatory, analgesic, hepatoprotective, antipyretic, antihyperglycaemic, antiulcer, and antidiabetic effects	[91]
71	*Madhuca indica Syn*	*Sapotaceae*	Leaves, 70% ethanol, 90% ethanol	Treatment of piles, emetic, laxative tonic, anti –burn, and wound healing	Antidiabetic, anti-inflammatory, analgesic, anti-pyretic, antiashmatic, antiulcer, anticancer, hepatoprotective, and antibacterial effects	[92]
72	*Mahonia oiwaken Hayata*	*Berberidaceae*	Root , 90% ethanol	Rheumarthritis, dysentery, hepatitis, antidote, and antiphylogistic agent	Hepatoprotection, antioxidant, and anti-inflammatory	[3]
73	*Mallotus philippensis Muell-Arg*	*Euphorbiaceae*	Leaves, methanol	Treatment of jaundice, threadworm, hookworm, and roundworm infections. As a purgative and carminative	Anticestodal, antibacterial, wound healing, antifilarial, antioxidant, anti-inflammatory, and immunoregulatory effects	[93]
74	*Memondica tuberosa Cogn*	*Cucurbitaceae*	Tubers, 70% ethanol	Used as abortifacient	Antioxidant, antihyperglycemic, anticonvulsant, anti-inflammatory, antiovulation, antidiarrhoeal, and nephroprotective activities	[94]
75	*Mentha piperita L*	*Lamiaceae*	Leaves (essential oil)	Treatment of nausea, bronchitis, flatulence, liver complaints, ulcerative colitis, and as carminative	Antioxidant and anti-inflammatory effects	[95]
76	*Menthe arvensis Linn*	*Lamiaceae*	Leaves, aqueous, chloroform, ethanol	Carminative, antispasmodic, and anti-peptic ulcer agent	Radioprotective, antispasmodic, antibacterial, anthelmintic, antifertility, hepatoprotective, antiulcer, and anti-inflammatory	[96]
77	*Mimosa pudica 2009*	*Fabaceae/Leguminosae.*	Leaves, methanol	Treatment of piles, fistula, insomnia, traumatic injury and jaundice	Hyperglycemic, antioxidant, anti-hepatotoxic, antidiabetic, wound healing, anti-inflammatory, and antimicrobial effects	[97]
78	*Mimosa pudica Linn*	*Fabaceae/Leguminosae.*	Leaves, ethanol	Treatment of wound, oedema, allergy, fever, diabetes, and indigestion	Hyperglycemic, antioxidant, anti-hepatotoxic, antidiabetic, wound healing, anti-inflammatory, and antimicrobial effects	[98]
79	*Momordica dioica Roxb*	*Cucurbitaceae*	Leaves, ethanol	Treatment of Jaundice, hepatic diseases, fever, asthma, and as anthelmintic. Used as stomach laxative	Hypoglycemic, gastroprotective, ulcer healing, and hepatoprotective effects	[99]

Table 1 (continued)

s/n.	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
80	*Nerium oleander Linn*	*Apocynaceae*	Flower, methanol	Treatment of malaria and venereal diseases. Used as diuretic, insecticide, abortifacient, and cardiotonic. Relieves Indigestion	Cardiac insufficiency, anticonvulsant, antitumor, and antioxidant effects	[100]
81	*Nicotiana plumbiginifolia .L*	*Solanaceae*	Whole plant, methanol	Treatment of cuts, wounds, toothache, and rheumatic swelling	Antispasmodic, leaves are effective lavicide, antioxidant, and antimicrobial	[101]
82	*Nymphaea alba. L*	*Nymphaeceae*	Leaves, 76% ethanol	Used as antiseptic, an astringent and as a rubefacient in insomnia	Antioxidant, anti-inflammatory, and hepatoprotective effects.	[6]
83	*Olea europaea .L.*	*Oleaceae*	Leaves, 20% oleuropein	Treatment of malaria and associated fever	Antimicrobial, anti-inflammatory, antioxidant, blood pressure lowering, lipid lowering, anticancer, and cardioprotective activities	[102]
84	*Origanum vulgare.*	*Lamiaceae*	Leaves, aqueous	Treatment of respiratory disorders, indigestion, and rheumatoid arthritis	Antihyperglycaemic, anti-inflammatory, cytotoxic, antioxidant, antithrombin, antimutagenic, and anti-carcinogenic effects	[103]
85	*Persea Americana mill*	*Lauraceae*	Leaves, aqueous	Remedy for pyorrhea. Toxic to silkworms	Antifungal, hypotensive, anti-inflammatory, anticonvulsant, antidiabetic, antioxidant, and vasorelaxant effects	[104]
86	*Phyllanthus niruri*	*Phyllanthaceae*	Aerial part, 80% ethanol	Treatment of urinary and bladder disorders, hepatic disorders, dyspepsia, influenza jaundice, and kidney stone	Hepatoprotective, antioxidant, antihyperuricemic, and lipid lowering effects	[105]
87	*Physalis peruviana (Golden berry)*	*Solanaceae*	Leaves, 50% methanol	Used as antispasmodic, diuretic, antiseptic, sedative, analgesic, and hepatitis	Antiulcer, antimicrobial, anti-inflammatory and antihypercholesterolemic activities	[106]
88	*Pleiogynium timorense (DC) Leenh*	*Anacardiaceae*	Bark, 70% methanol	–	Antimicrobial, hepatoprotective, antioxidant, anti-inflammatory, hypoglycemic, and cytotoxic effects	[107]
89	*Pleurotus ostreatus*	*Pleurotaceae*	Whole mushroom, 95% ethanol	Preventing heart disease, reduction in cholesterol, and treatment of diabetes	Inhibition of platelet aggregation, reduction of blood glucose and cholesterol, antibacterial, viral, and parasitic pathogens, and antioxidant activities	[108]
90	*Polygonum cuspidatum sieb et Zucc*	*Polygonaceae*	Rhizome, methanol	Treatment of jaundice, and to clear heat toxin, to promote blood circulation. Dispel stasis, suppress cough, and treat snake bites	Antidiabetic, anti-hepatitis B virus, antibacterial, anti-inflammatory, and antioxidant properties	[4]
91	*Premna esculenta Roxb*	*Verbenaceae*	Leaves, 95% ethanol	Treatment of hepatocellular jaundice, gout, hook worm infection, and snake bite	Antihyperlipidemic, hepatoprotective, antioxidant, analgesic, and anti-inflammatory activities	[109]

Table 1 (continued)

s/n.	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
92	*Raphanus sativus*	*Brassicaceae*	Leaves, aqueous and ethanol	Treatment of indigestion, abdominal bloating, diarrhea, bronchitis, intestinal parasites, and asthma	Antimicrobial, anticancer, antidiabetic, gastrointestinal, uterine tone modulatory, and cardio-modulatory activities	[110]
93	*Rourea induta planch*	*Connaraceae.*	Leaves, 99% ethanol	Treatment of respiratory and kidney diseases. Treatment of blood diarrhea, and as diuretics	Anti-inflammatory, hepatoprotective, antioxidant, and antipyretic activities	[111]
94	*Rubia cordifolia Linn*	*Rubiaceae.*	Root, 50% ethanol	Treatment of jaundice	Potent antioxidant property, inhibit lipid peroxidation, anti-inflammatory, immunomodulatory, anticonvulsant, anxiolytic and antitumor activities	[112]
95	*Rumex vasicarius L*	*Polygonaceae.*	Whole plant, methanol	Aperients, diuretic and cooling agent. Treatment of jaundice and dysentery. Curing stomach heat, toothache, and to promote appetite	Antimicrobial, anti-inflammatory, antioxidant, wound healing, and antitumor activities	[113]
96	*Semen celosia Cristatae.L*	*Amaranthaceae.*	Dry seeds, 60% ethanol	Treatment of hypertension, palsy, cataract, keratitis, diabetes, iridocyclitis, caligo corneal, and sarcoptidosis	Antibacterial, anticancer, antidiarrheal and anti-inflammatory effects	[114]
97	*Solanium trilobatum Linn*	*Solanaceae.*	Whole plant, 90% ethanol	Used as an expectorant in the treatment of respiratory diseases, asthma, tuberculosis, and liver diseases	Broad spectrum antibiotic, antibacterial, antimitotic, anticancer, and antioxidant properties	[115]
98	*Solanium xantholarpum*	*Solanaceae.*	Fruit, 50% ethanol	Laxative, treatment of enlargement of liver, anthelmintic, antipyretic, anti-inflammatory, antiasthmatic, and aphrodisiac activities.	Antiasthmatic, anti-nociceptive, antifungal, molluscicide, antispasmodic, antitumor, cardiotonic, hypotensive, antianaphylactic, and anti-urolithiatic activities	[116]
99	*Spondias mombim*	*Anacardiaceae*	Leaves and stem, 50% methanol	Treatment of hepatitis	Antimicrobial, antiviral, anti-inflammatory, anthelmintic, hematinic sedative, antioxidant, and hepatoprotective effects	[117]
100	*Stachys pilifera Benth*	*Lamiaceae*	Leaves, 70% ethanol	Treatment of asthma, rheumatoid arthritis, and asthma	Anti-inflammatory, antioxidant, antibacterial, antitumor, and antimicrobial effects	[118]
101	*Vitis thunbergii Var*	*Vitaceae*	Aerial part, ethanol	Treatment of hepatitis, jaundice, diarrhea, and arthritis	Antioxidant, anti-inflammatory, antihypertensive, neuroprotective, antibacterial, and inhibition of adipocyte differentiation	[119]
102	*Xylaria nigripes(Koltz) Sacc*	*Xylariaceae*	Solid cultured mycelia, aqueous	Treatment of insomnia, trauma, diuretic, and nerve tonic	Antioxidant and hepatoprotective effects	[120]

Table 1 (continued)

s/n.	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
103	*Zingiber officinale(Roscoe) rhizome (ginger)*	*Zingiberaceae*	Rhizome, 90% methanol	Nutraceutical. Treatment of stomach aches, nausea, diarrhea, as carminative, appetite stimulant, and choleretic	Antioxidant, anti-inflammatory, antitumor, antidiabetic, antimicrobial, neuro-protective, and gastro-protective potentials	[121]
104	*Zizyphus jujube Mill*	*Rhaminaceae*	Fruit, 70% ethanol	Invigorating the spleen, treatment of anorexia, lassitude, and control of hepatitis	Antioxidant and anti-inflammatory activities	[122]

Table 2 In vivo studies on medicinal plants with hepato protection against acute tetrachloride toxicity

s.no.	Botanical name	Animal model.	Maximum extract dose/route of administration	CCL4 dose/route of administration	Standard drug administered/route of administration	Result.	Active components.	Reference
1	*Abelmoselius manihot (L) medic*	Ku-Ming mice.	500mg/kg/b.w. (oral).	0.1 ml/kg/bw(0.12% v/v olive oil), i.p.	Biphenyl dicarboxylate (BDP) 150 mg/kg/b.w., oral.	ALT, AST, ALP, ϒ-GT, TNF-α, IL-1β, NO, MDA↓, GSH, SOD, GPx, CAT, GST↑.	Flavonoids, quercetin, hyperin, isoquercetin, quercetin-3′-0-glucoside, hibifolin, myricetin	[32]
2	*Acacia mellifera*	Wistar rats	500mg/kg/ b.w.	1.25 ml/kg/ b.w. (1:1 liquid paraffin) i.p	Silymarin, 100 mg/kg/bw	ALT, AST, GGT, ALP, T.B↓,T.P↑,MDA, NP-SH, T-chol, TG↓, NP-SH↑. (Nonprotein sulfhydryl)	Flavonoids, saponin, tannins, triterpenoids	[33]
3	*Aegle marmelos correa ex Roxb*	Albino Wistar rats	- (oral)	0.2 ml/100g/b.w. (olive oil), i.p.	–	AST, ALT, ALP, T.B↓	Flavonoids	[34]
4	*Aegle marmelos correa ex Roxb*	Wistar albino rats	50mg/kg/b.w. (oral)	3ml/kg/b.w., i.p.	Silymarin 200 mg/kg/b.w., (oral)	ALP, ALT, AST, T.B, LDH, MDA↓, SOD, CAT, GR, GSH, GST, GPx, G6PD, T.P↑, IL-10, TNF-α↓.	Rutin, piperine	[35]
5	*Alangium salviifolium*	Swiss albino mice	50mg/kg/b.w. (oral)	1 ml/kg/b.w. (1:1 in olive oil).	–	AST, ALT, ALP, MDA, LDH, CYT-P450 reductase, cyt b5 reductase↓, SOD, CAT, DT-diaphorase, glutathione-s-transferase↑	Piperine, ϒ-sistosterol	[36]
6	*Alhagi maurorum (camel thorn)*	Wistar rats	660 mg/kg/b.w. (oral)	1 ml/kg/b.w. (maize oil) oral.	–	ALT, AST↓	Flavonoids, phenols	[37]
7	*Alhagi maurorum Medikus*	Wistar rats	500 mg/kg/b.w.	0.125 ml/kg (liquid paraffin, 1:1), i.p	Silymarin, 10 mg/kg (oral)	SGOT, SGPT, ALP, T.B.	Flavonoids, tannins.	[38]
8	*Allium sativum (Single clove garlic)*	Male rabbits	0.8 g (oral)	3 ml/kg/b.w. (1:1, olive oil)	–	ALT, AST, ALP, T.B↓, T.P↑, MDA↓, CAT, GST, SOD↑	–	[39]
9	*Amaranthus spinosus*	Sprague-Dawley rats	400 mg/kg/b.w. (oral)	1 ml /kg/ b.w. (v/v olive oil) i.p.	–	AST, ALT, ALP, T.B, MDA↓, GSH, SOD, CAT↑	Flavonoids, phenols, betalains.	[40]
10	*Amorphophallus campanulatus (Roxb)*	Wistar albino rats and mice	500 mg/kg/b.w. (oral)	1 ml/kg/b.w., oral.	Silymarin, 50 mg / kg/b.w., (oral)	MDA, Hydroperoxides↓, GSH, SOD, CAT↑	Flavonoids	[41]
11	*Argemone Mexicana L*	Wistar rats	500 mg/kg/b.w. (oral)	0.5 ml/kg/b.w., i.p.	Silymarin, 100mg/kg (oral)	SGOT, SGPT, ALP, Total bilirubin↓	Leutolin, quercetin, quercetrin	[42]
12	*Artemisia iwayomogi*	Sprague-Dawley rats.	500 mg/ kg/b.w. (oral)	2 ml/kg/b.w. (50% oliveoil) i.p.	–	ALT, AST, ALP, MDA↓, TAC, GSH, SOD↑, Hydroxy proline↓	Scoparone	[43]
13	*Bauhinia variegate*	Sprague-Dawley rats	200 mg/kg/b.w. (oral)	1 ml/kg/b.w. (liquid paraffin, 1:1) subcutaneous.	–	AST, ALT, ALP, GGT↓, T.P↑, Total lipid↓	–	[44]
14	*Bougainullra spectabillis*	Wistar rats.	6 mg/kg/b.w. (oral)	1.5 ml/kg, oral.	–	AST, ALP, ALT↓	Esculetin	[45]
15	*Bryonia diocia Jacq*	Wistar albino rats	250 mg/kg/b.w. (gavage)	1 ml/kg/b.w. (corn oil,1:1v/v).	–	AST, AST↓	Flavonoids, terpenoids	[46]

Table 2 (continued)

s.no.	Botanical name	Animal model.	Maximum extract dose/route of administration	CCL4 dose/route of administration	Standard drug administered/route of administration	Result.	Active components.	Reference
16	*Brysocarpus coCCIneus.*	Albino rats	1000 mg / kg /b.w. (oral).	0.7 ml/kg/b.w. (1:1 in olive oil) i.p.	livolin®, 200 mg/kg/b.w., (oral)	ALT, AST, ALP, MDA↓, T.P, Albumin, CAT, SOD, GPx, GSH↑	Alkaloids, flavonoids	[47]
17	*Cajanus cajan.*	Wistar albino rats	400 mg/kg/b.w. (oral)	2 ml/kg/b.w. (1:1 liquid paraffin), oral.	Liv 52, 100 mg/kg/b.w. (oral)	AST, ALT↓, T.P↑	Alkaloid, flavonoids	[48]
18	*Calotropis gigantean R.Br.*	Wistar rats	500 mg/kg/b.w. (oral)	2 ml/kg/b.w. (1:1 olive oil), subcutaneous.	Silymarin, 100 mg/kg/bw., (oral)	AST, ALT, LPO↓, GSH, SOD, GPX, CAT↑	Calotropin DI and DII, calotropin FI and FII.	[49]
19	*Camellia ntidissima Chi.*	Sprague-Dawley rats	160 mg/kg/day (i.p)	2 ml/kg (50% v/v, olive oil), i.p.	Thiopronin 20 mg/kg/day, (i.p)	AST, ALT, MDA↓, GSH, SOD↑, TNF-α, IL-6, IL-1β, NF-kβ signaling↓, NrF2 signaling partway, HO-1, SOD, GSH↑	Polyphenols, flavonoids	[1]
20	*Canna indica L.*	Sprangue-Dawley rats	200 mg/kg/b.w. (oral)	1.0 ml/kg(liquid paraffin,1:2) i.p.	Silymarin, 25 mg/kg, (i.p)	SGPT, SGOT, ALP, T.B, L.P↓, GSH, CAT, T.P↑	Lutein	[50]
21	*Capparis spinosa.*	Mice	400 mg/kg/b.w. (oral)	0.2 ml/kg (olive oil 1:1), oral.	–	ALT, AST↓	Flavonoids, phenols, rutin, quercetin-3-O-glucoside, kaempherol, 3-O-rutinoside	[51]
22	*Capsella busa-pastoris (L.) Medik.*	Wistar rats	500 mg/kg/b.w.	0.125 ml/kg (liquid paraffin, 1:1), i.p	Silymarin, 10 mg/kg, (oral)	SGOT, SGPT, ALP, T.B	–	[38]
23	*Carissa opaca*	Sprague-Dawley rats	200 mg/kg/b.w. (intragastrically)	0.5 ml/kg/b.w. (20% v/v olive oil), i.p.	Silymarin, 50 mg/kg/b.w., (intragastrically)	AST, ALT, ALP, LDH, ɤ-GT↓, GSH-Px, GSR, SOD, GST, CAT, Peroxidase, Quinone reductase(QR) ↑, TBARS, GSH, H2O2↓, T.P↑	Isoquercetin, hyperoside, vitexin, myicetin, kaempherol	[52]
24	*Carthamus tinctorius L*	Sprangue-Dawley rats.	5 mg/kg/day	1.0 ml/kg (olive oil).	–	ALT, AST, Hydroxy proline↓	Hydroxysafflor yellow A, isocarthamidin, carthamin, luteolin	[53]
25	*Carthamus tinctorius. L*	Sprague-Dawley rats	20 mg/kg/b.w. (oral)	2 ml/kg/b.w. (1:1 olive oil), i.p.	Silymarin, 50 mg/kg/b.w., (oral).	ALT, AST, ALP, T.P↓, NrF2, GSTα, NQOI expression, GSH↑, TBARS↓, SOD, CAT↑.	Carthamin, carthamidin, polyphenols, carthamus red, flavonoids	[54]
26	*Carum carvil*	NMRI mice	0.13 g/kg/b.w. (oral)	2 ml/kg/b.w. (olive oil, 1:2), i.p.	–	AST, ALT, L.P↓, GSH, GSH-Px↑, Px, XOD↓, Protein↑	Carvon	[55]
27	*Cassia angustifolia Vahl*	Wistar albino rats	300 mg/kg/bw (oral)	2.5 ml/kg/b.w.	Silymarin, 100 mg/kg/bw, (oral)	AST, ALT, ALP, Acid phosphatase(ACP), LDH, T.B↓, T.P↑	Flavonoid, terpenoids, tannin, steroid	[56]
28	*Cassia angustofolia vahl*	Wistar rats	500 mg/kg/b.w. (oral)	4 ml/kg/b.w. (50% olive oil) oral	–	T.B, GOT, GPT↓, T.P, GSH↑, LPO↓	Flavonoids	[57]

Table 2 (continued)

s.no.	Botanical name	Animal model.	Maximum extract dose/route of administration	CCL4 dose/route of administration	Standard drug administered/route of administration	Result.	Active components.	Reference
29	*Cassia fistula Linn*	Wistar albino rats	500 mg/kg/ b.w. (oral)	0.1 ml/kg/b.w. (liquid paraffin)	–	MDA, AST, ALT, GSH, ALP, LDH, ɣ-glutamyltranspeptidase↓	Flavonoids	[58]
30	*Cichorium intybus*	Wister rats	6 mg/kg/b.w. (oral)	1.5 ml/kg(oral)	–	AST, ALP, ALT↓	Esculetin	[45]
31	*Cichorium intybus*	Albino wistar rats	500 mg/kg/b.w. (oral)	1.5 ml/kg(olive oil 50%), i.p.	Silymarin 10 mg/kg (oral)	SGOT, SGPT, ALKP↓, T.P, albumin↑	Cichotyboside	[59]
32	*Cichorium intybus*	Albino wistar rats	500 mg/kg/b.w. (oral)	1.5 ml/kg olive oil50%), i.p.	Silymarin 10 mg/kg (oral)	SGOT, SGPT, ALKP↓, T.P, albumin↑	Cichotyboside	[59]
33	*Cichorium intybus*	Albino rats	500mg/kg/b.w. (oral)	1.0 ml/kg olive oil 50%), i.p.	–	AST, ALP, ALT, T.B↓, T.P, albumin↑	Esculetin and cichotyboside	[60]
34	*Cinnamomum verum*	Wistar albino rats	100 mg/ kg/ b.w. (oral)	1 ml/kg/b.w. (olive oil), subcutaneous.	–	AST, ALT, MDA↓, SOD, CAT↑	–	[61]
35	*Cinnamomum verum*	Wistar albino rats.	100 mg/kg/ b.w. (oral)	1 ml/ kg/ b.w. (olive oil), i.p.	Silymarin 50 mg/ kg/b.w. (oral)	ALT, AST, ALP, ɣ-glutamyl transferase, LDH, TBARS↓		[62]
36	*Cinnamomum zeylanicum L.*	Wister rats	0.1 g/kg(oral)	0.5 ml/kg/b.w. (50% olive oil).	–	AST, ALT, MDA↓, SOD, CAT↑	Flavonoids	[63]
37	*Citrus aurantium (essential oil)*	Sprangue-Dawley rats	0.8 ml/kg/b.w. (i.p)	0.8 ml/kg(olive oil 1:1), i.p.	Silibinin 50 mg/kg (i.p).	AST, ALT↓.	Limonene, alpa-pinene	[64]
38	*Citrus limon(L.) Burm.F.*	Wistar rats	500 mg/kg/b.w. (oral)	1 ml/kg (olive oil,50:50).	Silymarin 100 mg/kg (oral).	ALT, AST, ALP, T, B, MDA↓, SOD, GSH, CAT, albumin↑	Coumarins, limonoids, flavonoids, eriocitrin, C-glycosyl flavones 6,8-di-C-β-glucosyl-diosmin	[65]
39	*Clerodendrum volubile.*	Wistar albino rats	500 mg/ kg/bw.(oral)	1 ml/kg/b.w. (olive oil), i.p.	–	ALT, AST, ALP, LDH ↓, HDL, GSH, CAT, SOD, GPx↑	Phenols	[66]
40	*Clitoria ternatea L.*	Wistar albino rats	300 mg/kg/bw (oral)	2.5 ml/kg/b.w.	Silymarin, 100 mg/kg/ bw, (oral)	AST, ALT, ALP, Acid phosphatase(ACP), LDH, T.B↓, T.P↑	Flavonoid, terpenoids, tannin, steroid, quericimetrin, rutin, scutellarein	[56]
41	*Corianderum sativum. L*	Wistar albino rats	300 mg/kg(i.p)	1 ml/kg/b.w. (liquid parafin, 1:1), oral.	Silymarin, 50 mg/kg (i.p)	SGOT, SGPT, ALP↓, T.B↑	Caffeic acid, quercetin, gallic acid, flavonoids, essential oil	[67]
42	*Corianderum sativum. L. (essential oil)*	NMRI mice	0.03 g/kg/b.w. (oral)	2 ml/kg/b.w. (olive oil, 1:2), i.p.	-	AST, ALT, L.Px, XOD, Px↓, GSH, GSH-Px, Protein↑	Carvon	[55]

Table 2 (continued)

s.no.	Botanical name	Animal model.	Maximum extract dose/route of administration	CCL4 dose/route of administration	Standard drug administered/route of administration	Result.	Active components.	Reference
43	*Coriandrum sativum*	Wistar albino rats	200 mg/kg/ b.w. (i.p)	1 ml/kg b.w. (1:1 olive oil), i.p.	Silymarin, 25 ml/ kg/b.w., (i.p)	ALP, AST, ALT↓, T.P↑, T.B, MDA↓, SOD, CAT, GPx↑	Caffeic acid, ferulic acid, Isoquercitrin, rutin, quercetin 3-glucuronide, Quercetin, hyperin, quercetin-3-0-β-xyloside, quercetin-3-0-α-arabinose	[68]
44	*Cortex dictamni*	Sprague-Dawley rats	320 mg/kg/b.w. (oral)	2 ml/kg/b.w., i.p.	-	AST, ALT, ALP↓, SOD, CAT, GSH-Px, GSH↑, MDA↓	Limonoids, furoquinoline, flavonoids, fraxinellone	[69]
45	*Curcuma longa. L.*	Sprague-Dawley rats	300 mg/kg/b.w. (intragastrically)	0.1 ml/kg/b.w., i.p.	Curcumin, 200 mg/ kg/b.w., (intragastrically)	AST, ALT, TBARS↓, SOD, GPx↑.	Curcumin, memethoxy curcumin, bisdemethoxy curcumin	[70]
46	*Cytisus scoparius L.*	Wistar albino rats	500 mg/kg/b.w. (oral)	5 ml/kg(50% olive oil), i.p.	Silymarin, 25 mg/ kg/b.w., (oral)	SGOT, SGPT, LDH↓, GSH, SOD, CAT, GPx, GRD, GST↑, TBARS↓	Rutin, quercetin, quercitrin, isorhamnetin, kaempferol	[71]
47	*Dicoma anomala Sond*	Wistar rats; Rattus norvegicus	500 mg/kg/b.w. (oral)	1 ml/kg/b.w. (1:1, olive oil), i.p.	Silymarin, 100 mg/ kg.b.w., (oral)	AST, ALT↓, SOD, CAT, GPx↑	Total flavonoid and phenol contents	[72]
48	*Dioscorea alata peel*	Wistar albino rats	433.42 mg/kg/b.w.	1 ml/kg (20% olive oil)	Silymarin, 200 mg/ kg/b.w.	ALT, ALP, AST, TBARS↓, SOD, CAT, GSH-Px↑, NO, TNF-α, TNF-Kb, iNOS, COX-2 expression↓	Hesperetin, quercetin, hesperidin	[73]
49	*Eclipta alba(L) Hassk*	Male albino rats	500 mg/kg/b.w. (oral)	2 ml/kg/b.w. (olive oil), i.p.	Silymarin, 50 mg / kg/b.w., (i.p).	ALT, AST, ALP, T.B↓, T.P↑	Flavonoids, luteolin, demethylivedelolactone.wedelolactone	[74]
50	*Emblica officinalis (Gaertn)*	–	200 mg/kg/b.w.	1 ml/kg/b.w. (corn oil), oral.	–	SGOT, SGPT, LDH, MDA↓, GSH, GST, GPx, GRx, T.P↑, DNA synthesis↓	Quercetin, ascorbic acid, ellagic acid	[75]
51	*Entada pursaetha*	Colony bred male Wistar rats	300 mg/kg/b.w. (oral)	2 ml/kg/b.w. (1:1 olive oil).	Silymarin, 50 mg / kg/b.w. (2% polysorbate 80), (oral).	ALT, AST, ALP, T.B↓, T.P↑, LDH, MDA, Nitrate-nitrite, myeloperoxidase↓, SOD, CAT, GSH↑	Flavonoids	[76]
52	*Ephedra foliate Boiss*	Wistar rats	500 mg/kg/b.w.	0.125 ml/kg (liquid paraffin, 1:1), i.p.	Silymarin, 10 mg/kg, (oral).	SGOT, SGPT, ALP, T.B	Flavonoids, tannins	[38]
53	*Euphorbia dracunculoides L.*	Sprague-Dawley rats	400 mg/kg/b.w. (oral)	1 ml/kg/b, w (30% olive oil), i.p.	Silymarin 50 mg/ kg/b.w.	AST, ALT, ALP↓, CAT, Peroxidase, SOD, GST, GSH↑, Lipid peroxides, TBARS, nitrite, hydrogen peroxide, DNA damage↓	Catechin, rutin, caffeic acid, mricetin, coumarins, flavonoids	[5]

Table 2 (continued)

s.no.	Botanical name	Animal model.	Maximum extract dose/route of administration	CCL4 dose/route of administration	Standard drug administered/route of administration	Result.	Active components.	Reference
54	*Fagonia schweinfurthii(Hadidi) Hadidi*	Wistar albino rats	400 mg/kg/ b.w. (oral)	1 ml/kg/b.w., i.p.	Silymarin 100 mg/kg/b.w., (oral).	ALT, AST, ALP, T.B, MDA↓, SOD, CAT, GSH↑	Flavonoids, phenolic compounds, quinines and, coumarin	[77]
55	*Fiscus carica Linn*	Wistar rats	100 mg/kg/b.w. (oral)	1 ml/kg/bw(v/v olive oil), i.p.	–	SGOT, SGPT, T.B. ↓	Psoralen, bergapten, xantho toxin, calotropenyl acetate, lupeol acetate	[78]
56	*Flemingia macrophylla*	Male SD rats	1.0 g/kg/b.w. (oral)	15 ml/kg/b.w. (20% olive oil), i.p.	Silymarin, 25 mg/kg/b.w. in carboxy methyl cellulose.	ALT, AST, MDA↓, SOD, CAT, GSH-PX, GSH↑, NO, TNF-α, IL-1β↓.	Genistein, lupeol, rutin, flavonoids, isoflavones	[79]
57	*Ginko biloba*	Sprague-Dawley rats	150 mg/ kg/ b.w. (oral)	1 ml/kg/b.w. (1:1 liquid paraffin).	-	ALP, ALT, AST, MDA↓, T.P, HDL-c, GSH↑	Kaempferol, quercetin, isorhamnetin, diterpene lactones	[80]
58	*Glyphae brevis*	Swiss albino mice	490 mg/kg/ b.w. (oral)	2 ml/kg/b.w. (liquid paraffin) i.p.	Silymarin, 100 mg/kg (oral)	GSH, CAT, SOD↑, TBARS, ALT, AST, ALP, T-chol, LDL, TG↓, T.P↑	Flavonoids	[81]
59	*Graptopetalum paraguayense E, Walter*	Sprague-Dawley rats	300 mg/kg/b.w. (oral)	0.5 ml/kg/b.w. (1:4 olive oil) oral.	Silymarin, 200 mg/kg/b.w., (oral).	AST, ALT, MDA↓, GSH, SOD, GR, SOD, CAT↑, TNF-α↓	Gallic acid, genistin, daidzin, quercetin	[82]
60	*Hibiscus sabdariffa. L.*	Wistar rats	500 mg/kg/b.w.	0.125 ml/kg (liquid paraffin, 1:1), i.p.	Silymarin, 10 mg/kg (oral)	SGOT, SGPT, ALP, T.B	–	[38]
61	*Hippophaerhamnoides L*	C57BL/6 mice	200 mg/kg/b.w. (oral)	5 ml/kg/b.w. (20% in peanut oil), i.p.	–	ALT, AST, T.B↓, PALB, SOD, GSH-Px, GSH↑, MDA, TNF-α, IL-1β, iNOS, NO, TLR4, p38MAPK, p-ERK, p-JNK, NF-KB↓	Isorhamnetein, quercetin, chlorogenic acid, myricetin, kaempferol, catechins	[83]
62	*Indigofera oblongifolia*	Wistar albino rats	300 mg/kg/ b.w. (oral)	1 ml /kg/ b.w. (30% olive oil), i.p.	–	ALT, AST, ALP, TBARS↓, GSH, SOD, CAT, GPX↑	Flavonoids, coumarins, indirubin	[84]
63	*Launaea procumbens*	Sprague-Dawley rats	200 mg/kg/b.w. (oral)	3 ml/kg/b.w. (30% olive oil), i.p.	Silymarin 100 mg/kg/b.w., (oral)	AST, ALT, ALP, LDH↓, GST, GSR, GSH, CAT, POD, SOD, GSH-Px↑	Salicylic acid, vanillic acid, synergic acid, 2-methyl-resorcinol, and gallic acid	[85]
64	*Lawson inermis L (Henna)*	Albino rats	200 mg/kg/b.w. (oral)	2 ml/kg/bw (1:1 olive oil).	Silymarin, 25 mg/kg/b.w. (oral).	ALT, AST, ALP, T.B↓, T.P↑	Flavonoids	[86]
65	*Lawsonia inermis Linn*	Wistar albino rats	400 mg/kg/b.w. (i.p.)	1.25 ml/kg(1:1 liquid paraffin), i.p.	Silymarin, 100 mg/kg/b.w. (i.p)	SGOT, SGPT, MDA↓, T.P, GSH. ↑	Flavonoids	[87]
66	*Leucas cephalotes Linn*	Wistar albino rats	200 mg/kg/ b.w. (liquid paraffin) (i.p).	1.25 mg/kg (1:1 liquid paraffin), i.p.	Silymarin, 200 mg/kg (i.p).	SGOT, SGPT, Alkaline phosphatase (ALKP), T.B↓, T.P, TC. ↑.	Flavonoids	[88]

Table 2 (continued)

s.no.	Botanical name	Animal model.	Maximum extract dose/route of administration	CCL4 dose/route of administration	Standard drug administered/route of administration	Result.	Active components.	Reference
67	*Lobularia maritima*	Mice	500 mg/kg/b.w. (i.p)	1 ml/kg/b.w. (1:1 olive oil), i.p.	–	ALT, AST, MDA, ROS, TNF-α, IL-1β, IL-6↓, SOD, CAT, GPx↑	p-coumaric acid	[7]
68	*Luffa acutangula (Var) amara*	Colony bred strain of Wistar rats	600 mg/kg/ b.w. (oral)	1 ml/kg/b.w., oral	Silymarin, 25 mg/ kg/b.w. (oral)	SGOT,S GPT, ALP, TC, TB ↓, TP, GPx, GST, GSH, SOD, CAT↑, LPO ↓ , Vit E, Vit C.↑	Flavonoids	[89]
69	*Lygodium flexuosum(L.) Sw*	Wistar rats	200 mg/kg/b.w.	150 µl /100 g (1:1 corn oil)	Silymarin, 50 mg/kg	AST, ALT, LDH, MDA↓, GSH↑	B-sitosterol, stigmasterol, kaempferol, tectoquinone	[90]
70	*Madhuca indica Syn*	Wistar rats	400 mg/kg/b.w (oral)	2 ml/kg/b.w. (olive oil), (i.p)	Silymarin, 100 mg/ kg/b.w.	T.B, SGOT, SGPT, ALP↓	Flavonoids	[91]
71	*Madhuca indica Syn*	Wistar rats	300 mg/ kg/ b.w.	0.5 ml/kg/b.w., i.p.	Silymarin, 100 mg/ kg/bw.	SGOT, SGPT, ALP, T.B↓	Flavonoids	[92]
72	*Mahonia oiwaken Hayata*	Wistar albino rats	500 mg/kg/b.w (oral)	1 ml/kg/b.w. (50% olive oil), i.p.	Silymarin, 200 mg / kg/b.w, (oral)	ALT, AST, MDA↓, SOD, GP-x, GR↑, TNF-α, NO↓	Berberine, palmatine, jatrorrhizine	[3]
73	*Mallotus philippensis Muell-Arg*	Wistar albino rats	200 mg/kg/b.w (oral)	600 mg/kg/ml, oral	Silymarin, 25 mg/ kg/b.w. (oral)	SGPT, SGOT, ALP, T.B↓, T.P, CAT, SOD↑, LPO↓	Flavonoids, phenols, isocoumarins, bergenin	[93]
74	*Memondica tuberosa Cogn*	Wistar rats	400 mg/kg/bw (oral)	2 ml/kg/b.w(1:1 liquid paraffin), subcutaneous	Silymarin, 100 mg/kg, (oral)	SGOT, ALPT, T.B, Cholesterol, TAG, MDA↓, GSH↑	Vitamin C, saponins, triterpenoids	[94]
75	*Mentha piperita L.*	Wistar rats	40 mg/kg/b.w (oral)	1 ml/kg (olive oil), i.p.	Silymarin, 50 mg / kg/b.w, (oral)	ALT, AST, ALP, LDH, ɤ-GT↓, SOD, CAT, GPx↑, TBARS↓	Spathulenol, cadinene, caryophyllene, caryophyllene oxide	[95]
76	*Menthe arvensis Linn*	Albino wistar rats	375 mg/kg/b.w (oral)	0.5 ml/kg/b.w., i.p.	Silymarin, 100 mg/ kg/b.w. (oral)	SGPT, SGOT, SALP, T.B↓	Luteolin, menthoside, rutin, hesperidin, phenolic acid, quercetin, isorhoifolin	[96]
77	*Mimosa pudica 2009*	Wistar albino rats	200 mg/kg/b.w (oral)	1.25 ml/kg/b.w. (1:1 liquid paraffin), i.p.	Silymarin, 100 mg/ kg/b.w.	SPGT, SGOT, ALP, TBL, T chol↓, T.P, albumin↑	Flavonoids, alkaloids, glycosides	[97]
78	*Mimosa pudica Linn*	Wistar albino rats	400 mg/kg/b.w. (oral)	1 ml/kg/b.w (1 : 2 liquid paraffin), subcutaneous.	Silymarin, 10 mg/ kg/b.w, (oral)	SGOT, ALP, T.B, SGPT↓	Flavonoids, phenols, gallic acid	[98]
79	*Momordica dioica Roxb*	Wistar albino rats	200 mg/kg/b.w. (oral)	2 ml/kg/b.w(1:1 liquid araffin).	Silymarin, 5 mg/kg/b.w. (oral)	AST, ALT, ALP, T.B, MDA↓, SOD, CAT, GSH↑, Hydroperoxides↓	Flavonoids, phenolic compounds	[99]
80	*Nerium oleander Linn*	Wistar rats	400 mg/kg/b.w. (oral)	1 ml/kg/b.w(1;1 olive oil), i.p.	Silymarin, 100 mg/ kg/b.w (oral).	AST, ALT, ALP, T.B, MDA↓, SOD↑	Oleandrin, Oleanolic acid	[100]
81	*Nicotiana plumbiginifolia .L.*	Male chicks	200 mg/kg/b.w. (oral)	1 ml/kg/b.w (30% olive oil), i.p.	Silymarin , 100 mg/ kg/b.w, (gavage).	CAT, Peroxidase, SOD, GP-X, GRS↑, TBARS, LDH, TAG, T.Chol, LDL↓, HDL↑	Rutin, chlorogenic acid, quercetin	[101]

Table 2 (continued)

s.no.	Botanical name	Animal model.	Maximum extract dose/route of administration	CCL4 dose/route of administration	Standard drug administered/route of administration	Result.	Active components.	Reference
82	*Nymphaea alba. L.*	Wistar albino rats	200 mg/kg/b.w. (oral)	0.5 ml/kg/b.w, i.p.	Silymarin, 100 mg/kg/b.w(oral).	MDA↓, GSH, CAT, SOD, TAC↑, TNF-α, Caspase-3↓	Phenols, flavonoids, quercetin, ellagic acid, gallic acid, kaempferol	[6]
83	*Olea europaea .L.*	Sprague-Dawley rats	80 mg/kg/b.w. (oral)	0.2 ml/kg/b.w, i.p.	–	ALP, AST, ALP↓, CAT, SOD↑	Caffeic acid, diosmetin, verbascoside, oleuropein, luteolin 7-O-glucoside, rutin, leuteolin 4′-O-glycoside, P-coumaric acid, vanillin	[102]
84	*Origanum vulgare.*	Wistar albino rats	150 mg/kg/b.w. (oral)	2 ml/kg/b.w (1:1 olive oil)	–	ALT, ALP, AST↓, LPO, GST, CAT, SOD, GP x, GR, GSH↑	Carvacrol, thymol	[103]
85	*Persea Americana mill*	Wistar albino rats	200 mg/kg/day	3 ml/kg(1:1 olive oil) subcutaneous	reducdyn®, 100 mg/kg/day	ALT, AST, ALP, T.B↓, CAT, SOD, GPx, GST↑, Protein carbonyl↓	Flavonoids	[104]
86	*Phyllanthus niruri*	Wistar rats	100 mg/kg/b.w. (oral)	1 ml/kg/b.w(50% in corn oil), i.p.	Silymarin, 1mg/ml, (i.p).	AST, ALT, ALP, LDH, T-chol, T.B↓, T.P↑, TNF-α, NF-Kβ, IL-6, IL-8, IL-10↓, GR, GP↑, MDA↓, GSH↑, ROS↓.	Quercetin, gallic acid, corilagin, isocorilagin, rhamnoside, brevifolin carboxylic acid	[105]
87	*Physalis peruviana*	Wistar albino rats	500 mg/ kg/ b.w (oral)	0.5 ml/kg/bw (olive oil), i.p.	legation®100 mg/kg/b.w, (oral).	MDA↓, SOD↑, NO, AST↓, ALT↑, ALP↓, T.B, T.P↓	Flavonoids, lupeol, ursoli acid	[106]
88	*Pleiogynium timorense (DC) Leenh*	Sprague-Dawley rats	300 mg/kg/b.w.	0.5 ml/kg(10% olive oil).	Silymarin 50 mg/kg/b.w.	AST, ALT↓, TAC↑	Catechin, gallic acid, kaempferol, quercetin, rutin, quercetrin, β-sitosterol, lupeol	[107]
89	*Pleurotus ostreatus*	Wistar albino rats	200 mg/ kg/ b.w. (i.p)	2 ml/kg/b.w (olive oil), i.p.	–	SGOT, SGPT, ALP, MDA↓, GSH, CAT, SOD, GPx↑	–	[108]
90	*Polygonum cuspidatum sieb et Zucc*	Male ICR mice	100 mg/kg/day (oral)	50 µl/kg (olive oil) i.p.	Bifendate, 150 mg/kg/b.w, (oral)	AST, ALT, MDA, TNF-α, IL-1β, COX-2, iNOS, NF-kβ↓, SOD, GST, GSH, CAT, GPx, TGF-β1↑	Polydatin, resveratrol, quercetin, emodin, citreorosein	[4]
91	*Premna esculenta Roxb*	Long-Evans rats (Rattus norvegicus)	400 mg/kg/day (oral)	1 ml/kg/bw. (1:1 olive oil), i.p.	Silymarin, 100 mg/kg/day, (oral)	SGPT, SGOT, SALP↓, T.P, ALB↑	Phenols, tannins, flavonoids	[109]
92	*Raphanus sativus*	Albino rats	300 mg/kg/b.w. (oral)	1 ml/kg/b.w (1:1 olive oil)	Silymarin, 50 mg/kg/b.w, (oral)	AST, ALT, ALP, T.B↓, CAT, GSH↑, MDA↓	Flavonoids, polyphenols	[110]
93	*Rourea induta planch*	Wistar albino rats	500 mg/kg/b.w. (oral)	2 ml/kg/b.w, i.p.	Legalon, 50 mg/kg/b.w, (oral)	AST, ALT, T.B↓, CAT, SOD, GPx, GSH↑, TBARS↓	Hyperin, quercetin-3-O-β-xyloside, quercetin-3-D-α-arabinofuranoside, quercetin	[111]

Table 2 (continued)

s.no.	Botanical name	Animal model.	Maximum extract dose/route of administration	CCL4 dose/route of administration	Standard drug administered/route of administration	Result.	Active components.	Reference
94	*Rubia cordifolia Linn*	Sprague-Dawley rats	200 mg/kg/b.w (oral)	0.1 ml/kg/b.w, i.p.	Silymarin, 100 mg/kg/b.w, (oral).	SGPT, SGOT, SAKP, ɤ-GT↓, GST, GR, GSH↑, MDA↓	Rubiadin	[112]
95	*Rumex vasicarius L*	Wistar albino rats	200 mg/kg/ b.w (oral)	1.5 ml/kg /b.w (1% tween 80) i.p.	Silymarin 50 mg/kg/b.w.	SGOT, SGPT, ALP↓, T.P↑, T.B↓, CAT, SOD↑, MDA↓	Phenols, flavonoids	[113]
96	*Semen celosia Cristatae.L*	Kunming mice	4.0 mg/kg/b.w (oral)	0.1% (edible oil), i.p.	Bifendate	AST, ALT, ALP, MDA↓, GSH-Px, CAT, SOD↑	Semenoside	[114]
97	*Solanium trilobatum Linn*	Wistar Albino rats	250 mg/ kg/ b.w (i.P)	1 ml/kg/bw(30% olive oil), i.p.	–	ALT, AST, ALP, LDH,↓T.P, GSH, GPx, CAT, SOD↑, Lipid peroxide↓	Sobatum, solasodine, β-solamarine, solaine	[115]
98	*Solanium xantholarpum*	Sprague-Dawley rats	400 mg/kg/bw (oral)	1 ml/kg (1:1 liquid paraffin)	Silymarin, 100 mg/kg/b.w, (oral)	AST, ALT, ALP, T.B, MDA↓, CAT, GSH, SOD↑	Flavonoids, quercetin	[116]
99	*Spondias mombim*	Wistar rats	1000 mg/kg/b.w (oral)	2 ml/kg/b.w. (1:1 liquid paraffin)	Silymarin, 100 mg/kg/b.w, (oral)	ALT, AST, ALP, T.B↓, GSH, CAT, SOD↑, TBARS↓	Flavonoids, phenols	[117]
100	*Stachys pilifera Benth*	Wistar rats	400 mg/kg/day (oral)	1 ml/kg/b.w. (50% olive oil)	–	AST, ALT, ALP, MDA↓, T.P, T.B↑.	Flavonoids, phenylethanoid glycosides, diterpenes, terpenoids	[118]
101	*Vitis thunbergii var*	Male SD rats	400 mg/kg/b.w.	1.5 ml/kg/b.w. (20% olive oil) i.p.	Silymarin, 200 mg / kg/b.w. in carboxy methylcellulose	ALT, AST, MDA↓, SOD, CAT, GPX, GSH↑, TNF-α, IL-1β, NO, INOS, COX-2↓	Resveratrol derivatives, polyphenols compounds, quercetin, oligostibenes	[119]
102	*Xylaria nigripes(Koltz) Sacc*	ICR mice	100 mg/kg/b.w. (intragastrically)	2 ml/kg/b.w. (40% olive oil). Subcutaneously	Silymarin, 100 mg/kg/b.w., (intragastrically)	SGOT, SGPT, TBARS↓, SOD, CAT, GPX, ↑	Epicatechin, P-coumaric acid, catechin	[120]
103	*Zingiber officinale (Roscoe) rhizome (ginger)*	Wistar rats	400 mg/kg/b.w. (oral)	0.7 ml/kg/b.w. (1:1, olive oil)	Livolin fort®, 5.2 mg/kg/b.w., (oral)	AST, ALT, ALP↓, T.P, GSH, CAT↑.	Flavonoids, 6-gingerol, shogaols	[121]
104	*Zizyphus jujube*	Male ICR mice	200 mg/kg/b.w. (intragastrically)	2 ml/kg/b.w. (40% v/v olive. oil), subcutaneously	Bifendate, 7.5 mg/kg/b.w., (intragastrically)	ALT, AST, MDA↓, SOD, CAT, GSH-Px, GSH↑	Flavonoids	[122]

↓ decrease in effect/activity; ↑ increase in effect/activity

formation of CCl_3^* and $CHCl_2^*$ and CCl_3-OO^* radicals, lipid peroxidation, membrane damage, the severe derailment of intracellular Ca^{2+} sequestration, apoptosis, and fibrosis [10, 30, 31].

Traditional plants with anti-hepatotoxic potential

In this review, numerous experimental studies on the medicinal plants effectiveness to ameliorate CCl_4-induced hepatotoxicity in animal models were presented. The botanical names, ethnopharmacological and pharmacological uses of plants traditionally used to treat liver-related diseases were presented in Table 1. The comprehensive details on in vivo studies of medicinal plants with hepatoprotection against CCl_4-induced hepatotoxicity alongside the active phytochemicals and their probable mechanisms of action are presented in Table 2.

Discussion

For about three decades, extracts from different natural products have been identified to be hepatoprotective at varied doses against CCl_4-induced toxicity by reducing oxidative stress on liver enzymes. The findings from this review show that only few studies tested these natural products on hepatic cell lines (Table 2). Without separating the whole extract to identify the active components, a large number of hepatoprotective products will increase without corresponding clinical relativity [123]. There is an urgent need to study individual components of the plant extract especially in experimental animal models. The major drawback of herbal medicine is its potential hepatotoxicity in man which could cause acute to chronic liver injury with underlining mechanism of toxicity not clearly understood due to factors such as the synergistic and multi-organ targeted nature of the various components [124–127].

The protection provided by herbal plants against CCl_4-induced hepatotoxicity is basically due to the inhibitory nature of the phytochemicals present in them [70, 101]. These phytochemicals are able to inhibit the microsomal enzymes to restrict the generation of free radicals and stop lipid peroxidation through its antioxidant ability [66]. They can also enhance the regeneration of liver cells, radical scavenging, and stimulation of the anti-inflammatory ability of the liver cells against the inflammation induced by CCl_4 [102].

The treatment of the animal models with these herbal extracts showed beneficial effects through several biochemical and histological results. From the results in Table 2, it is clear that these plants extract downregulated serum liver marker enzymes like aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), total bilirubin, and malondialdehyde (MDA) while upregulating the activity of antioxidant enzymes and total protein. The medicinal plants also downregulated the inflammatory markers expression in the hepatic cells. Some of these reported studies confirmed the hepatoprotective effectiveness of these medicinal plant products through histological reports [43, 54]. This review also reported numerous phytochemicals with possible hepatoprotective potentials ranging from flavonoids (quercetin, kaempferol), phenols, sobatum, courmarins, gallic acid, rutin, alkaloids, saponins, vitamin C, caffeic acid, etc. This review presented a number of plant species with ethnopharmacological relevance in the treatment of liver injury and their medicinal/pharmacological uses from literature.

Conclusion

We, therefore, conclude that there are a variety of phytochemicals in plant products with hepatoprotective activity against CCl_4-induced toxicity by downregulation of liver marker enzymes, and activation of antioxidative capacity of the liver cells that leads to the restoration of the liver architecture.

Future perspectives

There is need to validate the efficacy of some of the reported active components which can be likely candidate for therapeutic purposes. Research should move from whole plant extract experiment to isolation of bioactive components and testing the extract on culture cell lines.

Abbreviations

ALT: Alanine transaminase; AST: Aspartate transaminase; ALP: Alkaline phosphatase; ɤ-GT: Gamma glutamyltransferase; LDH: Lactate dehydrogenase; MDA: Malondialdehyde; GSH: Glutathione; GPx: Glutathione peroxidase; CAT : Catalase; SOD: Superioxide dismutase; POD: Peroxidase; GST: Glutathione *S*-transferase; GSTα: Glutathione *S*-transferase alpha; GR: Glutathione reductase; TBARS: Thiobarbituric acid reactive substance; NO: Nitric oxide; H_2O_2: Hydrogen peroxide; TNF-α : Tumor necrosis factor alpha; NF-kb: Nuclear factor-kappa B; INOS: Inducible nitric oxide synthase; COX-2: Cyclo oxygenase-2; IL-1β: Interlukin-1 beta; NrF-2: Nuclear factor erythroid-2-related factor 2; TGF-β(1): Hepatic growth factor-beta 1; IL-6: Intherleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; HO-1: Heme oxygenase-1; NP-SH: Nonprotein sulfhydryls; NQO1: Quinine oxidoreductase; TLR4: Hepatic toll-like receptor 4; P38MAPK: P38 mitogen-activated protein kinase; p-ERK: Extracellular signal-regulated kinase; p-JNK: C-jun N-terminal kinase; CYT: Cytochrome; DTdiaphorase: A phase II enzyme; T-cho: Total cholesterol; TG: Triglycerides; LDL: Low-density lipoprotein; TAG: Triacylglycerol; HDL: High-density lipoprotein; TP: Total protein; TB: Total bilirubin; XOD: Xanthine oxidase; Vit. A: Vitamin A; Vit. E: Vitamin E; Vit. C: Vitamin C; CNS: Central nervous system.

Acknowledgements

Not applicable.

Authors' contributions

CEU conceived the idea and wrote the initial draft. SMS did the literature search and data collection. Both authors proof read the final manuscript.

Funding

Not applicable.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declared no competing interests.

Received: 1 December 2020 Accepted: 23 November 2021
Published online: 09 December 2021

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