REVIEW

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

Chidiebere Emmanuel Ugwu* and Stephen Monday Suru

Abstract
Background: Carbon tetrachloride (CCl₄) 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 CCl₄-induced liver injury in animal models. The results show that herbal plants provide protection for the liver against CCl₄ 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 CCl₄-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 (CCl₄) 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 CCl₄ toxicity, the significance, effectiveness, and underlying mechanisms of herbal plant extracts on CCl₄-induced toxicity in experimental animal models.
Main text

Insight on the mechanism of carbon tetrachloride hepatotoxicity

Prior to the Montreal Protocol, CCl₄ 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 CCl₄-induced toxicity beginning with acute but progressive centrilobular injury that may culminate in cell death [10].

Experimental deductions

Due to the complex nature of CCl₄-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 CCl₄-induced glycogen depletion and attendant protection from carbohydrate-rich diets [12, 13]. Besides, CCl₄-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, CCl₄-induced hypomethylation of 2′-O-ribose moieties in rRNA might have resulted from transient increase in cytosolic Ca²⁺. This increase may activate the selective destruction of rRNA methylases via

![Fig. 1 Hepatotoxic mechanism of CCl₄](image-url)
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 CCl₄ hepatotoxicity (plasma membrane blebbing and fatty accumulation- steatosis); CCl₄ may elicit dramatic redistribution of intracellular Ca²⁺ stores, albeit no total cellular change [10]. Calcium ion (Ca²⁺) homeostasis is maintained by 3 mechanisms: (i) Ca²⁺ extrusion by plasma membrane ATPase, (ii) Ca²⁺ sequestration by mitochondria, and (iii) Ca²⁺ sequestration by liver ER. So, CCl₄ may cause decreased Ca²⁺ sequestration by ER and mitochondria, decreased extrusion by plasma membrane ATPase, as well as blockage of gap junctional intercellular communication may favor increase cytosolic Ca²⁺. An ATP-dependent Ca²⁺ sequestration by hepatic ER has been shown to be disrupted by CCl₄ [15]. Endoplasmic reticulum membrane permeability may also be altered, being one indicator of impending cell death [16].

- Rapid destruction/decrease in cytochrome P₄₅₀ in centrilobular regions (suggesting that CCl₄ 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 O₂ and CCl₄ for cytochrome P₄₅₀ binding (i.e., CCl₄ may readily bind to cytochrome P₄₅₀).

- Metabolic products [trichloromethyl (CCl₃⁺) or peroxoxytrichloromethyl (CCl₃-OO⁺) free radical] elicit damage: lipid peroxidation of vulnerable unsaturated fatty acids in membrane phospholipids and destruction of haem moiety of cytochrome P₄₅₀.

- Blockage of gap junctional communication by CCl₄ 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 CCl₄ primarily involves metabolic activation to transient reactive intermediates. Under low oxygen partial pressure, cytochrome P₄₅₀ catalyzes the reductive de-halogenation of CCl₄ resulting in predominant formation of CCl₃⁻ 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 CCl₄-induced damage of Golgi apparatus and eventual reduction in the activities of these enzymes may explain the observed decrease in lipoprotein secretion associated with CCl₄ intoxication. Thus, CCl₄-induced inhibition of lipoprotein secretion, and its attendant hepatic steatosis mainly result from covalent binding of CCl₄ metabolites to cell constituents, but not due to lipid peroxidation.

Under high oxygen partial pressure, however, CCl₃⁺ may interact with oxygen to form CCl₃-OO⁺. The peroxo 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 CCl₄ metabolites and lipid peroxidation work in tandem to elicit the hallmark of damage seen in CCl₄-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 Ca²⁺ homeostasis/dramatic redistribution of Ca²⁺ in hepatocytes, leakage/efflux of K⁺, and influx of Na⁺ [10, 26].

Beside the peroxidative action, CCl₄-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 CCl₄-induced hepatocellular damage [28]. At lower doses of CCl₄, 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, CCl₄ hepatotoxicity may be due to a combination of factors such as the thorough inhibition of protein synthesis, the severe derailment of intracellular Ca²⁺ 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;
| s/n. | Botanical name | Family | Plant part/extract | Folkloric use | Pharmacological use | Reference |
|------|----------------|--------|--------------------|---------------|---------------------|-----------|
| 1    | Abelmoschus 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, anti-cancer, 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, anti-diabetic, 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, migraine 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) | Amaryllidaceae | 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, immunomodulatory, 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   | Argyemone Mexicana L | Papaveraceae | Crude powder leaf | Treatment of malaria, fevers, abdominal pains, and jaundice | Antibacterial, anti-inflammatory, wound-healing, antifertility, anti-stress, anti-allergic, cytopoietic, antidiabetic, and antihypertensive activities | [42] |
| 12   | Artemisia iwayomogi | Compositae | Aqueous | Treatment of hepatic disorders | Antioxidant, cytoprotection, choleretic, hepatoprotection, antimicrobial, anti-inflammatory and anti-fibrotic effects | [43] |
| s/n. | Botanical name                | Family       | Plant part/extract | Folkloric use                                                                 | Pharmacological use                                                                                                                                                                                                 | Reference |
|------|------------------------------|--------------|-------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 13   | Bauhinia variegata           | Leguminasea. | Stem bark, alcohol | Treatment of bronchitis, leprosy, diarrhea, piles, and tumor. Used as astringent | Hypoglycaemic, haemagglutinating, antibacterial, and antifungal effects                                                                                                                                                     | [44]      |
| 14   | Bougainvillea spectabilis    | Nyctaginaceae| Esceletin         | Treatment of liver damage, cough, pertussis, and bronchitis                  | Antimicrobial, anticancer, anti-diabetic, anti-inflammatory, antihyperlipidaemic, antioxidant, antinociception, and antihypertensive activities                                                                              | [45]      |
| 15   | Bryonia dioica Jacq          | Cucurbitaceae| Leaves, 80% ethanol| Treatment of various inflammatory conditions, bronchial complaints, asthma, intestinal ulcer, hypertension, and arthritis. Applied as a rubefacient to muscular pains. Treatment of fever and bronchitis | Antinociceptive, antimicrobial, antioxidant, anti-inflammatory, cytototoxic, and hepatoprotective                                                                                                                                          | [46]      |
| 16   | Bryocarpus cocCineus Schum   | Conneraiceae | Leaves, aqueous   | Mouth and skin sores, swellings, tumors, earache, muscular pain, and jaundice | Antioxidant and hepatoprotective                                                                                                                                                                                                                                                  | [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 | Antidiarreheal, analgesic, CNS activity, and pregnancy interceptive properties                                                                                                                                               | [49]      |
| 19   | Camellia nitidissima 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, hypolipidemic, antidepressant, antiallergic, and immunomodulatory activities                                                                 | [1]       |
| 20   | Canna indica L               | Cannaceae    | Aerial part, methanol | Treatment of diuresis, fever, dropsy, earache, and eye disease                  | Analgesic, antioxidant, and hepatoprotective effects                                                                                                                                                                      | [50]      |
| 21   | Capparis spinosa             | Cappridaceae | Root bark, 80% ethanol | Treatment of hepatic diseases. Reducing flatulence, treatment of rheumatism, anemia, and gout. Used as diuretics | Antidiabetic, hypoglycaemic, antioxidant, antitumor, antibacterial, antihyperlipidaemic, 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, antinociceptive, 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 dysmenorrea, 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]      |
| s/n | Botanical name          | Family        | Plant part/extract | Folkloric use                                                                                                           | Pharmacological use                                                                                                           | Reference |
|-----|-------------------------|---------------|-------------------|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----------|
| 25  | *Carthamus tinctorius* L | Asteraceae    | Flower, Na$_2$CO$_3$ | Treatment of gynecological diseases, osteoporosis, cardiovascular diseases, and angiitis                                  | Nutraceutical, hepatoprotective, antioxidant, promoting blood circulation, and inhibiting platelet aggregation, anti-inflammatory, antipyretic, anti-tumor, and anti-diabetic activities | [54]      |
| 26  | *Carum carvi*           | Apiaceae      | Fruit, aqueous    | Treatment of jaundice, indigestion and pneumonia. As appetizer, diuretic and gastric stimulant                           | Anti-inflammatory, spasmolytic, antimicrobial, antioxidant, camphor, antidiabetic, immunomodulatory, antitumor, 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 angustifolia* Vahl | Leguminosea   | Leaves, 90% alcohol | Used as laxative, febrifuge, treatment of anemia, typhoid, 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, hypolipidemic, antipyretic, and analgesic activities               | [61]      |
| 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’s disease | [62]      |
| 36   | *Cinnamomum zeylanicum* L      | Lauracea   | Bark, 80% ethanol          | Flavoring for foods and in traditional medicine to treat variety of health conditions | Antimicrobial, insecticidal, antitrypanosomal, anti-inflammatory, hypotensive, and cholesterol-lowering effects | [63]      |
| 37   | *Citrus aurantium* (essential oil) | Rutaceae   | Peel skin, aqueous oil     | Treatment of liver ailments and jaundice. Treatment of sluggish liver, rheumatism, fever, and febrile diseases | Analgesic, anti-inflammatory, anti-fungal, and antibacterial activities            | [64]      |
| 38   | *Citrus limon* (L.) Burm.F      | Rutaceae   | Fruit, 70% ethanol         | Treatment of liver ailments and jaundice. Treatment of sluggish liver, rheumatism, fever, and febrile diseases | Chemoprevention, lipid peroxidation inhibitor, hypcholesterolemic, 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 | Antihelminthic, antihistaminic, antimicrobial, cytotoxic, anti-inflammatory, wound healing, proteolytic, hypoglycemic, and antioxidant activities | [67]      |
| 41   | *Corianderum sativum* L        | Apiaceae   | Leaves, ethanol            | Treatment of jaundice                                                         | Anxiolytic, antidepressant and sedative-hypnotic effects. Neuroprotective, antibacterial, anti-inflammatory, analgesic, anti-diabetic, antifungal, and hypolipidemic effects | [68]      |
| 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, anti-diabetic, antifungal, and hypolipidemic effects | [69]      |
| 43   | *Coriandrum sativum*           | Umbellifera| 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 | [70]      |
| 44   | *Cortex dictamni*              | Rutaceae   | Whole plant, aqueous       | Treatment of Jaundice, chronic hepatitis, cough rheumatism and some skin diseases. To clear heat, dry dogmamess, displace wind, treatment of arthritis, eczema, rubella, and urticarial | Good scavenger of free radicals and inhibition of lipid peroxide                   | [71]      |
| s/n. | Botanical name                  | Family                    | Plant part/extract | Folkloric use                                                                 | Pharmacological use                                                                 | Reference |
|------|--------------------------------|---------------------------|--------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------|
| 45   | *Curcuma longa* L              | Zingiberaceae             | 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                    | Antiplasmodial, antibacterial, antihelminthic, 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       | Asteraceae                | 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 antinocaragenic effects | [75]      |
| 51   | *Entada puraetha* DC          | Fabaceae                  | Stem, 85% ethanol  | Used as narcotic. Treatment of Jaundice. As an anthelmintic, incurring 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 draconcoloides* 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   | *Ficus carica* Linn           | Moraceae                  | Leaves, ethyl acetate | Treatment of vitiligo, diabetes, cough, asthma, constipation, and gingivitis. | Cytotoxic, hypoglycemic and antihelminthic activities                             | [78]      |
| 56   | *Flemingia macrophylla*        | Fabaceae/Leguminosae      | Root, aqueous      | Treatment of rheumatism, arthropathy, chronic nephritis, menaliga, and menopausal syndrome. | Antioxidative, anti-inflammatory, analgesic, hypotetic-sedative and anxiolytic effects. | [79]      |
| s/n. | Botanical name                  | Family                | Plant part/extract            | Folkloric use                                                                 | Pharmacological use                                                                                                           | Reference |
|------|--------------------------------|-----------------------|--------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-----------|
| 57   | Ginkgo 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   | Hippophae rhhamnoides L         | Elaegnaceae           | Seabuckthorn berry polysaccharide, alcohol. | Treatment of asthma and circulatory disorders | Antioxidative, antimicrobial, antithromogenic, 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   | Lawsonia 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, anti-hyperglycaemic, 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]       |
| 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, biliary disease, 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 CCl₄                                                                                                                                                                                                                                           | [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 anti-diabetic effects                                                                                                                                                     | [91]      |
| 71   | Madhuca indica Syn             | Sapotaceae              | Leaves, 70% ethanol, 90% ethanol | Treatment of piles, emetic, laxative toxic, anti-burn, and wound healing                                                                                                                               | Antidiabetic, anti-inflammatory, analgesic, anti-pyretic, anti-asthmatic, antiulcer, anticancer, hepatoprotective, and antibacterial effects                                                                                                                                  | [92]      |
| 72   | Mahonia aiwaken Hayata         | Berberidaceae           | Root, 90% ethanol                | Rheumarthritis, dysentery, hepatitis, antidote, and antiphlogistic 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 pungent 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, anti-phytogenic, anticancer, anti-inflammatory, anticoagulant, 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, antihelminitic, 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, anti-diabetic, 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, anti-diabetic, 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 plumbaginifolia L     | Solanaceae       | Whole plant, methanol | Treatment of cuts, wounds, toothache, and rheumatic swelling.                  | Antispasmodic, leaves are effective laxative, antioxidant, and antimicrobial.                               | [101]     |
| 82   | Nymphaea alba L                 | Nymphaeaceae     | 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 | Antisulox, antimicrobial, anti-inflammatory and antihypercholesterolemic activities.                     | [106]     |
| 88   | Pleogynium 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]     |
| 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   | Rouea induta planch               | Connaraceae     | Leaves, 99% ethanol | Treatment of respiratory and kidney diseases. Treatment of blood diarrhea, and as diuretics | Anti-inflammatory, hepatoprotective, antioxidant, and antiapoptotic activities    | [111]     |
| 94   | Rubia cordifolia Linn             | Rubiaceae       | Root, 50% ethanol  | Treatment of jaundice                                                         | Potent antioxidant property, inhibit lipid peroxidation, anti-inflammatory, immunomodulatory, anticongestant, 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, indolcylitis, calico corneal, and sarcoidosis | Antibacterial, antacnes, antidiarhoeal and anti-inflammatory effects | [114]     |
| 97   | Solanum 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, antitumor, and antioxidant properties | [115]     |
| 98   | Solanum xantholarpum              | Solanaceae      | Fruit, 50% ethanol  | Laxative, treatment of enlargement of liver, anthelmintic, antipyretic, anti-inflammatory, antiasmatic, and aphrodiasic activities. | Antiasthmatic, anti-nociceptive, anti-fungal, molluscicide, antispasmodic, antitumor, cardiotoxic, hypotensive, antianaphylactic, and anti-urolithic activities | [116]     |
| 99   | Spondias mombin                   | 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, anti bacterial, 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, antibiotic, 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]     |
| s/n. | Botanical name                        | Family         | Plant part/extract | Folkloric use                                                                 | Pharmacological use                                                                 | Reference |
|------|--------------------------------------|----------------|--------------------|------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------|
| 103  | Zingiber officinale (Roscoe) rhizome | 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                  | Rhamnaceae     | 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    | Abelmoschus 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, γ-GT, TNF-α, IL-1β, NO, MDA↓, GSH, SOD, GPx, CAT, GST↑ | Flavonoids, quercetin, hyperin, isoquercetin, quercetin-3′-O-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, F-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/bw, (olive oil), i.p | – | AST, ALT, ALP, T.B↓ | Rutin, piperine | [34] |
| 4    | Aegle marmelos correa ex Roxb | Wistar albino rats | 50mg/kg/b.w. (oral) | 3ml/kg/bw, , i.p | Silymarin 200 mg/kg/bw, (oral) | ALP, AST, ALT, T.B, LDH, MDA↓, SOD, CAT, GR, GSH, GST, GPx, G6PD, TP↑, IL-10, TNF-α↓ | Flavonoids, 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, γ-sisosterol | [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↑ | – | – | [39] |
| 9    | Amaranthus spinosus | Sprague-Dawley rats | 400 mg/kg/b.w. (oral) | 1 ml/kg/bw. (v/v olive oil), i.p | – | ALT, ALP, MDA↓, 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 (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/bw. (50% olive oil), 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 spectabilis | Wistar rats. | 6 mg/kg/bw. (oral) | 1.5 ml/kg, oral. | – | AST, ALP, ALT↓ | Esculetin | [45] |
| 15   | Bryonia dioica Jacq | Wistar albino rats | 250 mg/kg/bw. (gavage) | 1 ml/kg/bw. (corn oil,1:1 v/v) | – | AST, AST↓ | Flavonoids, terpenoids | [46] |
| 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 coCClneus.    | Albino rats  | 1000 mg / kg /b.w. (oral)                    | 0.7 ml/kg/b.w. (1:1 in olive oil) | 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 Dil, calotropin Fl and Fil. | [49] |
| 19    | Camellia nitissima Chi.   | Sprague-Dawley rats | 160 mg/kg/day (i.p)                      | 2 ml/kg (50% w/v, olive oil), i.p | Thiopronin 20 mg/kg/day, (i.p)                  | AST, ALT, MDA↓, GSH, SOD↑, TNF-α, IL-6, IL-1β, NF-κB signaling↓, NF2 signaling partway. HO-1, GSH↑ | Polyphenols, flavonoids | [1] |
| 20    | Canna indica L.           | Sprangue-Dawley rats | 200 mg/kg/b.w. (oral)                      | 1.0 ml/kgliquid paraffin,1:2, p. | Silymarin, 25 mg/kg, (i.p)                       | SGPT, SGOT, ALP, T.B, L.P↓, GSH, CAT, TP↑ | 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 bursa-pastoris (L.) Medik. | Wistar rats | 500 mg/kg/b.w.                            | 0.125 ml/kg (liquid paraffin, 1:1), i.p. | Silymarin, 10 mg/kg, (i.p)                       | SGOT, SGPT, ALP, T.B | – | [38] |
| 23    | Carissa opoca             | Sprague-Dawley rats | 200 mg/kg/b.w. (intra-gastrically) | 0.5 ml/kg/b.w. (20% v/v olive oil), i.p | Silymarin, 50 mg/kg/bw, (intragastro- | AST, ALT, ALP, LDH↑, GGT↓, GSH-Px, GSR, SOD, GST, CAT, Peroxidase, Quinone reductase (QRI)↑, TBARS, GSH, H2O2↓, TP↑ | 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↓ | Hydroxyaffl sor yellow A, isocarthusin, carthamin, luteolin | [53] |
| 25    | Carthamus tinctorius L.   | Sprangue-Dawley rats | 20 mg/kg/b.w. (oral)                      | 2 ml/kg/b.w. (1:1 olive oil), i.p. | Silymarin, 50 mg/kg/bw, (oral).                   | ALT, AST, ALP, T.P↑, NF2, G6, NQOl expression, GSH↑, TBARS↓, SOD, CAT↑ | Carthamin, carthaminidin, carthamin, luteolin | [54] |
| 26    | Carum carvi              | 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↑, TP↑ | Flavonoid, terpenoids, tannin, steroid | [56] |
| 28    | Cassia angustofolia vahl  | Wistar rats   | 500 mg/kg/bw(oral)                        | 4 ml/kg/b.w. (50% olive oil) oral | –                                                   | T.B, GOT, GPT↓, T.P, GSH↑, LPQ↓ | 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, ɤ-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%)        | Silymarin 10 mg/kg (oral)                         | SGOT, SGPT, ALKP↓, TP, albumin↑ | Cichotyboside | [59] |
| 32    | 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↓, TP, albumin↑ | Cichotyboside | [59] |
| 33    | Cichorium intybus                     | Albino rats           | 500 mg/kg/b.w. (oral)                       | 1.0 ml/kg olive oil 50%, i.p.    | -                                                 | AST, ALP, ALT, T.B↓, TP, albumin↑ | Esculetin and cichotyboside | [60] |
| 34    | Cinnamomum verum                     | Wistar albino rats    | 100 mg/ kg/b.w. (oral)                      | 1.0 ml/kg/b.w. (olive oil), subcutaneous | -                                                 | AST, ALT, MDA↓, SOD, CAT↑ | Flavonoids | [61] |
| 35    | Cinnamomum verum                     | Wistar albino rats.   | 100 mg/kg/b.w. (oral)                       | 1 ml/kg/b.w. olive oil (oral)    | Silymarin 50 mg/kg/b.w. (oral)                    | AST, ALP, ALT, ɤ-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, alpha-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)                        | AST, ALP, T, B, MDA↓, SOD, GSH, CAT, albumin↑ | Coumarins, limonoids, flavonoids, eriocitrin, C-glycosyl flavones 6,8-di-C-β-glucosyldiosmin | [65] |
| 39    | Clerodendrum volubile.               | Wistar albino rats    | 500 mg/kg/b.w. (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/b.w (oral)                        | 2.5 ml/kg/b.w.                  | Silymarin, 100 mg/kg/bw. (oral)                   | ALT, AST, ALP, Acid phosphatase(ACP), LDH, TB↓, TP↑ | Flavonoid, terpenoids, tannin, steroid, quercimetrin, rutin, sguettarein | [56] |
| 41    | Corianderum sativum L.               | Wistar albino rats    | 300 mg/kg (i.p)                              | 1 ml/kg/b.w. (liquid paraffin, 1:1), oral | Silymarin, 50 mg/kg (i.p)                         | SGOT, SGPT, ALP↓, TB↑ | Caffeic acid, quercetin, gallic acid, flavonoids, essential oil | [57] |
| 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, XO↓, PX↑, GSH, GSH-Px, Protein↑ | Caffon | [55] |
| 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†, TP†, TB†, MDA†, SOD, CAT, GPx† | Caffeic acid, ferulic acid, isoquercitrin, rutin, quercetin 3-glucuronide, Quercetin, hyperin, quercetin-3-O-β-glucopyranoside, quercetin-3-O-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, GSHT†, MDA† | Limonoids, furqui-noline, flavonoids, fraxinellone                                | [69]      |
| 45    | Curcuma longa. L.           | Sprague-Dawley rats           | 300 mg/kg/b.w. (intra-gastrically)            | 0.1 ml/kg/b.w., i.p.              | Curcumin, 200 mg/kg/b.w., (intragastrically)      | AST, ALP, TBARS†, SOD, GPx† | Curcumin, memethoxycurcumin, bisdemethoxycurcumin                              | [70]      |
| 46    | Cytisus scoparius L.        | Wistar albino rats            | 500 mg/kg/b.w. (oral)                         | 5 ml/kg/b.w. (50% olive oil), i.p.| Silymarin, 25 mg/kg/b.w., (oral)                  | SGOT, SGPT, LDH†, GSH†, SOD, CAT, GPx, GRx, GST†, MDA† | Rutin, quercetin, quercitrin, isorhamnetin, kaempferol                           | [71]      |
| 47    | Diocoma 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 flavonoids and phenol contents                                              | [72]      |
| 48    | Dioscorea alata peel        | Wistar albino rats            | 433.42 mg/kg/b.w.                             | 1 ml/kg/b.w. (20% olive oil)      | Silymarin, 200 mg/kg/b.w.                         | AST, ALP, TBARS†, SOD, CAT, GSH-Px†, NO, TNF-α, TNF-Kβ, 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, ALP, TBJ†, TP† | Flavonoids, luteolin, demethylhexedolactone, hexedolactone                        | [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, TP†, 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)| AST, ALP, TBJ†, TP†, 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, TP† | Flavonoids, tannins                                                              | [38]      |
| 53    | Euphorbia dracunculoides L. | Sprague-Dawley rats           | 400 mg/kg/b.w.                                | 1 ml/kg/b.w. (30% olive oil), i.p.| Silymarin 50 mg/kg/b.w.                           | AST, ALP, TBJ†, CAT, Peroxidase, SOD, GST, GSH†, Lipid peroxides, TBARS, nitrite, hydrogen peroxide, DNA damage† | Catechin, rutin, caffeic acid, mcinetin, coumarins, flavonoids                    | [51]      |
### 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) Haddi | 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, TB, MDA, SOD, CAT, GSH↑ | Flavonoids, Phenolic Compounds, Quinines and Coumarin | [77]      |
| 55   | Fiscus carica Linn          | Wistar rats           | 100 mg/kg/bw. (oral)                        | 1 ml/kg/bw(v/v olive oil), i.p.| Silymarin, 25 mg/kg/bw in carboxymethyl cellulose | ALT, AST, MDA, SOD, CAT, GSH↑, NO, TNF-α, IL-1β↓ | Psoralen, Bergapten, Xantho Toxic, Calotropenyl Acetate, Lupeol Acetate | [78]      |
| 56   | Flemingia macrophylla       | Male SD rats          | 1.0 g/kg/bw. (oral)                         | 15 ml/kg/bw. (20% olive oil), i.p.| Silymarin, 25 mg/kg/bw, (oral).                 | ALT, AST, ALP, TB, MDA, TP, HDL-c, GSH↑ | Genistein, Lupeol, Rutin, Flavonoids, Isoflavones | [79]      |
| 57   | Ginkgo biloba               | Sprague-Dawley rats   | 150 mg/ kg/bw. (oral)                       | 1 ml/kg/bw. (1:1 liquid paraffin), | Silymarin, 100 mg/kg (oral).                      | ALP, ALT, AST, MDA, TP, IL-1β↓ | Kaempferol, Quercetin, Isorhamnetin, Diterpene Lactones | [80]      |
| 58   | Glyphae brevis              | Swiss albino mice     | 490 mg/kg/bw. (oral)                        | 2 ml/kg/bw. (liquid paraffin), | Silymarin, 100 mg/kg (oral)                      | ALP, ALT, AST, MDA, TP, IL-1β↓ | Gallic Acid, Genistin, Daidzin, Quercetin | [81]      |
| 59   | Gaertnaria paraguayensis E. Walter | Sprague-Dawley rats | 300 mg/kg/bw. (oral)                        | 0.5 ml/kg/bw. (14 olive oil), | Silymarin, 200 mg/kg/bw, (oral).                 | ALT, AST, MDA, GSH, SOD, CAT, GR, IL-1β↑ | Isorhamnetin, Quercetin, Chlorogenic Acid, Myricetin, Kaempferol, Catechins | [82]      |
| 60   | Hibiscus sabdariffa L.      | Wistar rats           | 500 mg/kg/bw.                              | 0.125 ml/kg (liquid paraffin, 1:1), i.p.| Silymarin, 10 mg/kg (oral)                      | ALT, AST, ALP, T-chol, LDL, TG↓, TP↑ | Gallic Acid, Genistin, Daidzin, Quercetin | [38]      |
| 61   | Hippophae rhamnoides L.     | C57BL/6 mice          | 200 mg/kg/bw. (oral)                        | 5 ml/kg/bw. (20% in peanut oil), i.p.| Silymarin, 10 mg/kg (oral).                      | ALT, AST, TB↓, PALB, SOD, GSH↑, GST, CAT↑, TNF-α↑, iNOS, NO, TLR4, p38MAPK, p-ERK, p-JNK, NF-KB↓ | Isorhamnetin, Quercetin, Chlorogenic Acid, Myricetin, Kaempferol, Catechins | [83]      |
| 62   | Indigofera oblongifolia     | Wistar albino rats    | 300 mg/kg/bw. (oral)                        | 1 ml/kg/bw. (30% olive oil), i.p.| Silymarin, 100 mg/kg (oral)                      | ALT, AST, ALP, TB↓, SOD, CAT, GPX↑ | Flavonoids, Coumarins, Indirubin | [84]      |
| 63   | Launaea procumbens          | Sprague-Dawley rats   | 200 mg/kg/bw. (oral)                        | 3 ml/kg/bw. (30% olive oil), i.p.| Silymarin, 100 mg/kg (oral)                      | ALT, AST, ALP, TB, SOD, GST, CAT, POD, GSH↑ | Salicylic Acid, Vanillic Acid, Synergic Acid, 2-Methyl-Esorcinol, and Gallic Acid | [85]      |
| 64   | Lawsonia inermis L. (Henna) | Albino rats           | 200 mg/kg/bw. (oral)                        | 2 ml/kg/bw. (1:1 olive oil), | Silymarin, 25 mg/kg/bw, (oral).                 | ALT, AST, ALP, TB↓, TP↑ | Flavonoids | [86]      |
| 65   | Lawsonia inermis Linn       | Wistar albino rats    | 400 mg/kg/bw. (i.p)                         | 1.25 ml/kg (1:1 liquid paraffin), i.p.| Silymarin, 100 mg/kg (b.w., l.p.)                | Silymarin, 200 mg/kg (l.p) | Flavonoids | [87]      |
| 66   | Leucas cephalotes Linn      | Wistar albino rats    | 200 mg/kg/bw. (liq-uid paraffin) (l.p.)     | 1.25 mg/kg (1:1 liquid paraffin), i.p.| Silymarin, 200 mg/kg (l.p)                      | Silymarin, 200 mg/kg (l.p) | Flavonoids | [88]      |
| 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-a, 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, SGPT, ALP, TC ↓, 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/b.w. | SGOT, SGPT, ALP, T.B↓ | Flavonoids | [92]      |
| 72    | Mahonia owaken 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, GPx↑, TNF-a, 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) | SGOT, SGPT, ALP, T.B↑, TP↑, CAT, SOD↑, LPO↓ | Flavonoids, phenols, isocoumarins, bergenin | [93]      |
| 74    | Memordica tuberosa Cogn | Wistar rats | 400 mg/kg/b.w. (oral) | 2 ml/kg/b.w(1:1 liquid paraffin), subcutaneous | Silymarin, 100 mg/kg, (oral) | ALT, AST, ALP, LDH, x-GT↓, 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, 100 mg/kg/b.w. | T.B, SGOT, SGPT, ALP ↓ | Flavonoids | [95]      |
| 76    | Mentha 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. | SGPT, SGOT, ALP, T.B↓ | Luteolin, mentholide, rutin, hesperidin, flavonoids, quercetin, isorhoidulin | [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, T.B↑, T.chol↑, TP↑, 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 paraffin). | Silymarin, 5 mg/kg/b.w. (oral) | ALT, 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, Oleandonic acid | [100]     |
| 81    | Nicotiana plumbaginifolia L | Male chicks | 200 mg/kg/b.w. (oral) | 1 ml/kg/b.w (80% olive oil), i.p. | Silymarin, 100 mg/kg/b.w. (gavage) | AST, ALT, ALP, T.B, MDA↓, SOD↑ | Rutin, chlorogenic acid, quercetin | [101]     |
| 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, luteolin 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↑, LPO↑, P-chol↑, CAT↑, SOD↑, GPx↑, GST↑ | 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↑, ALP↑, TB↓, CAT↑, SOD↑, GPx↑, GST↑, Protease in carboxyl | 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, 1 mg/ml, (i.p.)                        | AST↑, ALT↑, LDH↑, T-chol↑, TB↓↑, TP↑↑, TAC↑↑, TNF-α↑, IL-6↑, IL-10↑, IL-13↑, GR↑↑, MDA↑, GSH↑↑, ROS↑↑ | Quercetin, gallic acid, corilagin, isocorilagin, rhamnoside, brefirolin carboxylic acid | [105]     |
| 87    | Physalis peruviana  | Wistar albino rats    | 500 mg/kg/b.w. (oral)                         | 0.5 ml/kg/b.w (olive oil), i.p.   | legation® 100 mg/kg/b.w (oral)                     | MDA↑, SOD↑↑, NO↑, AST↑↑, ALT↑↑↑, ALP↑↑↑, TB↑↑↑, TP↑↑↑, TAC↑↑↑ | Flavonoids, lupeol, ursolic acid | [106]     |
| 88    | Pleogynium timorense (DQ 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, quercetin, 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.     | –                                                 | AST↑, ALT↑↑↑, SGPT↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑∪
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, v-GT↓, GST, GR, GSH↑, MDA↓   | Rubidin | [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↓, TP↑, TB↓, 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.         | Bilendate                                         | AST, ALT, ALP, MDA↓, GSH-Px, CAT, SOD↑        | Semenoside | [114] |
| 97    | Solanum trilobatum Linn       | Wistar Albino rats   | 250 mg/ kg/ b.w (L.P)                       | 1 ml/kg/bw(30% olive oil), i.p. | –                                                 | ALT, AST, ALP, LDH↓, TP, GSH, GPx, CAT, SOD↑, Lipid peroxide↓ | Solatam, solasodine, β-solamarine, solaine | [115] |
| 98    | Solanum xantholarpum          | Sprague-Dawley rats  | 400 mg/kg/bw (oral)                        | 1 ml/kg (1:1 liquid paraffin)   | Silymarin 100 mg/kg/b.w, (oral)                  | AST, ALP, T.B, MDA↓, CAT, GSH, SOD↑           | Flavonoids, quercetin | [116] |
| 99    | Spondias mombim               | Wistar rats          | 1000 mg/kg/bw (oral)                       | 2 ml/kg/b.w. (1:1 liquid paraffin) | Silymarin 100 mg/kg/b.w, (oral)                  | ALT, 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↓, TP, TB↑                   | 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/bw. in carboxy methylcellulose | ALT, MDA↓, SOD, CAT, GPX, GSH↑, TNF-α, IL-1β, NO, INOS, COX-2↓ | Resveratrol derivaives, polyphenols compounds, quercetin, oligostibenes | [119] |
| 102   | Xylaria nigripes(Koltz) Sacc  | ICR mice             | 100 mg/kg/bw (intragastrically)            | 2 ml/kg/b.w. (40% olive oil). Subcutaneously | Silymarin, 100 mg/kg/bw, (intragastrically) | SGOT, SGPT, TBARS↓, SOD, CAT, GPX, ↑ | Epicatechin, P-coumaric acid, catechin | [120] |
| 103   | Zingiber officinale (Roscoe)   | Wistar rats          | 400 mg/kg/bw (oral)                        | 0.7 ml/kg/b.w (11, olive oil)   | Livolinfort®, 5.2 mg/kg/bw, (oral)               | AST, ALT, ALP↓, TP,GSH, CAT↑                  | Flavonoids, 6-gingerol, shogaols | [121] |
| 104   | Zizyphus jujube               | Male ICR mice        | 200 mg/kg/bw (intragastrically)            | 2 ml/kg/bw. (40% v/v olive oil), subcutaneously | Bilendate, 7.5 mg/ml/kg/bw, (intragastrically) | ALT, AST, MDA↓, SOD, CAT, GSH-Px, GSH↑ | Flavonoids | [122] |

↓ decrease in effect/activity; ↑ increase in effect/activity
formation of CCl₃⁺ and CHCl₃⁺ and CCl₃-OO⁻ radicals, lipid peroxidation, membrane damage, the severe derailment of intracellular Ca²⁺ 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 CCl₄-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 CCl₄-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 CCl₄-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 CCl₄-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 CCl₄ [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, coumarins, 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 CCl₄-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; γ-GT: Gamma glutamyltransferase; LDH: Lactate dehydrogenase; MDA: Malondialdehyde; GSH: Glutathione; GPx: Glutathione peroxidase; CAT: Catalase; SOD: Superoxide dismutase; POD: Peroxidase; GST: Glutathione S-transferase; GSTα: Glutathione S-transferase alpha; GR: Glutathione reductase; TBARS: Thiobarbituric acid reactive substance; NO: Nitric oxide; H₂O₂: Hydrogen peroxide; TNF-α: Tumor necrosis factor alpha; NF-κB: Nuclear factor-kappa B; INOS: Inducible nitric oxide synthase; COX-2: Cyclooxygenase-2; IL-1β: Interleukin-1 beta; TNF-α: Tumor necrosis factor alpha; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; HD-1: Heme oxygenase-1; NQO1: Quinine oxidoreductase; p-ERK: Extracellular signal-regulated kinase; p-JNK: C-jun N-terminal kinase; CYT: Cytochrome; DT-diaphorase: 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.

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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.

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References
1. Zhang X, Feng J, Su S, Huang L (2020) Hepatoprotective effects of *Camellia* *nissima* aqueous ethanol extract CCl4-induced acute liver injury in SD rats related to Nrf2 and NF-kB signaling. Pharm Biol 58(1):239–246
2. Wang S, Luan JJ, Lv XW (2019) Inhibition of endoplasmic reticulum stress attenuated ethanol-induced exosomal miR-122 and acute liver injury in mice. Alcohol Alcohol 54:465–471
3. Chao J, Lee M-S, Amagaya S, Liao J-W, Ho L-K, Peng W-H (2009) Hepatoprotective effect of *Shiadagano* on acute liver injury induced by carbon tetrachloride. Am J Chin Med 37(6):1085–1097
4. Zhang H, Yu C-H, Jiang Y-P, Peng C, He K, Tang J-Y, Xin H-L (2012) Protective effects of polydatin from *Polygonum cuspidatum* against carbon tetrachloride-induced liver injury in mice. PLoS One 7(9):e46574. https://doi.org/10.1371/journal.pone.0046574
5. Batool R, Khan MR, Majid M (2017) *Euphoria dracunculoides* L. abrogates carbon tetrachloride induced liver and DNA damage in rats. BMC Complement Altern Med 17:23. https://doi.org/10.1186/s12906-017-1562-2
6. Bakr RO, El-Naa MM, Zaghloul SS, Omar MM (2017) Profile of bioactive compounds in *Nymphapha obi* L. leaves growing in Egypt: hepatoprotective, antioxidant and anti-inflammatory activity. BMC Complement Altern Med 17:52. https://doi.org/10.1186/s12906-017-1560-4
7. Hisouna AB, Dhibi S, Dhifi W, Saad RB, Brini F, Hfaidh N, da Silva Almeida JRG, Mnif W (2020) Protective effects of *Euphoria dracunculoides* L. on acute liver injury induced in rats. BMC Complement Altern Med 17:52. https://doi.org/10.1186/s12906-017-1560-4
8. Jones I (1983) Chloroform anaesthesia in Liverpool. Anaesthesia 38:578–580
9. Agency for Toxic Substances and Disease Registry (ATSDR) (2005) Toxicological profile for carbon tetrachloride. U.S. Department of Health and Human Services, Public Health Service, Atlanta
10. Clawson GA (1989) Mechanism of carbon tetrachloride toxicity. Pathol Immunopathol Res 8:104–112
11. Recknagel R, Lombardi B (1961) Studies of biochemical changes in subcellular particles of rat liver and their relationship to a new hypothesis regarding the pathogenesis of carbon tetrachloride fat accumulation. J Biol Chem 236:564–569
12. Judah J (1969) Biochemical disturbances in liver injury. Br Med Bull 25:274–277
13. de Vries J (1983) Induction and prevention of biochemical disturbances in hepatic necrosis. Trends Pharmacol Sci 4:393–394
14. Smuckler E, Iseri O, Bendit E (1962) An intracellular defect in protein synthesis induced by carbon tetrachloride. J Exp Med 116:55–72
15. Moore L, Chen J, Knapp H, Landon E (1975) Energy-dependent calcium sequestration activity in rat liver microsomes. J Biol Chem 250:4562–4568
16. Fulceri R, Benedetti A, Compotti M (1984) On the mechanisms of the inhibition of calcium sequestering activity of liver microsomes in bromothrichloromethane intoxication. Res Commun Chem Pathol Pharmacol 46:235–243
17. Christie G, Judah J (1954) Mechanism of action of CCl4 on liver cells. Proc R Soc Lond Ser B 142:241–257
18. de Groot L, Littauer A, Hugo-Wissemann D, Wissemann P, Noll T (1988) Lipid peroxidation and cell viability in isolated hepatocytes in a redesigned oxystat system: Evaluation of the hypothesis that lipid peroxidation, preferentially induced at low oxygen partial pressure, is decisive for CCl4 liver cell injury. Arch Biochem Biophys 264:591–599
19. Masuda Y, Nakamura Y (1990) Effects of oxygen deficiency and calcium omission on carbon tetrachloride hepatotoxicity in isolated perfused livers from phenobarbital-pretreated rats. Biochem Pharmacol 40:1865–1876
20. Kieczka H, Kappus H (1980) Oxygen dependence of CCl4-induced lipid peroxidation *in vitro* and *in vivo*. Toxicol Lett 5:191–196
21. Dianzani MU, Poli G (1985) Lipid peroxidation and haloalkylation in CCl4-induced liver injury. In: Poli G, Cheeseman KH, Dianzani MU, Slater TF (eds) Free Radicals in Liver Injury. IRL Press, Oxford
22. Dianzani MU (1984) Lipid peroxidation and haloalkylation: Two distinct mechanisms for CCl4-induced liver damage. In: Calandra S, Carulli N, Salviodi G (eds) Liver and Lipid Metabolism. Excerpta Medica, Elsevier, Amsterdam, New York, Oxford
23. Marinini UM, Pronzato MA, Cortalasso D, Zicca-Cadoni A, Nanni G, Poli G, Chiapotteto E, Albano E, Biasi F, Dianzani MU (1985) CCl4-induced early functional impairments of rat liver Golgi apparatus. In: Poli G, Cheeseman KH, Dianzani MU, Slater TF (eds) Free Radicals in Liver Injury. IRL Press, Oxford
24. Cheeseman KH, Albano EF, Tomasi A, Slater TF (1985) Biochemical studies on the metabolic activation of halogenated alkanes. Environ Health Perspect 84:65–81
25. Boll M, Weber LWD, Becker E, Stampfl A (2001a) Mechanism of carbon tetrachloride-induced hepatotoxicity. Hepatocellular damage by reactive carbon tetrachloride metabolites. Z Naturforsch C J Biosci 56(7-8):649–659
26. Ozaki M, Masuda Y (1993) Carbon tetrachloride-induced cell death in perfused livers from phenobarbital-pretreated rats under hypoxic conditions and various ionic milieu. Further evidence for calcium-dependent irreversible changes. Biochem Pharmacol 46:2039–2049
27. Liu SL, Degli Esposti S, Yao T, Diehl AM, Zern MA (1995) Vitamin E therapy of acute CCl4-induced hepatic injury in mice is associated with inhibition of nuclear factor Kappa B binding. Hepatology 22:1474–1481
28. Czaja MJ, Xu J, Alt E (1995) Prevention of carbon tetrachloride-induced liver injury by soluble tumor necrosis factor receptor. Gastroenterology 108:1849–1854
29. Kull FC, Cuacresas P (1981) Possible measurements of internalization in the mechanism of *in vitro* cytotoxicity of tumor necrosis serum. Cancer Res 41:4885–4890
30. Boll M, Weber LWD, Becker E, Stampfl A (2001b) Pathogenesis of carbon tetrachloride-induced hepatocyte injury. Bioactivation of CCl4 by cytochrome P450 and effects on lipid homeostasis. Z Naturforsch 56c:111–121
31. Boll M, Weber LWD, Becker E, Stampfl A (2001c) Hepatocyte damage induced by carbon tetrachloride. Inhibited lipoprotein secretion and altered lipoprotein composition. Z Naturforsch 56c:283–290
32. Al G, Liu Q, Hua W, Huang Z, Wang D (2013) Hepatoprotective evaluation of the total flavonoids extracted from flowers of *Aegle marmelos* manihot (L) Medic. *In vivo* and *in vitro* studies. J Ethnopharmacol 146:794–802
33. Arbab AH, Parvez MK, Al-Dosai AS, Al-Rehaili AJ, Al-Sohabani M, Zarouq EE, Alsaid MS, Rafatullah S (2015) Hepatoprotective and antiviral efficacy of *Acazia millifera* leaves fractions against Hepatitis B virus. Biomed Res Int. https://doi.org/10.1155/2015/929131
34. Singh R, Rao HS (2008) Hepatoprotective effect of the pulp/seed of *Aegle marmelos* corea ex *Roxb* against carbon tetrachloride induced liver damage in rats. Inter J Green Pharm 2:232–234
35. Rathee D, Kamboj A, Sidhu S (2018) Augmentation of hepatoprotective potential of *Aegle marmelos* in combination with piperine in carbon tetrachloride model in wistar rats. Chem Cent J 12:94. https://doi.org/10.1186/s3065-018-0463-9
79. Hsieh PC, Ho YL, Huang GJ, Huang MH, Chiang YC, Huang SS, Hou WC, Chang YS (2012) Hepatoprotective activity of the aqueous extract of *Flemingia macrophylla* on carbon tetrachloride-induced acute hepatotoxicity in rats through anti-oxidant activities. Am J Chin Med 40(2):349–365

80. Khattab HAH (2012) Effect of *Ginkgo biloba* leaves aqueous extract on carbon tetrachloride induced acute hepatotoxicity in rats. Egypt J Hosp Med 48:483–495

81. Nwodu LL, Oboma YL, Elmorey C, Carter WG (2018) Alleviation of carbon tetrachloride-induced hepatocellular damage and oxidative stress with a leaf extract of *Glyphae brevis* (*Tiliaciaceae*). J Basic Clin Physiol Pharmacol 29(6):609–619

82. Duh P-D, Lin S-L, Wu S-C (2011) Hepatoprotective of *Graptopterum paraguayense* E. Walther on CCl₄-induced liver damage and inflammation. J Ethnopharmacol 134:379–385

83. Zhang W, Zhang X, Xie J, Zhao S, Liu J, Liu H, Wang J, Wang Y (2017) Seabuckthorn berry polysaccharide protects against carbon tetrachloride-induced hepatotoxicity in mice via anti-oxidative and anti-inflammatory activities. Food Funct. https://doi.org/10.1039/C7FO03999D

84. Shahjahan M, Vani G, Shyamala Devi CS (2005) Protective effect of *Mentha arvensis* Linn. on carbon tetrachloride induced acute hepatotoxicity in rats. J Ethnopharmacol 105:105–109

85. Khan RA, Khan MR, Ahmed M, Saheen S, Shah AN, Shah MS, Bokhari J, Rashid U, Ahmed B, Jan S (2012) Hepatoprotection with a chloroform extract of *Launaea procumbens* against CCl₄-induced injuries in rats. BMS Compl Altern Med 12:114 http://www.biomedcentral.com/1472-6882/12/114

86. Mohamed MA, Bidin IM, Mohamad AH, Hassan HM (2016) Effects of *Lawsonia inermis* L. (*Henna*) leaves' methanolic extract on carbon tetrachloride-induced hepatotoxicity in rats. J Tertiart Ethnopharma 5(1):22–26. https://dx.doi.org/10.4172/2155-9671.1000043

87. Hossain CM, Maji HS, Chakraborty P (2011) Hepatoprotective activity of *Leucas cephalotes* spreng on CCl₄-induced hepatic injury in Wistar rats. Asian J Pharm Clin Res 4(3):106–109

88. Salari GJ, Daudhreivy A, Seth AK, Maheshwari R, Shah N, Aundhia C (2010) Hepatoprotective effect of *Leucas cephalotes* spreng on CCl₄ induced liver damage in rats. Pharmacology Online 1:30–38

89. Uluganathan I, Divya D, Radha K, Vijayakumar TM, Dhanaraju MD (2010) Protective effect of *Luffa acuangular* (Var) amara against carbon tetrachloride-induced hepatotoxicity in experimental rats. Res J Biol Sci 5(9):615–624

90. Willis PJ, Asha VV (2006) Protective effect of *Lygodium flexuosum* (L.) Sw. extract against carbon tetrachloride-induced acute liver injury in rats. J Ethnopharmacol 108:320–326

91. Chaudhary A, Bhandari A, Pandurangan A (2011) Hepatic activity of methanolic extract of *Madhuca indica* on carbon tetrachloride-induced hepatotoxicity in rats. Pharmacology Online 1:803–808

92. Patel PK, Sahu J, Prajapati NK, Dubey BK, Alia A (2012) Hepatoprotective effect of ethanolic and hydro alcoholic leaf extract of *Madhuca indica* in carbon tetrachloride intoxicated rat. Res J Pharmaco Pharmacodynamics 4(5):311–314

93. Ramakrishna S, Geetha KM, Bhaskargopal PVVS, Ranjit Kumar P, Charan Madav P, Umachandr L (2011) Effect of *Mallotus philippensis* Muell-Arag leaves against hepatotoxicity of carbon tetrachloride in rats. JPSR 2(2):74–83

94. Pramod K, Deval RG, Lakshmayya RSS (2008) Antioxidant and hepatoprotective activity of tubers of *Momordica tuberosa* Cogn. against CCl₄-induced liver injury in rats. Indian J Exp Biol 46:510–513

95. Bellaisoued S, Houssna AB, Athmouni K, Pelt J, Ayadi FM, Rebai T, Elfeki M (2015) Hepatoprotective and antioxidant activity of methanolic extract of flowers of *Nerium oleander* against CCl₄-induced liver injury in rats. Asian Jt J Trop Med 5(9):677–683

96. Abdus SS, Rahmat AK, Moustah A, Nawshad M (2016) Hepatoprotective and antioxidant activity of *Nicotiana plumaginifolia* Linn. against carbon tetrachloride-induced injuries. Toxicol Ind Health 32(2):292–298. https://doi.org/10.1177/0748233714504848

97. Ustuner D, Colak E, Dincer M, Tekin N, Donmez DB, Akyuz F, Colak E, Kolac UK, Entek D, Ustuner MC (2018) Post treatment effects of *Olea europaea* L. leaf extract on carbon tetrachloride-induced liver injury and oxidative stress in rats. J Med Food 00(0):1–6

98. Sikander M, Malik S, Parveen K, Ahmad M, Yadav D, Hafeez B, Bansal M (2013) Hepatoprotective effect of *Ostegaria vulgaris* in Wistar rats against carbon tetrachloride-induced hepatotoxicity. Protoplasma 250:483–493

99. Wills P, Daudhreivy A, Seth AK, Maheshwari R, Shah N, Aundhia C (2010) Hepatoprotective effect of *Ostegaria vulgaris* leaves against CCl₄-induced damage in rats. Afr J Tradit Complement Altern Med 7:237–244

100. Ezzat MM, Okba MM, Ahmed SH, El-Banna AP, Mohamed SO, Ezzat SM (2020) In vitro hepatoprotection of *Anacardium occidentale* seeds against carbon tetrachloride-induced acute liver damage in rats. Am J Pharm Res 10(5):378–392

101. Abdel Raouf GF, Sadi AA, Mohamed KY, Gomaa HA (2020) Phytoconstituents and bioactivities of the bark of *Pleuropogon timorensis* (DC) Leenh (*Anacardiaceae*). J Herbsmed Pharmacol 9(1):20–27

102. Jayakumar T, Ramesh E, Geraldine P (2006) Antioxidant activity of the oyster mushroom, *Pleurotus ostreatus*, on CCl₄ induced liver injury in rats. Food Chem Toxicol 44:1989–1996

103. Mahmud ZA, Bachor QC, Qais N (2012) Antioxidant and hepatoprotective activities of ethanolic extracts of leaves of *Peruna esculenta* Roxb against carbon tetrachloride-induced liver damage in rats. J Young Pharm 4(1). https://doi.org/10.4103/0975-1483-103460

104. Syed SN, Rizvi W, Kumar A, Khan AA, Moiin S, Ahsan A (2014) In vitro antioxidant and in vivo hepatic protective activity of leave extract of *Rhapontichristus nitavi* in rats using CCL₄ model. Afr J Tradit Complement Altern Med 11(3):102–106

105. Kalegari M, Gemin CAB, Araujo-silva N, de Brito NJ, Lopez JA, Tozzeto S, Almeida M, Migue IMD, Stien D, Miguel OG (2014) Chemical composition, antioxidant activity and hepatoprotective potential of *Rourea induta* planch (*Connaraceae*) against CCl₄-induced liver injury in female rats. Nutr 30:173–718

106. Rao GMM, Rao CV, Pushpangadan P, Shrivakar A (2006) Hepatoprotective effects of rubadin, a major constituent of *Rudia cordifolia* Linn. J Ethnopharmacol 103:484–490

107. Tukiaoppo NK, Londonkar RL, Nayaka HB, Kumar SCB (2015) Cytotoxicity and hepatoprotective attributes of methanolic extract of *Rumex vesicarius* L. Biol Res 48(19). https://doi.org/10.1186/s40659-015-0009-8

108. Sun ZL, Gao GL, Xia YF, Qiao ZY (2011) A new hepatoprotective saponin from *Semen celosia cristata*. Fitoterapia 82(4):591–594

109. Shahjahan M, Sabitha KE, Jainu M, Shyamala Devi CS (2004) Effect of *Solanium tuberosum* against carbon tetrachloride induced hepatic damage in albino rats. Indian J Med Res 120:194–198

110. Gupta RK, Hussain T, Panigrahi G, Das A, Singh GN, Sweety K, Faiyazuddin MD, Rao CV (2011) Hepatoprotective effect of *Solanium xanthocar- pum* fruit extract against CCl₄-induced acute liver toxicity in experimental rats. Asian Pac J Trop Med 4(12):964–968

111. Nwodu LL, Elmosry E, Oboma YI, Carter WG (2018) Hepatoprotective and antioxidant activities of *Spondias mombin* leaf and stem extracts against carbon tetrachloride-induced hepatotoxicity. J Taibah Univ Med Sci 13(3):262–271

112. Kokhdan EP, Ahmad K, Sadeghi H, Dadgary F, Danene N, Aghamali MR (2017) Hepatoprotective effect of *Stachys pilifera* ethanol extract
in carbon tetrachloride-induced hepatotoxicity in rats. Pharm Biol 55(1):1389–1393

119. Deng J-S, Chang Y-S, Wen C-L, Liao J-C, Hou W-C, Amagaya S, Huang S-T, Huang G-J (2012) Hepatoprotective effect of the ethanol extract of Vitis thunbergii on carbon tetrachloride-induced acute hepatotoxicity in rats through anti-oxidative activities. J Ethnopharmacol 142:795–803

120. Song A, Ko HJ, Lai MN, Ng LT (2011) Protective effects of Wu-Liang-Shen (Xylaria nigripes) on carbon tetrachloride-induced hepatotoxicity in mice. Immunopharmacol Immunotoxicol 33(3):453–460

121. Oke GO, Abiodun AA, Imafidon CE (2019) Zingiber officinale (Rosco) mitigates CCl4-induced liver histology and biochemical derangements through antioxidant, membrane-stabilizing and tissue-regenerating potential. Toxicol Rep 6:416–425

122. Shen X, Tang Y, Yang R, Yu L, Fang T, Duan J (2009) The protective effect of Zizyphus jujube fruit on carbon tetrachloride-induced hepatic injury in mice by anti-oxidative activities. J Ethnopharmacol 122:555–560

123. Chang L, Xu D, Zhu J, Ge G, Kong X, Zhou Y (2020) Herbal therapy for the treatment of acetaminophen-associated liver injury: recent advances and future perspectives. Front Pharmacol 11:313. https://doi.org/10.3389/fphar.2020.00313

124. Stickel F, Shouval D (2015) Hepatotoxicity of herbal and dietary supplements: an update. Arch Toxicol 89(6):851–865

125. Janghel V, Patel P, Chandel SS (2019) Plants used for the treatment of icterus (jaundice) in Central India: A review. Ann Hepatol 18:658–672

126. Zhu J, Chen M, Borlak J (2019) The landscape of hepatobiliary adverse reactions across S3 herbal and dietary supplements reveals immunemediated injury as a common cause of hepatitis. Arch Toxicol 94(1):273–279

127. Shakya AK (2020) Drug-induced hepatotoxicity and hepatoprotective medicinal plants: a review. Indian J Pharm Edu Res 54(2):234–247

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