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Systematic Review

Traditional Medicinal Plants with Significant Protection Against Antitubercular Drug-induced Liver Injury: A Systematic Review

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Abstract

Background and objectives: Tuberculosis remains a global health concern, and its treatment usually involves potent first-line antitubercular drugs which are tempered by the risk of associated hepatotoxicity leading to noncompliance and drug resistance. In this review, medicinal plants with the potential of protection against antitubercular drug-induced hepatotoxicity in animal models were explored from scientific literature.

Methods: From literature published between 1999 and 2022, this review systematically extracted 68 studies that reported on medicinal plants with protection against antitubercular drug-induced liver toxicity in animal models.

Results: Isoniazid, pyrazinamide, rifampicin, and ethambutol were the first-line drugs reported in the reviewed studies. The liver enzymes, antioxidant status, inflammatory markers, and improvement in the liver architecture were the criteria most frequently used by the reported studies to access hepatoprotection. These plants are rich in bioactive phytochemicals which exhibit their hepatoprotective properties via mechanisms such as antioxidant activity, anti-inflammatory effects, and detoxification enhancement.

Conclusions: This review provides the hepatoprotective properties and mode of action of medicinal plants and encourages future perspectives marked by rigorous scientific research, clinical trials, and integrative medicine approaches. Albeit the challenges of standardization of herbal formulation, safety concerns and hurdles of the regulatory framework must be addressed as traditional medicinal plants offer a promise to mitigate antitubercular drug hepatotoxicity.

Keywords: Antitubercular drugs; Medicinal plants; Hepatoprotective; Toxicity.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; ARE, antioxidant response element; AST, aspartate transaminase; ATD, antituberculosis drug; ATPase, adenosine triphophatase; BALB/c, Bagg albino cold spring mice; CAT, catalase; COX-2, cyclo-oxygenase-2; CCl_4, carbon tetrachloride; CNS, central nervous system; ETM, ethambutol; GcLc, Glutamate-cysteine ligase catalytic subunit; GGT/GGTP, gamma glutamyl transpeptidase; GPx, gluthathione peroxidase; GR, gluthathione reductase; GSH, gluthathione; GSR, glutathione reductase; GST, gluthathione s-transferase; G6Pase, glucose 6-phosphatase; G6PDH, glucose-6- phosphate dehydrogenase; HDL, high density lipoprotein; HMOX1, heme oxygenase 1 gene; IL, interleukin; INH, isoniazid; Keap l, Kelch-like ECH-associated protein 1; LDH, lactate dehydrogenase; LPx, lipid peroxide; LPO, lipid peroxidation; MDA, malondialdehyde; NADPH, nicotinamide adenine dinucleotide phosphate; NADH, nicotinamide adenine dinucleotide; NK cells, natural killer cells; Nrf2, nuclear factor erythroid 2-related factor 2; PPIX, protoporphyrin IX; PZA, pyrazinamide; RIF, rifampicin; ROS, reactive oxygen species; SOD, superoxide dismutase; TAC, total antioxidant capacity; TB, tuberculosis; TBARS, thiobarbituric acid reactive substance; TMP, traditional medicinal plant; TNF-α, tumor necrosis factor-alpha; TP, total protein.

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Introduction

Tuberculosis (TB) remains a lethal communicable ailment of global public health concern despite the intensified research to understand and eradicate it.[1–3] In 2021, about 10.6 million people were estimated to fall ill with TB worldwide with the incident rate rising by 3.6% between 2020 and 2021 with eight countries having two-thirds of the disease's global burden.[4,5] The emergence of drug resistant TB continues to undermine the gains of global eradication efforts and as such TB has remained a public health scourge. This scenario is worsened by the reliance on a limited number of antitubercular drugs (ATDs) for decades, though there are about 26 drugs that are in various phases of trials as of September 2022.[4] In order to curtail the emergence of ATD resistance, modern TB control strategy relies mainly on the use of combination therapy.

Thus, the World Health Organization recommends that effective standard treatment of TB should go with a combination therapy of some of the first-line ATDs.[6] The first-line drugs of choice include isoniazid (INH), pyrazinamide (PZA), rifampicin (RIF), ethambutol, and streptomycin. These first-line medications are documented to induce mild to severe liver injury leading to the discontinuance of treatment that give rise to drug resistance and a cure not being achieved.[7] For instance, RIF causes thrombocytopenia, pain, nausea, and hepatitis in combination with other drugs; PZA leads to oxidative stress, arthralgia, and hepatitis through the 5-hydroxypyrazinoic acid; neuritis and color blindness are linked to ethambutol toxicity; while ethionamide leads to diarrhea and hepatotoxicity.[8,9] Collectively, these ATDs elicit toxic metabolites, free radicals and reactive oxygen species (ROS) to become the main cause of injury to the liver.[10] Studies are in progress to find alternate medications from plant sources to avoid such side effects.[9] The use of combination therapy can cause drug-drug interactions that affect metabolism, treatment, and toxicity in the individual.[11] More so, factors such as acetylator status, drug-drug interactions, body mass index, sex, age, and alcohol consumption have made it difficult to foretell the event of drug-induced liver injury due to the administration of ATD.[12]

The incidence of drug-induced hepatotoxicity varies among the different regions of the world while the bulk of epidemiological studies were reported in Europe, Asia, and the USA.[13] The percentage is greater in developing countries compared with the developed ones. The mixture of RIF/ INH/PZA has been reported to cause up to 30% of hepatotoxicity in India, while this percentage is 23% in other countries.[13] In Sub-Saharan Africa, the incidence of hepatotoxicity has not been reported but this type of study has also been conducted.[7,14] Yearly, the incidence rate of drug-induced liver damage is increasing.[15,16] In China, among the drugs that cause liver injury, 21.99% of incidences are from antituberculosis drugs.[17] The combined or single administration of INH and RIF can lead to liver damage, causing liver failure, resulting in 5%–22% of acute liver failure cases.[18] In a study, the combination of INH and RIF therapy for TB treatment was associated with 2–6% hepatotoxicity.[19]

The liver is continuously exposed to diverse toxic and chemotherapeutic agents due to its key role in xenobiotic metabolism. This chronic exposure damages liver cells and impairs their ability to function.[13,20] Collectively, these ATDs produce toxic metabolites, free radicals, and ROS, which are the main causes of liver injury.[10] The mechanism of ATD-induced hepatotoxicity is not yet clearly understood but is believed to result from the initial events of phase I or phase II metabolism.[10] The initial event is typically the generation of a reactive drug metabolite. The buildup of toxic metabolites causes an excessive amount of ROS and metabolite-protein adducts, which causes lipid peroxidation, a stress response in the mitochondria and endoplasmic reticulum, and the activation of stress-kinases. The loss of hepatocyte membrane integrity and depletion of antioxidant status leaves the hepatocytes vulnerable to ATD-induced hepatic damage.[14,21,22] These events eventually cause cellular damage and apoptotic cell death.[23]

The risk of patients developing drug-induced liver injury is of primary concern in the treatment of TB,[24] which also leads to nonadherence to the treatment regimen and the attendant drug resistance. In order to mitigate these arrays of adverse effects of ATDs, plant-derived phytochemicals are being explored to determine their hepatoprotective potentials without interfering with the action of these ATDs. More so, studies are in progress to find alternate medications from plant sources without significant side effects.[9] Plant-derived phytochemicals have unique benefits in improving patient symptoms, lowering the risk of liver injury, delaying the progression of liver injury, and enhancing the body's ability to repair itself.[25] They likewise possess the features of multilevel, multitarget, and broad regulation.[16] Plant extracts containing bioactive compounds have demonstrated a protective effect against liver damage caused by INH and RIF.

Because of the threat that TB poses to public health, a lot of emphasis has been placed on developing complementary traditional herbal treatments that are effective against *Mycobacterium* TB. Prior to this review, some publications recapped the role of medicinal plants as a source of ATDs and ATD-induced hepatotoxicity.[10,26–30] Among the several studies on the protective effects of crude extracts and bioactive compounds isolated from plants against hepatotoxicants (acetaminophen, ethanol, carbon tetrachloride, methotrexate and valproate), only a fraction of these studies focus on the protective role of traditional medicinal plants (TMPs) against ATD-induced liver toxicity. In this present review, the primary focus is the use of TMPs with reported hepatoprotective potential against ATD-induced toxicity in animal models. Also included is a brief description of the botanical classification, the plant component used, the method of extraction, and the traditional and pharmacological properties. Next, *in vivo* studies on these reported hepatoprotective plants are described with the following headings: the extract dose/mode of administration, the animal model, the ATD combinations, the mode of action of the plant extracts, and the reported phyto-active components. The hepatoprotective mechanisms of the plant extract reviewed were highlighted. Finally, we discussed the role of phytochemicals in the hepatoprotective properties of TMPs and future research trends. With the large number of reported medicinal plants with hepatoprotective potentials, this review will generate interest in the identification and development of new compounds derived from plants that may have clinical significance.

Methods

The information presented was derived from scientific papers published in English or French that were obtained from the Internet search engines Google, Google Scholar, PubMed/Medline, and Scopus. An in-depth search was undertaken on the hepatoprotective effect of extracts and/or compounds obtained from TMPs against liver injury induced by ATDs (RIF/INH/PZA/ethambutol (ETM) or combinations) in experimental animal models. We used the following keywords: medicinal plant, protective effect, hepatoprotective effect, ATD toxicity, RIF/INH/PZA/ETM-induced liver/hepatotoxicity and phytochemical compounds. To obtain a higher quality of screening literatures, we further searched each keyword with one drug and with their different combinations. For inclusive search, the search employed the terms including "herbal plant extract AND antituberculosis drugs" or "antituberculosis drugs AND liver damage," or "RIF/INH/PZA/ETM AND plant extract" or "hepatoprotection/ plant extract AND antitubercular drug-induced liver damage" in rat from 1990 to 2023. After excluding duplicate and unrelated studies, the articles identified from search engines were reviewed by two persons and a decision was taken. The articles were screened for studies on paracetamol, carbon tetrachloride, or any other hepatotoxic substance–induced liver damage and these were excluded. Poly herbal formulations, *in vitro* studies, studies not mentioning the animal model and nephrotoxic studies were further excluded. The screening processes for inclusion included only studies on single plant extract with reported hepatoprotection against ATD-induced liver damage. Also, the inclusion

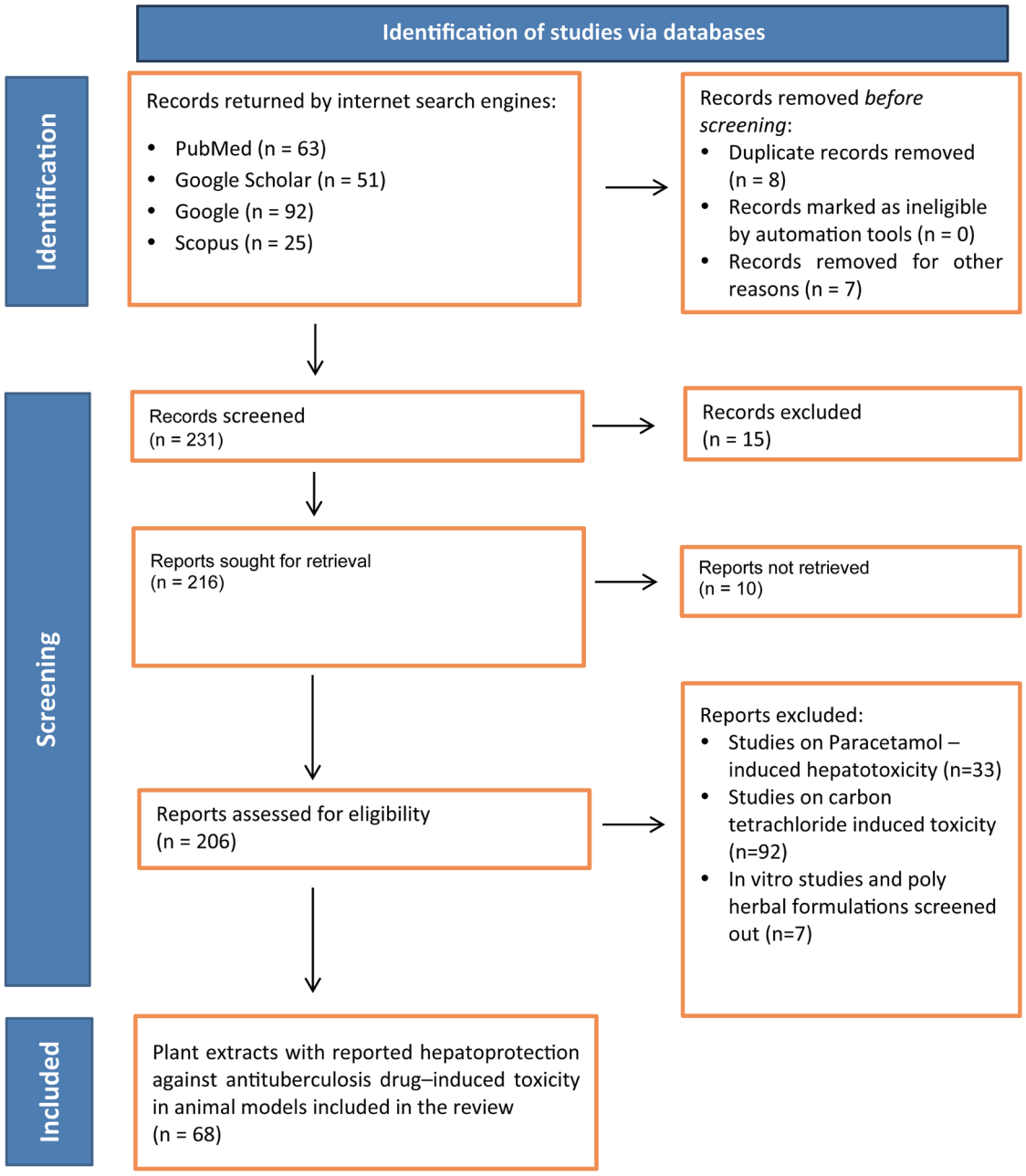

Fig. 1. PRISMA flow diagram.

criteria included botanical name, plant family, experimental design, animal model, extraction method, mode of administration of extract, and results clearly stated. Finally, a total of 68 scientific publications were included and used in the review. The PRISMA flow diagram on the process of exclusion, inclusion, and search strategy is presented in Figure 1.

Results

Hepatoprotective medicinal plants

The classification of the traditional hepatoprotective medicinal plants against anti-TB drugs in this study belongs to 48 families and 67 species. The top eight families with at least three plant species include *Asteraceae* (three species), *Curcurbitaceae* (three species), *Euphorbiaceae* (five species), *Nyctaginaceae* (four species), *Ranunculaceae* (three species), and *Zigiberaceae* (three species). Thirty-three plant families were reported once in this study while 5 plant families were reported twice (Table 1).[31–96] The hepatoprotective TMP species were reported from different parts of the plants including leaves, stem, root, aerial, fruits, bulbs, rhizomes, dry peel, seeds, root, tuber, whole plant, flower (petals), shoot and stem bark. From Table 1 the major parts of the plants that were studied were leaves (19 studies), root (9), fruit (8), whole plant (5),

Table 1. List of traditional plants with hepatoprotective potential against antituberculosis drug-induced toxicity

s/n	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
1	*Acanthospermum hispidum*	*Asteraceae*	Whole plant (ethanol)	Treatment of constipation, fever, jaundice, malaria, stomach ache, and viral infections	Hepatoprotective, antimicrobial, antiplasmodial, antidiarrheal, antitumor, antidiabetic, anthelmintic, and antioxidant activities	31
2	*Alchornea cordifolia* (Shum & Thon)	*Euphorbiaceae*	Leave (methanol)	The roots of the plant are used to treat venereal diseases, amoebic dysentery, and diarrhea. It is used to make drops to cure eye diseases like conjunctivitis	Antiinflammation, anticancer, antioxidant, antidiarrheal, antimicrobial, hepatoprotective, and antiplasmodial effects	32
3	*Allium sativum*	*Amaryllidace*	Bulbs (aqueous)	Used as nutraceuticals. Treatment of asthma, cold, diabetes, and paralysis	Antidiabetic, anticancer, antioxidant, immune modulation activities, and lowering of blood pressure	33
4	*Allium sativum*	*Amaryllidace*	Garlic tablets (aqueous)	Used as nutraceuticals. Treatment of asthma, cold, diabetes, and paralysis	Antimicrobial, hypocholesterolemic, antihypertensive, antirheumatic, anticancer effects	34
5	*Allium sativum*	*Amaryllidace*	Bulbs (aqueous)	Used as nutraceuticals. Treatment of asthma, cold, diabetes, and paralysis	Antibiotic, antioxidant, anticancer, immunomodulatory, anti-inflammatory, hypoglycemic, and antidiabetic, activities	35
6	*Aloe vera*	*Asphodelaceae (Liliaceae)*	Whole plant	Treatment of Alopecia, bacterial and fungal skin infections, chronic leg wounds, parasitic infections, systemic lupus erythematosus, and arthritis	Wound healing, anti-inflammatory, antitumor, laxative, antidiabetic, anticancer, antimicrobial, antioxidant, and antiviral activities	36
7	*Amaranthus graecizans subsp Silvestris*	*Amaranthaceae*	Whole plant (90 % methanol)	Treatment of inflammation, sore throat, immune booster, relieve of joint pain Used to treat piles and gonorrhea	Antioxidant, analgesic, and anti-inflammatory, anticholinesterase, and anti-protease activities	37
8	*Anacylus pyrethrum (Linn)*	*Asteraceae*	Root (ethanol)	Used as a tonic to rejuvenate the nervous system, treatment of epilepsy, paralysis, toothache, and rheumatism	Immunostimulator, anti-inflammatory, antibacterial, insecticidal, antidiabetic, aphrodisiac, and antioxidant activities	38
9	*Annona squamosa (Linn)*	*Annonaceae*	Leaves (methanol)	Treatment of fever and chills, dysentery, internal and external parasites, and as a sedative	Insecticidal agent, anthelmintic, antigenotoxic, free radical scavenger, hepatoprotective, hypoglycemic, antidiabetic, antibacterial, antitumor, and antimalarial, activities	39
10	*Artemisia vulgaris L*	*Asteraceae*	Leaves (aqueous)	Treatment of asthma, itching, menstrual pains, fever, rheumatism, and gout	Antimicrobial, anti-inflammatory, antimalarial, antioxidant, hypolipidemic, analgesic, hypotensive, antispaspolytic, antihelminthic, antifungal, and broncholytic properties	40
11	*Asparagus racemosus*	*Asparagaceae*	Root (95% methanol)	Used as a galactagog, aphrodisiac, diuretic, nerve tonic, and antispasmodic	Antioxidant, tetratogenicity, antistress, antidiarrheal, anti-ulcerogenic, and cardioprotection, properties	41

(continued)

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Table 1. *(continued)*

s/n	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
12	*Asteracantha longifolia (Nees)*	*Acanthaceae*	Aerial (95% ethanol)	Treatment of jaundice, hepatic obstruction, rheumatism, inflammation, pain, urinary infections, edema, and gout	Antitumor, hypoglycemic, antibacterial, antioxidant, hepatoprotection and hematopoietic activities	42
13	*Azadirachta indica (Neem)*	*Meliaceae*	leaves (Aqueous)	Used as an insecticide, but also for cosmetic, treatment of dental, and gastrointestinal disorders, malaria fevers, skin diseases, and as an insect repellent	Anti-inflammatory, antipyretic, antimicrobial, antioxidant, antidiabetic, hepatoprotection against paracetamol –induced liver damage, antiangiogenic, immunomodulatory, and apoptotic properties	43
14	*Bacopa monnieri*	*Scrophulariaceae*	Commercial *B monnieri* extract powder Bacoside –A (aqueous)	Used to improve loss of memory, reducing anxiety, treating epilepsy, allergic conditions, irritable bowel syndrome, and as a general tonic to fight stress	Antidepressant, antioxidant, anti-inflammatory, antimicrobial, antidiabetic, hepatoprotection against alcohol-CCl_4 induced hepatotoxicity	44
15	*Boerhaavia diffusa L*	*Nyctaginaceae*	Leaves (aqueous)	Used as a remedy in jaundice, hepatitis, edema, oligurea, anemia, inflammation, and eye diseases	Hepatoprotective, diuretic, anti-inflammatory, antistress, immunomodulation, antifertility, antimicrobial, antiviral, insecticidal, anticonvulsant, and antioxidant, activities	45
16	*Bombax ceiba Linn*	*Bombacaceae*	Flower (methanol)	For the treatment of numerous ailments like algesia, hepatotoxicity, hypertension, fever, dysentery, inflammation, catarrhal affection, ulcer, acne, gynecological disorders, piles, and urinary infections	Hypotensive, antioxidant, analgesic, anti-inflammatory, antipyretic, antiangiogenic, anti- bacterial, cytotoxic, hepatoprotective, diuretic, anthelmintic, anticancer, spermatogenic, and antihelicobacter pylori activities	46
17	*Cassia auriculata L*	*Caesalpiniaceae*	Root (methanol)	Treatment of skin diseases, asthma, conjunctivitis, renal disorders, liver ailments, anthelmintic, antiulcer, skin diseases, and leprosy. Used in rheumatoid arthritis, diarrhea, ringworm, skin diseases, dysentery, and as laxatives	Antioxidant, antidiabetic, immunomodulatory, hepatoprotective, anthelmintic, antibacterial, and neuroprotective effects	47
18	*Cassia fistula (Amaltas)*	*Casesalpinaceae/ leguminasae*	Leaves (ethanol)	Used as a laxative, purgative, and in wound healing	Antipyretic, analgesic, antitumor, hepatoprotective, antifertility, and antioxidant effects	48
19	*Centella asiatica*	*Umbellifere (Apiceae)*	Leaves	Wound healing, treatment of jaundice, various skin conditions like leprosy, lupus, varicose ulcers, eczema, psoriasis, diarrhea, fever, and amenorrhea	Hepatoprotection against CCl_4, wound healing, antidepressant, antiepileptic, cognitive, antioxidant, antiulcer, antinociceptive, and anti-inflammatory activities	49

(continued)

Table 1. *(continued)*

s/n	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
20	*Cissampelos pareira L*	*Menispermaceae*	Root (hydroalcohol)	Treatment of cough, dysentery, dyspepsia, diarrhea, dropsy, and calcular nephritis	Astringent, diuretic, analgesic, antipyretic, anti-inflammatory, antihistaminic, hypotensive, antispasmodic, hypoglycemic, anti-SARS-CoV-2 activity *in vitro*, and anticonvulsant properties	50
21	*Citrus sinensis L Osbeck*	*Rutaceae*	Dry peel (90% ethanol)	Treatment of constipation, cramps, colic, diarrhea, bronchitis, tuberculosis, cough, cold, anxiety, and depression	Anti-inflammatory, antibacterial, antioxidant, antidiabetic, anticholesterol, antibacterial, hepatoprotection against CCl_4, antifungal, antiparasitic, and antiproliferative activities	51
22	*Cnidoscolus chayamansa (McVaugh)*	*Euphorbiaceae*	Leaves and stem ($CHCl_3$:MeoH)1:1	Treatment of diabetes, rheumatism, gastrointestinal disorders, weight control, and vaginal infection	Anti-inflammatory, antiprotozoal, antimycobacterial, gastroprotective, cardioprotective, antioxidant, and hepatoprotection	52
23	*Cnidoscolus chayamansa (Mc Vaugh)*	*Euphorbiaceae*	Leaves (ethanol)	Treatment of diabetes, kidney stones, hemorrhoids, obesity, acne, and eye problems. Also used as a laxative, diuretic, and to stimulate lactation	Anti-inflammatory, antiprotozoal, antimycobacterial, gastroprotective, cardioprotective, antioxidant, and hepatoprotective properties	53
24	*Crocus sativus L*	*Iridaceae*	Petals (90 % ethanol)	Treatment of asthma, cough, whooping cough, insomnia, flatulence, pain, and heartburn. Also used as a spice, yellow food coloring, and as a flavoring agent	Antihypertensive, neuroprotective, aphrodisiac, antioxidant, antinoceptive, and anti-inflammatory activities	54
25	*Cucumis trigonus Roxb*	*Cucurbitaceae*	Fruit (ethanol)	Fruit used in treatment of leprosy, diabetes, jaundice, and abdominal pain	Antidiabetic, cardioprotective, analgesic, anti-inflammatory, diuretic, and hepatoprotective activities	55
26	*Curcuma longa*	*Zigiberaceae*	–	Used for the treatment of chronic diseases like diabetes mellitus, dermatological infection, and depression	Anti-inflammatory, antioxidant, antimutagenic, antitumor, antifungal, antiviral, antibacterial, antispasmodic, and hepatoprotective activities	56
27	*Curcuma longa*	*Zigiberaceae*	Rhizome	Used for the treatment of chronic diseases like diabetes mellitus, dermatological infection, and depression	Anti-inflammatory, antioxidant, antimutagenic, antitumor, antifungal, antiviral, antibacterial, antispasmodic, and hepatoprotective activities	57
28	*Embelia tsjeriam-cottam*	*Myrsinaceae*	Fruit (alcohol, aqueous)	Treatment of piles and jaundice. Used as a carminative	Anthelmintic, anti- inflammatory, hepatoprotective, antidiabetic, antioxidant, 'anticancer, antitubercular, and antibacterial activities	58
29	*Emblica officinalis*	*Euphorbiaceae*	–	Relieving cough and skin diseases	Antidiabetic, cytoprotective, antiulcerogenic, immunomodulatory, antioxidant, and anticataractogenic effects	59

(continued)

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Table 1. *(continued)*

s/n	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
30	*Erythrina indica Lam*	*Papilionaceae*	Leaves (95% methanol)	Leaves are used as laxative, diuretic, emmenagogue, galactagog. Treatment of worm infections, liver disorders, and joint pains	Antiosteoporetic, cytotoxic, cardiovascular, anthelmintic, analgesic, antiulcer, antioxidant, and diuretic activities	60
31	*Eucleana talensis A,DC*	*Ebenaceae*	Shot (95% ethanol)	Treatment of chest pains, bronchitis, pleurisy, and asthma. Treatment of diabetes, diarrhea, malaria, roundworms, stomach problems, toothache, venereal diseases, and wounds	Antibacterial, antidiabetic, antifungal, antimycobacterial, antiviral, antioxidant, antiplasmodial, larvicidal, antischistosomal, molluscicidal, and hepatoprotective activities	61
32	*Ficus religiosa*	*Moraceae*	Leaves (methanol)	Treatment of ulcer, wounds, as astringent, and tonic to treat disease Treatment of inflammation and diabetes	Anticonvulsant, antidiabetic, hepatoprotective, antibacterial, antihelminthic, immunomodulatory, antioxidant, wound healing, hypolipidemic, and hypoglycemic activities	62
33	*Hemidesmus indicus*	*Apocynaceae*	Root (ethanol)	Used as a blood purifier and to cure fever, leprosy, rheumatism, snake bite, and to treat liver disorders	Antidiarrheal, anti-inflammatory, wound healing, hepatoprotective, antivenom, antimicrobial, anticancerous, antiarthritic, and antileprotic activities	63
34	*Hibiscus vitifololius (Linn)*	*Malvaceae*	Root (methanol, chloroform, petroleum, water)	Treatment of jaundice, head lice, inflammation, and pulsating anterior fontanalle	Anti-inflammatory, hypoglycemic, antibacterial, and antioxidant properties	64
35	*Lasianthera africana*	*Icacinaceae*	Leaves (hot aqueous)	Treatment of hepatitis, inflammation, diabetes, and hypertension. Management of diarrhea, malaria, ulcers, constipation, and aches	Analgesic, antipyretic, antimalarial, antiulcerogenic, antimicrobial, antidiabetic, and antioxidant activities	65
36	*Lawsonia inermis*	*Lythraceae*	Leaves (aqueous Na_2CO_3)	Used as cosmetic agent for both skin and hair Used as antiseptic and antipyretic in traditional medicine Used to treat jaundice, leprosy, small pox, chicken pox, and tumors	Antibacterial, antifungal, antitumor, hepatoprotective, anti-inflammatory, antiapoptotic, antihyperglycemic, antilipidemic, and antiviral, effects	66
37	*Leucas cephalotes*	*Lamiaceae*	Whole plant (methanol)	Remedy for snake bite, cough, fever scorpion stings, liver disorders, jaundice, asthma, and cough cold	Hepatoprotection against CCl_4, antiprotozoan, antioxidant, antidiabetic, and antimicrobial activities	67
38	*Luffa acutangula*	*Cucurbitaceae*	Fruits (70 % ethanol)	Treatment of jaundice, biliousness, bronchitis, and asthma	Central nervous system depressant, antioxidant, and larvicidal activities	68
39	*Maytenus royleans*	*Celastraceae*	Leaves (methanol)	Treatment of gastrointestinal disorders Microbial infection, analgesic, gastric ulcers, inflammation problems and allergy	Anti-inflammatory, antioxidant, hepatoprotective, and anticancer activities	69

(continued)

Table 1. *(continued)*

s/n	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
40	*Menthe peprita L*	*Lamiaceae*	Leaves (90% ethanol)	Alleviating nausea, flatulence, and vomiting. Treatment of cold, fever, digestive and throat inflammation	Antioxidant, antimicrobial, antiviral, anti-inflammatory, biopesticidal, larvicidal, anticancer, radioprotective and antidiabetic activities	70
41	*Millettiapulchra (Benth) Kurz Var Laxio (Dunn)ZWei*	*Fabaceae-papilionoideae*	Root (aqueous)	Used for hepatic protection, treatment of neurological, and cardiovascular diseases	Antioxidant, and hepatoprotection against CCl_4 in mice	71
42	*Mirabilis jalapa Linn*	*Nyctaginaceae*	Leaves (ethanol)	Treatment of diarrhea, dysentery, conjunctivitis, edema, inflammation, swelling, muscular pain, and abdominal colic	Antibacterial, antiviral, antifungal, antispasmodic, and antinoceptive effects	72
43	*Monotheca buxlfolia*	*Sapotaceae*	Fruits (70% ethanol)	Used as helmanthinic, laxative, purgative, vermicidal, antipyretic, and in the management of gastro-urinary ailments	Antioxidant, antipyretic, CNS depressant, anti-inflammatory, anthelmintic, and antinociceptive activities	73
44	*Moringa oleifera Lam*	*Moringaceae*	Leaves (95% ethanol)	Treatment of inflammation, cardiovascular action, liver diseases, hematological, and hepatorenal disorders	Antileishmanial, antiviral, antimicrobial, antitrypanosomal, antioxidant, anti-inflammatory, anticancer, antitumor, hypotensive, antiulcer, antidiabetic, and hypocholesterolemic properties	74
45	*Mucuna pruriens*	*Fabaceae*	Leaves (50% ethanol)	Treatment of Parkinson's diseases, edema, impotence, diarrhea, snake bite, cough, tuberculosis, rheumatic disorders, muscular pain, gout, menstrual disorder and diabetes. Prophylactic oral antisnake remedy and treatment of anemia	Diuretic, antimicrobial, anti-infertility, anticataleptic, antiepileptic, antidiabetic, antioxidant, and cardioprotective effects	75
46	*Nigelia sativa Linn*	*Ranunculaceae*	Seed (70% ethanol)	Treatment of fungal infection and inflammation	Antifungal, antioxidant, genoprotective, anti-inflammatory, and antineoplastic effects	76
47	*Nigella sativa (black seeds)*	*Ranunculaceae*	Seeds (aqueous)	Widely used as antihypertensive, liver tonics, diuretics, digestive, antidiarrheal, appetite stimulant, analgesics, antibacterial, and in skin disorders	Anti-inflammatory, anti-angiogenesis, hepato-protective, gastroprotective, immunomodulatory, analgesic, anticancer, antidiabetic, antioxidant, antischistosomiasis, antifungal, and antibacterial effects	77
48	*Nigella sativa*	*Ranunculaceae*	Seed	Widely used as an antihypertensive, liver tonic, diuretic, digestive, antidiarrheal disorders, appetite stimulant, analgesic, and for antibacterial and skin disorders	Immunopotentiation, antihistamine, antidiabetic, antihypertensive, anti-inflammatory, and antimicrobial effects	57

(continued)

Table 1. *(continued)*

s/n	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
49	*Nymphaea alba Linn*	*Nymphaeaceae*	Flower (ethanol)	Treatment of anxiety, insomnia	Anti-inflammatory, astringent, antiscrophulatic, cardiotonic	78
50	*Ocimum sanctum*	*Lamiaceae*	–	Treatment of asthma, fever, colds, cough, malaria, dysentery, diarrhea, arthritis, emetic syndrome, and insect bites	Hypoglycemic, immunomodulatory, analgesic, antipyretic, anti-inflammatory, antiulcerogenic, antihypertensive, central nervous system depressant, hepatoprotective, chemopreventive, radioprotective, antitumor, and antibacterial activities	56
51	*Origanum vulgare*	*Lamiaceae*	Leaves (90% ethanol)	Used as a food preservative, treatment of digestive disorders, headaches, sore throat and as a digestive stimulant, antispasmodic, calmative, carminative, diaphoretic, expectorant	Antioxidant, antimicrobial, antiviral, anti-inflammatory, antispasmodic, antiurolithic, antiproliferative, and neuroprotective activities	70
52	*Pergularia daemia(Forssk) Chiov*	*Asclepiadaceae*	Leaves (70% ethanol)	Treatment of liver disorders, diabetes, and fungal infection	Antioxidant property	79
53	*Phyllanthus debilis*	*Euphorbiaceae*	Whole plant (100% ethanol)	Treatment of ailments such as liver complications, diabetes mellitus and skin diseases Used as remedy for jaundice and diarrhea	Hypoglycemic, anticancer, anti-inflammatory, antioxidant, antiglycation, and hepatoprotective activities	80
54	*Picrorhiza Kurroa Royle ex Benth*	*Scrophulariaceae*	Rhizomes and roots (ethanol)	Treatment of jaundice, anemia, abdominal pains, heart problems, and viral hepatitis	Antioxidant, immunomodulatory, anti-inflammatory, antimicrobial, antidiabetic, anti-asthmatic, nephroprotective, hepatoprotective, analgesic, cardioprotective, and anticancer effects	81
55	*Pimpinella anisum*	*Apiaceae (Umbelliferae)*	Leaves (90% ethanol)	Used as analgesic in migrane, as a carminative, disinfectant, as diuretic, treatment of epilepsy and seizures	Antibacterial, antifungal, anticonvulsant, antiulcer, antibacterial, and antioxidant properties	70
56	*Pisonia aculeata*	*Nyctaginaceae*	Leaves (95% methanol)	Treatment of liver diseases, inflammation, swelling, cough, and tumors	Anti-inflammatory, analgesic, antioxidant, and hepatoprotective effects	82
57	*Punica granatum*	*Punicaceae*	Fruit (70% acetone)	Treatment of diarrhea, sore throat, cough, urinary infections, digestive disorders, arthritis, and as a worm expeller	Anthelmintic, antidiabetic, antidiarrheal, antibacterial, antifungal, antiatherogenic and antihepatotoxic activities	83
58	*Saccharum officinarum L (sugar cane juice)*	*Poaceae*	Stem (juice)	Remedy for arthritis, bedsores, boils, cancer, colds, cough, diarrhea, dysentery, fever, hiccups, inflammation, laryngitis, and sore throat	Antioxidant, anticancer, antiproliferative, cholesterol lowering and antiplatelet effects, analgesic, antihepatotoxic, antihyperglycemic, diuretic, anti-inflammatory, and antithrombotic activities	84

(continued)

Table 1. *(continued)*

s/n	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
59	*Sagittaria sagittifolia polysaccharide*	*Alismataceae*	Root tuber (aqueous)	Treatment of wounds and sores	Antioxidant, antimicrobial, anti-inflammatory, antitumor, antiscorbutic, diuretic, immunomodulatory, antidiarrheal, antiseptic, anthelmintic, and antiviral activities	85
60	*Solanum xanthocarpum*	*Solanaceae*	Fruit	Antihelmintic and antipyretic Used in wound healing, as a laxative, treatment of liver enlargement, asthma, and aphrodisiac	Antispasmodic, cardiotonic, hypotensive, antianaphylactic, anti-urolithiatic, natricuretic, anticancer, antinoceptive, antioxidant, and hypoglycemic activities	86
61	*Spirulina fusiformis*	*Pseudomonadaceae*	Commercial Spirulinafusiformis extract powder	Wound healing, remedy for digestion and weight loss Used to increase hair growth	Antitumor, hepatoprotective, metalloprotective, radioprotective, antimicrobial, and anti-inflammatory effects	87
62	*Spirulina maxima*	*Oscillatoriaceae*	Whole plant	Used as a food supplement	Antidiabetic, anti-inflammatory, antiviral, and anticancer activities	88
63	*Tamarindus indica Linn*	*Leguminosae(Fabaceae)*	Fruit (aqueous)	Treatment of digestive disorders, wound healing, abdominal pain, diarrhea, dysentery, constipation, and cough. Used as a blood tonic	Antioxidant, antimicrobial, antidiabetic, anthelmintic, anti-inflammatory, analgesic, antivenom, immunomodulatory, antidiarrheal, anti- dysentery, wound healing, hepatoprotective, anti-emetic, antihistaminic, antipyretic, and antimalarial activities	89
64	*Tamarindus indica Linn*	*Leguminosae (Fabaceae)*	Stem bark (ethanol)	Treatment of jaundice and other liver diseases	Antibacterial, antidiabetic, antifungal, anti-inflammatory, antimalarial, and antioxidant activities	90
65	*Tamarix gallica*	*Tamaricaceae*	Leaves	Used as a prophylactic and therapeutic remedy for malaria, leucodema, eye diseases, and spleen trouble It has expectorant, laxative, astringent, diuretic, antigingivitis, antihemorrhoidal, antidiarrheal, and antidysentery uses	Antioxidant, antimicrobial, antimalarial, laxative, expectorant, antidiarrheal, anthelmintic, antihemorrhoid, astringent, inhibitor of nephrolithiasis, diuretic, hepatoprotective, antioxidant, antihyperlipidemic, antinociceptive, antidiarrheal, anticancer, and antimicrobial activities	91
66	*Telfairia occidentalis*	*Cucurbitaceae*	Fruit pulp (aqueous)	Used as a hematic, treatment of jaundice, pulp juice serves as an antidote against poison	Antioxidant, antimicrobial, hepatoprotective, anti-inflammatory, immunomodulatory, anticancer and hypoglycemic effects	92

(continued)

Table 1. *(continued)*

s/n	Botanical name	Family	Plant part/extract	Folkloric use	Pharmacological use	Reference
67	*Terminalia chebula*	*Combretaceae*	Fruit (95% ethanol)	Used in the treatment of dementia, constipation, diabetes, asthma, sore throat, vomiting, hiccup, diarrhea, dysentery, bleeding piles, ulcers, gout, heart and bladder diseases	Antioxidant, antimicrobial, antidiabetic, hepatoprotective, anti-inflammatory, antimutagenic, antiproliferative, radioprotective, cardioprotective, antiarthritic, anticaries, gastrointestinal motility, and wound healing activities	93
68	*Tinospora cordifolia*	*Menispermaceae*	–	Used in general debility, digestive disturbances, loss of appetite, and fever in children Effective immunostimulant	Antioxidant, antihyperglycemic, antihyperlipidemic, hepatoprotective, cardiovascular protective, neuroprotective, osteoprotective, radioprotective, anti-anxiety, adaptogenic agent, analgesic, anti-inflammatory, antipyretic, antidiarrheal, antiulcer, antimicrobial, and anticancer activities	56
69	*Trapa natans*	*Trapaceae*	Fruit peel (50% ethanol)	Used as antidiarrheal, refrigerant, nutritive, and tonic. Treatment of sexual weakness, spermatorrhea, general debility, dysentery, dry cough, bleeding disorders, anal fissure, lumbago, dental caries, and sore throat	Neuroprotective, immunomodulatory, anti-inflammatory, anticancer, analgesic, antiulcer, antioxidant, antidiabetic, antifungal, antibacterial, hepatoprotection against $CCl_{4,}$ and paracetamol	94
70	*Vitex negundo*	*Verbenaceae*	Leaves (70% ethanol)	Treatment of jaundice, wounds, body ache, toothache, asthma, eye pain, and migraine	Analgesic, anti-inflammatory, anticonvulsant, antioxidant, and hepatoprotection	95
71	*Ziziphus oenoplia (L) Mill*	*Rhamnaceae*	Root (50%ethanol)	Wound healing and relief of stomach ache. Stem barks used as a mouthwash for sore throats, dysentery, and inflammation of the uterus	Antiplasmodial, antibacterial, antimicrobial, antihepatotoxicity, antiulcer, wound healing, anthelmintic, antiplasmodial, antioxidant, anticancer, hypolipidemic, analgesic, and antinociceptive activities	96
72	*Ziziphus mauritiana Lam*	*Rhamnaceae*	–	Used in the treatment of diarrhea, wounds, abscesses, swelling, gonorrhea, liver diseases, asthma, and fever	Cytotoxic, immunological adjuvant, and hepatoprotective activity	56

CCl_4, carbon tetrachloride; CNS, central nervous system.

seeds, stem (3 each), and rhizome and bulbs (2 studies each), *etc*. The folkloric and pharmacological uses of the plants reported in the literature cited are also summarized in this review.

Among the extraction mediums, ethanol, methanol and water were the most frequently used (Table 1). In the reported studies one or more of these reagents were adopted in the extraction of the crude extracts from the medicinal plants: ethanol (31 studies), methanol (12 studies), aqueous extraction (15 studies), while chloroform/methanol, acetone, aqueous sodium carbonate were used only once. It has been reported that the extraction method and medium influence the isolation of the active components and antibacterial activity of the extracts.[14] There are difficulties regarding the screening of medicinal plant extracts and the challenge of not having a single standard extraction method for extracting the active components from the plant.[14,15] As evidenced in this report (Table 1) some of the studies did not report the part of the plant and extraction methods adopted in their studies.

In vivo studies on the hepatoprotective TMPs

As noted in this report (Table 2) and observed in many animal studies,[31–96] the animal model most frequently used was the Wistar albino rats (47 studies) and followed by the Sprague-Dawley rats (13 studies). The Duncan Hartley guinea pig (four studies), and BLAB/c mice models (three studies) were the next frequently used animal models while the Kumming mice and rabbit models were seldom used. The use of different animal studies may have affected the results and route of administration of extracts. The oral and intraperitoneal routes were the principal routes of administration of the crude extracts as reported in this review.

As noted and seen in this report, many of the reports lacked adequate standard control for comparing the hepatoprotective activities of the medicinal plants. The standard hepatoprotective drugs used in the reviewed studies were silymarin and Liv 52. Silymarin is a known hepatoprotective drug from the plant *Silybum marianum* and is used in the treatment of liver diseases.[9] The first-line drug combinations used and reported by the studies are INH, RIF, PZA, and ethambutol. From this review, 41 studies used the RIF/INH combination while 15 studies used the RIF/INH/PZA combination in their reports (Table 2). Only seven studies used all four drugs in combination with RIF/INH/PZA/ETM while five studies used only INH as the test drug. It is clear from this report that most of the studies did not adopt a single standard drug combination during the course of their studies. The major criteria used in accessing the hepatoprotective properties of the medicinal plants against the hepatotoxicity induced by the antituberculosis drugs were mostly on the liver enzymes and antioxidant indices (Table 2) while most of the studies reported on the histoarchitecture of the liver (not shown). Some of the reported studies also evaluated the inflammatory markers as an index of protection.

Summary of traditional plants with hepatoprotective activity against ATDs

Acanthospermum hispidum

Ethanolic whole plant extract of *A. hispidum* was reported to offer protection against RIF/INH/PZA/ETM (40/27/66/53 mg/kg bw)-induced hepatotoxicity in Wistar rats.[31] The extract improved liver enzyme and protein recovery and the results were comparable to those of the silymarin. These observed hepatoprotective effect is evidently corroborated by histological examination of the liver which showed fewer hemorrhage and hepatocellular necrosis.[31] The plant is rich in flavonoid content and may contribute to the beneficial effect via antioxidant mechanism.

Alchornea cordifolia

Methanolic extract of *A. cordifolia* leaf (800 mg/kg/day, oral) was shown to protect against hepatotoxicity caused by a mixture of INH/RIF/PZA (100 mg each, oral) in Wistar rats.[31] The study showed that the extract restored plasma levels of liver enzymes, alanine transaminase (ALT) and aspartate transaminase (AST), similar to those obtained with silymarin.[32] The presence of phytochemicals such as flavonoids, polyphenols, and saponosides may have contributed to the observed hepatoprotective effect.

Allium sativum

Allium sativum has been used in folk medicine to treat colds, diabetes, asthma, and other diseases.[33–35] Oral administration of *A. sativum* has been found to restore plasma levels of liver enzymes and prevent lipid peroxidation induced by ATDs such as INH/RIF.[33–35] The observed hepatoprotective benefits of *A. sativum* are attributable to its high concentration of bioactive phytochemicals, including allicin,[33–35] phenols, and flavonoids. These phytochemicals have antioxidant properties and are known to modulate cytochrome P450.[98]

Anacyclus pyrethrum

The ethanolic root extract of *A. pyrethrum* (400 mg/kg bw) has been shown to elicit hepatoprotective effects against ATD-induced liver injury in Sprague-Dawley rats. The root extract considerably reduced serum levels of hepatic enzymes AST, ALT, and alkaline phosphatase (ALP) resulting from ATD toxicity.[38] Furthermore, the extract enhanced glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) levels while lowering malondialdehyde (MDA), suggesting an antioxidant mechanism of hepatoprotection. Furthermore, histopathological findings aptly corroborated the serum biochemical restoration, evidently confirming the hepatoprotective benefits of the extract. These findings were comparable to those of silymarin. *Anacyclus pyrethrum* contains levulinic acid, catechins, flavonoids, coumarin, and gallic acid, which are natural constituents capable of scavenging free radicals and hepatoprotection.[38]

Annona squamosal Linn

Methanolic leaf extract of *A. squamosal L* has been shown to exhibit hepatoprotective effects against RIF/INH-induced hepatotoxicity in rats and mice. At an oral dosage of 500 mg/kg, the extract considerably lowers the heightened plasma levels of ALP, AST, ALT, gamma glutamyl transpeptidase (GGT), and thiobarbituric acid reactive substance (TBARS) resulting from RIF/INH-induced hepatotoxicity. The extract additionally enhanced serum levels of total protein and GSH. These findings were comparable to that of silymarin, and histological findings confirmed the reported biochemical changes.[39]

Artemisia vulgaris

The aqueous leaf extract of *A. vulgaris* has been found to exhibit hepatoprotective properties against RIF/INH/PZA (54/27/135 mg/kg)-induced liver damage in rats. The leaf extract, given orally at a dose of 1 mL/kg, proved to be effective by restoring serum ALT and bilirubin levels while improving protein concentration.[40] Quercetin, a polyphenolic flavonol present in the extract, has been shown to elicit hepatoprotective effects through its interaction with various intracellular signaling cascades to prevent oxidative damage.[101]

Table 2. *In vivo* **studies on medicinal plants with hepatoprotection against antitubercular drug-induced toxicity**

s/n	Botanical name	Animal model	Maximum extract dose/route of administration	Anti -tuberculosis drug(s) dose/route of administration	Standard drug administered/ route of administration	Results	Active components	Reference
1	*Acanthospermum hispidum*	Wistar rats	400 mg/kg bw (oral)	RIF/INH/PZA/ETM, 40/27/66/53 mg/ kg bw (oral)	Silymarin, 100 mg/kg bw (oral)	AST, ALT, ALP, TB↓, TP↑	Flavonoids	31
2	*Alchornea cordifolia* (Shum & Thon)	Wistar rats	800 mg/kg/day (oral)	INH (100 mg/kg/day) (oral) RIF/INH (100 mg/ kg/day each) (oral); RIF/INH/PZA (10 mg/ kg/day, each) (oral)	Silymarin, 100 mg/kg/ day (oral)	AST, ALT↓	Anthraquinones, polyphenols, triterpenes, steroids, saponins, tannins, ellagic acid protocatechuic acid, quercetin, quercetin arabinose, and stigmasterol	32
3	*Allium sativum*	Rats	025 g/kg/day (oral)	INH, 50 mg/kg/day (oral)	Silymarin, 200 mg/kg/ day (oral)	AST, ALT, ALP, TB↓	Lauric acid, myristic acid, thiosulfinates, steroids, terpenes, flavonoids, and phenols	33
4	*Allium sativum*	Wistar rats	200 mg/kg bw (oral)	RIF/INH, 54/27 mg/ kg bw (oral)	–	ALT, AST, ALP, conjugated bilirubin↓	Lauric acid, myristic acid, thiosulfinates, steroids, terpenes, flavonoids, and phenols	34
5	*Allium sativum*	Wistar rats	025 mg/kg/day	RIF/INH, 50 mg/ kg bw each	–	AST, ALT, Bilirubin, MDA↓, nonprotein thiols↑	Lauric acid, myristic acid, thiosulfinates, steroids, terpenes, flavonoids, and phenols	35
6	*Aloe vera*	Sprague-Dawley rats	120 mg/ kg bw	RIF/INH, 50 mg/ kg bw each (oral)	–	TNF-α, NK cells, Th I7↑	Chromone, flavonoids, coumarins, phytosterol, luteolin, kaempferol, quercetin, rutin, catechins, and naphthoquinnes	36
7	*Amaranthus graecizans subsp Silvestris* (VIII) *Brenan*	Wistar rats	400 mg/kg/bw (oral)	RIF/INH, 50/100 mg/kg bw (oral)	Silymarin, 100 mg/kg bw (oral)	ALT, AST, ALP, TB ↓	Phenolic compounds, flavonoids, and saponin	37
8	*Anacyclus pyrethrum (Linn)*	Sprague-Dawley rats	400 mg/kg bw (oral)	RIF/INH, 50mg/kg/ bw each (oral)	Silymarin, 100 mg/kg bw	AST, ALT, ALP, TB, MDA↓, GSH, SOD, CAT↑, LDH, bilirubin↓, albumin↑, cholesterol↓	Levulinic acid, gallic acid, cathechins, flavonoids, coumarin, and N-isobutyldienediynamide	38

(continued)

Table 2. *(continued)*

s/n	Botanical name	Animal model	Maximum extract dose/route of administration	Anti -tuberculosis drug(s) dose/route of administration	Standard drug administered/ route of administration	Results	Active components	Reference
9	*Annona squamosal Linn*	Wistar rats and mice	500 mg/kg bw (oral)	RIF/INH, 100 mg/ kg bw each (ip)	Silymarin, 25 mg/kg bw (oral)	TBARS, AST, ALT, ALP, GGT↓, TP, GSH↑	Acetogenin, flavonoids, aporphine alkaloids, glycoside, and squamoline	39
10	*Artemisia vulgaris L*	Wistar rats	1 mL/kg bw (oral)	RIF/INH/PZA, 54/27/135 mg/kg/day (oral)	–	ALT, TB↓, TP↑	Essential oils, phenolic acids, coumarins, apigenin, quercetin, luteolin, and rutoside	40
11	*Asparagus racemosus*	Wister rats	100 mg/kg bw (ip)	INH, 100 mg/kg bw (ip)	–	AST, ALT, ALP, GGT, TP, albumin, TBARS↓, SOD, CAT, GPx, GSH, vitamin C and E↑, CYP2E↓	Quercetin, rutin, hyperosides, diosgenin, quercetin-3glucuronide, racemoside A, racemoside B, racemofuran, and quercetin-3-glucuronide	41
12	*Asteracantha longifolia (Nees)*	Sprague-Dawley rats	500 mg/kg/day (oral)	RIF/INH, 50 mg/ kg bw each (oral)	–	AST, ALT, ALP, bilirubin↓, TP, Albumin↑	β-sitosterol, lupeol, flavonoids, terpenoids, butelin, and stigmasterol	42
13	*Azadirachta indica (Neem)*	Wistar rats	1 mL/kg	RIF/INH/PZA, 54/27/135 mg/kg/day (oral)	–	AST, ALT, ALP↓, TP↑, TB↓	Nimbolide, azarirachtin, and gedunin	43
14	*Bacupa monnieri*	Wistar rats	500 mg/kg bw, (oral)	RIF/INH, 50 mg/ kg bw each (oral)	Silymarin, 25 mg/kg (oral)	AST, ALP, ALT↓, TP, albumin↑, TB↓, GSH, SOD, CAT, GST, GPx, IL-10↑, MDA↓	Bacoside-A, bacoside-B, betulinic acid, oroxindin, rosavin, and β-sitosterol	44
15	*Boerhaavia diffusa L*	Wistar rats	500 mg/kg bw (oral)	RIF/INH, 10 g/kg bw, each (oral)	Silymarin, 25 mg/kg bw (oral)	AST, ALT, ALP, TB, cholesterol↓, Protein↑	Flavonoids, and β-sitosterol	45
16	*Bombax ceiba Linn*	Wistar rats	450 mg/kg bw (ip)	RIF/INH, 100 mg/ kg bw (ip)	Silymarin, 25 mg/kg bw (ip)	ALT, AST, ALP, T,B, TBARS↓, GSH↑	Flavonoids, sesquiterpenoids, kaempferol, quercetin, vitexin, and rutin,	46
17	*Cassia auriculata*	Wistar rats	600 mg/kg bw	RIF/INH/PZA, 54/27/135 mg /kg bw	Silymarin, 100 mg/kg bw	ALT, AST, ALP, TB, cholesterol↓, TP↑, albumin↓, CAT, GSH, SOD↑, MDA↓	Avaraoside, avaraol, pseudosemiglabrin, (2 s) -7,4′-dihydroxyflavan (4β→8) –catechin, (2 s) -7,4′-dihydroxyflavan (4β→8) –gallocatechin	47
18	*Cassia fistula (Amaltas)*	Wistar rats	400 mg/kg bw (oral)	RIF/INH, 50 mg/ kg bw (oral)	–	ALT, AST, ALP, TB↓	Flavonoids	48

(continued)

Table 2. *(continued)*

s/n	Botanical name	Animal model	Maximum extract dose/route of administration	Anti -tuberculosis drug(s) dose/route of administration	Standard drug administered/ route of administration	Results	Active components	Reference
19	*Centella asiatica*	Wistar rats	40 mg/kg bw (oral)	RIF/INH, 50 mg/ kg bw each (oral)	Silymarin, 50 mg/kg bw (oral)	ALT, AST, TB, ALP↓, CAT, GSH, SOD↑	Flavonoids (derivates of chercetin and kempferol)	49
20	*Cissampelos pareira L*	Sprague-Dawley rats	400 mg/kg bw (ip)	RIF/INH, 50 mg/ kg bw each (ip)	Silymarin, 200 mg/kg bw (ip)	ALT, AST, ALP, TB↓, TP, albumin↑	Alkaloids, glycosides, essential oil, saponins, tannins, steroids, terpenoids, resins, and flavonoids,	50
21	*Citrus sinensis L Osbeck*	Wistar rats	600 mg/kg bw (oral)	RIF/INH, 50 mg/ kg bw each (oral)	–	ALT, AST↓	Phenols, coumarins, flavonoids, kaemferol, and carotenoids	51
22	*Cnidoscolus chayamansa (McVaugh)*	BALB/c mice	400 mg/kg bw	RIF/INH/PZA, 50/50/100 mg/kg bw	Silymarin, 25 mg/kg bw	AST, ALT, ALP, cholesterol↓, TG, HDL↑, CAT, LPx, oxidized protein↓	Moretenol, moretenyl acetate, kaempferol-3,7-dimethyl ether, 5-hydroxy-7,3′,4′-trimethoxyflavanone, hesperidin, procatechic acid, quercetin, and rutin	52
23	*Cnidoscolus chayamansa (McVaughn)*	Wistar rats	400 mg/kg bw (oral)	RIF/INH, 100 mg/ kg bw each (ip)	Silymarin, 25 mg/kg bw (oral)	AST, ALP, ALT↓, TP, TB↑	Flavonoids, ametoflavone, astragatin, and kaempferol-3O-Ruttinoside, dihydromyricetin	53
24	*Crocus sativus*	Wistar albino rats	200 mg/kg/bw (oral)	RIF/INH 100 mg/ kg bw each (ip)	Silymarin, 10 mg/kg bw	AST, ALT, ALP↓, TP, CAT, SOD↑, MDA, TNF-α, COX-2↓	Flavonol, fisetin, morin, quercetin, rutin, crocetin, crocin, picrocrocin, and safranal	54
25	*Cucumis trigonus Roxb*	Wistar rats	500 mg/kg bw (ip)	RIF/INH, 50 mg/ kg bw each (ip)	Silymarin, 25 mg/kg bw (ip)	ALT, AST, ALP, GGT, TB, MDA↓, TP, CAT, GSH, GPx, GRD, SOD, Albumin↑	Cucurbitacin, phenolic compounds, and vitamins	55
26	*Curcuma longa*	Duncan Hartlay guinea pig	200 mg / kg bw	RIF/INH/PZA, 50/100/300 mg/kg bw	–	ALT, AST, ALP↓	Curcumin, memethoxycurcumin, bisdemethoxycurcumin, and curcuminoid demethoxycurcumin	56

(continued)

Table 2. *(continued)*

s/n	Botanical name	Animal model	Maximum extract dose/route of administration	Anti -tuberculosis drug(s) dose/route of administration	Standard drug administered/ route of administration	Results	Active components	Reference
27	*Curcuma longa*	Sprague-Dawley rats	200 mg/kg bw	RIF/INH, 100/50 mg/kg bw each	–	AST, ALT, ALP↓, albumin, TP↑, TB↓, GSH, SOD, GSH Peroxidase↑, MDA, TNFα, caspase↓	Curcumin, memethoxycurcumin, bisdemethoxycurcumin, and curcuminoid demethoxycurcumin	57
28	*Embelia tsjeriam-cottam*	Wistar rats	200 mg/kg bw (oral)	INH, 50 mg/kg bw (oral)	Liv 52, 5 mL/ kg bw	ALT, AST↓, TP↑, TB↓, MDA↓, GSH, SOD, CAT↑	Quercetin, rutin, hyperin, ferulic acid, embelin (2,5-dihydroxy-3-undecyl-2,5-cyclohexadiene-1,4-benzoquinone), and gallic acid	58
29	*Emblica officinalis*	Wistar rats	50 mg/kg bw (oral)	RIF/INH/PZA, 250/50/100 mg/kg bw	–	ALT, AST, ALP, bilirubin↓, CAT, SOD, GPx, LP↑	Chebulagic acid, chebulinic acid, pendunculagin, corilagin, quercetin, gallicacid, ellagicacid, emblicanin A and B, panigluconin	59
30	*Erythrina indica Lam*	Sprague-Dawley rats	200 mg/kg bw (oral)	RIF/INH, 50 mg/ kg bw each (oral)	Silymarin, 100 mg/kg bw (oral)	AST, ALT, ALP, TB, TP, LDH↓, Albumin, SOD, CAT, GSH↑, LPO↓	Campesterol, β-sitosterol, β-amyrin, indicanines D and E, apigenin, genkwanin, isovitexin, swertisin, and saponarin	60
31	*Euclea natalensis A DC*	Sprague-Dawley rats	150 mg/kg/ bw	RIF/INH, 50 mg/ kg bw each (ip)	Silymarin, 50 mg/kg bw	ALT↓, TNFα, IL 12, IL 2, ↑, IL 10↓	Lupeol 2, β-sitosterol	61
32	*Ficus religiosa*	Wistar rats	300 mg/kg bw (oral)	RIF/INH, 100 mg/ kg bw each (ip)	Liv 52, 10 mg/ kg bw (oral)	AST,ALT↓, ALP↑, TB↓, Albumin↑, TBARS↓, GSH↑, TP↓	Lupenol, myricetin, catechol, β-sitosterol, kaempeferol, quercetin	62

(continued)

Table 2. *(continued)*

s/n	Botanical name	Animal model	Maximum extract dose/route of administration	Anti -tuberculosis drug(s) dose/route of administration	Standard drug administered/ route of administration	Results	Active components	Reference
33	*Hemidesmus indicus*	Wistar rats	100 mg/kg/day (oral)	RIF/INH, 50 mg/ kg bw each (ip)	–	Protein, isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, succinate dehydrogenase, malate dehydrogenase, NADH dehydrogenase, cytochrome C-oxidase, SOD, CAT, lipid peroxide↓	Isoquercitin, rutin, β-sitosterol, coumarino-ligoids, coumarins, hemidesminin, and hemidesmin-1 and 2	63
34	*Hibiscus vitifolius Linn*	Wistar rats	400 mg/kg bw	RIF/INH/PZA, 10/75/35 mg/kg bw	Silymarin, 100 mg/kg bw	AST, ALT, ALP↓, LDH↓, cholesterol, TP, albumin↑, bilirubin, CAT, SOD↑, TBARS↓	Gossypin, hilifolin, flavonoids, and vitiquinolone	64
35	*Lasianthera africana*	Wistar rats	10 g/kg	RIF/INH, 100 0 mg/ kg bw (oral)	Silymarin, 50 mg/kg bw	AST, ALT, ALP, GSPx, TB, ↓, GSH, CAT, SOD, TP, albumin, TG, HDL, LDL, cholesterol↑	Quercetin, caffeic acid, gallic acid, kaempferol, chlorogenic acid, and isoquercitrin	65
36	*Lawsonia inermis L*	Wistar rats	100 mg/kg bw	RIF/INH, 100/50 mg/kg bw (ip)	Silymarin, 100 mg/kg bw	ALP, ALT, AST, LDH, MDA, TB↓, albumin↑	Apigenin, kampferol, quercetin, luteolin, chlorogenic acid, ferulic acid, isoferulic acid, gallic acid, o-coumaric acid, m-coumaric acid, myricetin, naringenin-7-o-rutinoside, catechin, catechin gallate, epicatechin gallate, and vitexin-2′-o-rhamnoside	66

(continued)

Table 2. *(continued)*

s/n	Botanical name	Animal model	Maximum extract dose/route of administration	Anti -tuberculosis drug(s) dose/route of administration	Standard drug administered/ route of administration	Results	Active components	Reference
37	*Leucas cephalotes*	Sprague-Dawley rats	400 mg/kg/day (oral)	RIF/INH, 100mg/kg/day each (ip)	Silymarin, 200 mg/kg/day (oral)	AST, ALT, LP↓, GSH, GSH-Px, SOD, CAT↑, MDA, bilirubin↓	Triterpens, oleanolic acid, sterols, flavones, luteolin 4-O-beta-D-glucuronopyranoside, leucasdins A, B, and C, lauric acid, tridecanoic acid, leucastrins A and B, adipic acid, glutaric acid, and labellenic acid	67
38	*Luffa acutangula*	Wistar rats	400 mg/kg bw (oral)	RIF, 100 mg/kg bw (oral)	Silymarin, 200 mg/kg (oral)	AST, ALT, ALP↓, TP↑, LDH, MDA↓, GSH, CAT, SOD ↑	β-carotenes, flavonoids, acutosides a-g, and oleanane type triterpenesaponins	68
39	*Maytenus royleans*	BALB/c mice	400 mg/kg bw	RIF/INH/PZA/ETM, 135, 675, 36, 248 mg/kg bw	–	LDH, AST, ALP, GGT↓, peroxidase, CAT, SOD, TP, GSR, GST, GPx↑, TBARS↓, GSH, cholesterol↓, TG↓, HDL↑, LDL↓	Quercitin, gallic acid, luteolin, vitexin, apigenin, kaempferol, and myricetin	69
40	*Menthe peprita L*	Sprague-Dawley rats	100 mg/kg bw (oral)	RIF/INH/PZA /ETM, 135/675/360/248 mg/kg bw (oral)	Silymarin, 100 mg/kg bw (oral)	AST, ALT, ALP, TB, LPO, MDA, protein carbonyl, conjugated diene ↓ LDH, TP, TAC, GSH↑	Pulegone, and piperitenone oxide	70
41	*Millettia Pulchra (Benth) Kurz var Laxio (Dunn) Z Wei*	Kumming mice	400 mg/kg/day	RIF/INH, 100 mg/kg/day each (oral)	Dimethyl diphenyl bicarboxylate, 200 mg/kg (oral)	ALT, AST, GSH↓, CAT, GSH-Px↑, MDA↓	Flavonoids	71
42	*Mirabilis jalapa Linn*	Wistar rats	500 mg/kg bw (oral)	RIF/INH/PZA/ETM, 40/27/66/53 mg/kg bw (oral)	Silymarin, 100 mg/kg bw (oral)	AST, ALT, ALP↓, TB↑, cholesterol↓, HDL↑, SOD, CAT, GSH, GPx↑, TBARS↓	Flavonoids, beta-amyrins, campesterol, C-methylabroniso flavone, and stigmasterol	72
43	*Monotheca buxlfolia*	Sprague-Dawley rats	300 mg/kg bw	RIF/INH, 50 mg/kg bw each	Silymarin, 100 mg/kg bw	ALT, AST, ALP, TB↓, TP↑	Gallic acid, catechin, caffeic acid, oleanolic acid, isoquercetin, and rutin	73

(continued)

Table 2. *(continued)*

s/n	Botanical name	Animal model	Maximum extract dose/route of administration	Anti -tuberculosis drug(s) dose/route of administration	Standard drug administered/ route of administration	Results	Active components	Reference
44	*Moringa oleifera Lam*	Wistar rats	250 mg/kg bw (oral)	RIF/INH/PZA, 10/75/35 mg/kg bw (oral)	Silymarin, 200 mg/kg bw (oral)	AST, ALT, ALP, TBARS, Hydroperoxides↓, vitamins C and E, GSH, SOD, CAT, GPx, GST↑,	β-Carotene, gallic acid, myricetin, kaempferol, lutein, rutin, rhamnetin, and apigenin	74
45	*Mucuna pruriens*	Wistar rats	400 mg/kg bw (oral)	RIF/INH 100 mg/ kg bw each (ip)	Silymarin, 50 mg/kg bw (oral)	ALP, ALT, AST, TB, MDA↓, SOD, CAT, GSH↑	Glutathione, gallic acid, beta-sitosterol, phenols, and tannins	75
46	*Nigella sativa*	–	500 mg/kg/ bw (oral)	RIF/INH/PZA/ETM, 52/70/175/40 mg/kg bw	Silymarin, 50 mg/kg bw	AST, ALT, albumin, cholesterol, TBARS, ATPase, G6Pase↓	Thymoquinone, anetholeterpineol, thymol, α-pinene, carvacrol, *P*-cymene, and thymohydroquinone	76
47	*Nigella sativa (black seed)*	Rabbits	10 g/kg/day	INH, 50 mg/kg bw (oral)	–	AST, ALT, ALP, MDA↓	Thymoquinone, ρ-cymene, and carvacrol	77
48	*Nigella sativa*	Sprague-Dawley rats	200 mg/kg bw	RIF/INH, 100/50 mg/kg bw each	-	AST, ALT, ALP↓, albumin, TP↑, TB↓, GSH, SOD, GSH Peroxidase↑, MDA, TNF-α, caspase↓	Thymoquinone 2-isopropyl-5-methyl-1,4-bezoquinone	57
49	*Nymphaea alba Linn*	Wistar rats	400 mg/kg bw	INH, (50 mg/kg bw)	Silymarin, 100 mg/kg bw	AST, ALT, ALP, TB↓, CAT, GSH↑, MDA↓	Nupharine, nymphaeine, quercetin, kaempferol, apigenin cardiac glucoside, and nymphalin	78
50	*Ocimum sanctum*	Duncan Hartley guinea pig	200 mg/kg bw	RIF/INH/PZA, 50/100/300 mg/kg bw	–	ALT, AST, ALP↓	Eugenol, caryophyllene, linalool, cirsilineol, cirumaritin, isothymusin, apigenin, rosameric acid, orientin, and vicennin	56
51	*Origanum vulgare*	Sprague-Dawley rats	100 mg/kg bw (oral)	RIF/INH/PZA/ETM, 135/675/360/248 mg/kg bw (oral)	Silymarin, 100 mg/kg bw (oral)	AST, ALT, ALP, TB, LPO, MDA, Protein carbonyl, conjugated diene ↓ LDH, TP, TAC, GSH↑	Polyphenols, triterpenoids, carvacrol, rutin, luteolin, quercetin, and quercitrin	70

(continued)

Table 2. *(continued)*

s/n	Botanical name	Animal model	Maximum extract dose/route of administration	Anti -tuberculosis drug(s) dose/route of administration	Standard drug administered/ route of administration	Results	Active components	Reference
52	*Pergularia daemia (Forssk) Chiov*	Wistar rats	400 mg/kg bw (oral)	RIF/INH/PZA/ETM, 52/70/175/140 mg/kg) (oral)	Silymarin, 50 mg/kg bw (oral)	AST, ALT, ALP, TB↓, cholesterol, triacylglycerol, albumin, glucose, GSH↑, TBARS, aniline hydroxylase↓, SOD CAT, GPx, GR, G6PDH↑	Flavonoids, quercetin, β-sitosterol, β-amyrin, betaine, isorhamnetin, chrysoeriol, taxifolin, and naringenin	79
53	*Phyllanthus debilis*	Wistar rats	400 mg/kg bw (oral)	RIF/INH/PZA, 100/50/350 mg/kg bw	Silymarin, 50 mg/kg bw (oral)	AST, ALT, ALP↓, MDA↓, Thiols↑	Phytosterols, lignans, polyphenols, and debelactone	80
54	*Picrorhiza Kurroa Royle ex Benth*	Wistar rats	50 mg/kg bw	RIF/INH, 200 mg/ kg bw each	–	GSH, CAT, SOD, GPx, GST↑	Apocynin and vanillic acid,	81
55	*Pimpinella anisum*	Sprague-Dawley rats	100 mg/kg/ bw (oral)	RIF/INH/PZA/ETM, 135/675/360/248 mg/kg bw (oral)	Silymarin, 100 mg/kg bw (oral)	AST, ALT, ALP, TB, LPO, MDA, protein carbonyl, conjugated diene ↓ LDH, TP, TAC, GSH↑	Quercetin 3-glucuronide, rutin, luteolin 7-glucoside, isoorientin, and isovitexin	70
56	*Pisonia aculeata*	Wistar rats	500 mg/kg bw (oral)	RIF/INH, 50/100 mg/kg bw (oral)	Silymarin, 50 mg/kg bw (oral)	AST, ALT, ALP, TB, GGTP, MDA↓, TP, SOD, CAT, GPx, GSH, GR, GST, vitamins C and E↑, Cyt P450, NADPH Cyt C reductase↓	Flavonoids, isoflavonoids, chromones, and alkaloids	82
57	*Punica granatum*	Wistar rats	400 mg/kg (oral)	RIF/INH, 50mgkg bw (ip)	–	AST, ALT, ALP, LDH ↓, GPx, GST, SOD, CAT, vitamin C and E↑, MDA↓	Catechins, ellagic acid, tannins, luteolin, caffeic acid, punicalin, punicic acid, isoquerrecitrin, daucosterol, and β-sitosterol	83
58	*Saccharum officinarum L*	Mice	15 mL/kg/day (oral)	INH, 100 mg/kg bw (oral)	–	ALT, AST, ALP, total bilirubin↓	Caffeic acid, chlorogenic acid, coumaric acid, apigenin, tricin, and luteolin derivatives	84

(continued)

Table 2. *(continued)*

s/n	Botanical name	Animal model	Maximum extract dose/route of administration	Anti -tuberculosis drug(s) dose/route of administration	Standard drug administered/ route of administration	Results	Active components	Reference
59	*Sagittaria sagittifolia L Polysaccharide*	BALB/c mice	800 mg/kg/day	RIF/INH, 100 mg/kg/day each, (ip)	Silymarin, 100 mg/kg/day	ALT, AST, LDH, MDA↓, GSH↑, SOD, CAT↑, CYP2E1, CYP3A4↓, Nrf2, *HMOX 1*, GcLc↑, keapL↓	Chrysin, quercetin, rutin, catechol, and epicatechin	85
60	*Solanum xanthocarpum*	Wistar rats	400 mg/kg bw (oral)	RIF/INH/PZA, 10/75/35 mg/kg bw (oral)	Silymarin, 100 mg/kg (oral)	ALT, AST, ALP, total bilirubin, LDH, cholesterol, MDA↓, GSH, SOD, CAT, TP, albumin↑	Solanacarpine, solanacarpidine, solasonine, solamargine, caffeic acid, aesculentin, aesculin, steroids, carpesterol, diosgenin, and campesterol	86
61	*Spirulina fusiformis*	Wistar rats	800 mg/kg bw (oral)	RIF/INH, 50 mg/kg bw each (oral)	Silymarin, 25 mg/kg bw (oral)	AST, ALT, ALP, bilirubin, lipid peroxidation↓, SOD, CAT, GST, glutathione reductase↑	vitamins E and C, beta carotene, selenium, phycocyanin, allophy, aocyanin, and phenols	87
62	*Spirulina maxima*	Wistar rats	500 mg/kg bw (oral)	RIF/INH, 50/75 mg/kg bw (oral)	Silymarin, 100 mg/kg bw (oral)	ALT, AST, ALP↓, TB↑, SOD, CAT, GSH↑, TBARS↓	β-carotene, vitamin E, and lutein	88
63	*Tamarindus indica L*	Wistar rats	500 mg/kg bw (oral)	RIF/INH, 50/100 mg/kg bw each (ip)	–	AST, ALP, ALT, TB, TBARS↓, GSH, SOD, CAT, albumin↑	Flavonoid, glycosides, vitexin, orientin, homoorientin, and hordenine	89
64	*Tamarindus indica Linn*	Sprague-Dawley rats	200 mg/kg bw	RIF/INH, 50 mg kg/bw each (oral)	Silymarin, 100 mg/kg bw, (oral)	ALT, AST, ALP, bilirubin, cholesterol↓, albumin, total protein↑, LDH↓	Naringenin, leupeol, eriodectin, catechin, epicatechin, apigenin, taxifolin and procyanidin	90
65	*Tamarix gallica*	Sprague-Dawley rats	200 mg/kg bw (oral)	RIF/INH, 50 mg/kg bw each	Silymarin, 100 mg/kg bw (oral)	ALT AST, ALP, cholesterol↓, total protein, total albumin↑	Isoquercitin, catechin, phenols, tamarixin, tamarixetin, troupin, 4-methyl coumarin, quercetol, flavonones, isoflavonones, resveratrol, ellagic acid, and carotenoids	91

(continued)

Table 2. *(continued)*

s/n	Botanical name	Animal model	Maximum extract dose/route of administration	Anti -tuberculosis drug(s) dose/route of administration	Standard drug administered/ route of administration	Results	Active components	Reference
66	*Telfairia occidentalis*	Wistar rats	500 mg/kg bw	RIF/INH, 100 mg/ kg bw each (oral)	Silymarin, 50 mg/kg bw	AST, ALT, ALP↓, CAT, Glutathione reductase, SOD↑, albumin, bilirubin ↓, TP↑	Flavonoids, kaempferol-3-O-rutinoside, kaempferol, phenol, and coumarins	92
67	*Terminalia chebula*	Wistar rats	200 mg/kg bw (oral)	RIF/INH/PZA, 250/50/100 mg/kg bw	–	AST, ALT, ALP, bilirubin, LP↓, GSH, GPx, CAT ↑	Gallic acid, chebulic acid, corilagin, punicalagin, chebulanin, terflavin, ellagic acid, phenols, rutin, quercetin, luteolin, β-sitosterol, and daucosterol	93
68	*Tinospora cordifolia*	Duncan Hartley guinea pig	200 mg/kg bw	RIF/INH/PZA, 100/50/300 mg/kg bw	–	ALT, AST, ALP↓	Berberine, magnoflorine, jatrorrhizine, syringin, β-sitosterol, choline, and tinosporine	56
69	*Trapa natans*	Wistar albino rats	400 mg/kg bw (oral)	RIF/INH, 50m/kg/g bw each (oral)	Silymarin, 100 mg/kg bw	AST, ALT, ALP, LDH, albumin, cholesterol, bilirubin, lipid peroxidation↓, GSH, SOD, CAT↑	gallic, ellagic, ferulic acid, quercetin 3-O-galactoside (hyperoside), quercetin, pinobanksin, kaempferol-3-O-glucoside, quercetin 3-O-rhamnoside, and rutin	94
70	*Vitex negundo*	Wistar rats	500 mg/kg bw (oral)	RIF/INH/PZA, 10/75/35 mg/kg bw	Lv 52, 500 mg/ kg bw, (oral)	ALT, AST, ALP, bilirubin↓, TP↑	Flavonoids, vitexin, isovitexin, viridifol, β-sitosterol, luteolin, and caffeic acid	95
71	*Ziziphus oenoplia (L) Mill*	Wistar rats	300 mg/kg bw (oral)	RIF/INH, 50 mg/ kg/ bw each (oral)	Silymarin, 100 mg/kg bw (oral)	ALT, AST, GGT, ALP, TB↓,TP↑, SOD, CAT, GST, GSH-px, MDA↑	Ziziphine and phenols	96
72	*Ziziphus mauritiana*	Duncan Hartley guinea pig	200 mg/kg bw	RIF/INH/PZA, 50/100/300 mg/kg bw	-	ALT, AST, ALP↓	Spinosin, frangufoline, and flavonoids	56

↓, decrease in activity/concentration; ↑, increase in activity/ concentration. ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; ATPase, adenosine triphosphatase; BALB/c, Bagg albino cold spring mice; CAT, catalase; CNS, central nervous system; COX-2, cyclo-oxygenase-2; ETM, ethambutol; GcLc, Glutamate-cysteine ligase catalytic subunit; GGT/GGTP, gamma glutamyl transpeptidase; GPx, gluthathione peroxidase; GR, gluthathione reductase; GSH, gluthathione; G6Pase, glucose 6-phosphatase; G6PDH, glucose-6- phosphate dehydrogenase; HDL, high density lipoprotein; HMOX1, heme oxygenase 1 gene; INH, isoniazid; IL, interleukin; Keap l, Kelch-like ECH-associated protein 1; LDH, lactate dehydrogenase; LPO, lipid peroxidation; LPx, lipid peroxide; MDA, malondialdehyde; NADH, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; Nrf2, nuclear factor erythroid 2-related factor 2; NK cells, natural killer cells; PZA, pyrazinamide; RIF, rifampicin; SOD, superoxide dismutase; TAC, total antioxidant capacity; TB, Tuberculosis; TBARS, thiobarbituric acid reactive substance; TNF-α, tumor necrosis factor-alpha; TP, total protein.

Asparagus racemosis

Hydromethanolic root extract of *A. racemosis* has been shown to protect the liver against INH-induced hepatotoxicity.[41] Pretreatment with the root extract, at a dose of 100 mg/kg bw, protected the liver against oxidative injury by improving the INH-induced depletion of serum antioxidant capacity with an attendant reduction in elevated serum levels of AST, ALT, ALP, and GGT. The plant contains quercetin, which is known to protect against oxidative liver damage.[102]

Asteracantha longifolia

Oral administration of hydroethanolic extract of *A. longifolia* at a concentration of 50 mg/kg has been proven to protect the liver against RIF/INH-induced hepatotoxicity in Sprague-Dawley rats. The extract was able to lower serum levels of ALT, AST, ALP, and bilirubin while increasing albumin levels.[42] The extract contains many beneficial phytochemicals, including β-sitosterol, lupeol, flavonoid, and stigmasterol.[42]

Azadirachta indica

A study examined the effects of an aqueous leaf extract of *A. indica* (1 mL/kg) on the toxicological and histological alterations caused by ATDs in Wistar rats. The investigators observed that the extract provided hepatoprotection by significantly lowering the levels of ALT, AST, ALP, and total bilirubin while increasing the total protein level. The extract treatment maintained the histological structure of the liver by significantly reducing ATD-induced degeneration, necrosis, and fibrosis score with signs of considerable regeneration.[43]

Bacopa monnieri

Bacopa monnieri (Brahmi) has been shown to protect against RIF/INH-induced hepatotoxicity (50 mg/kg bw each) in Wistar rats. The plant extracts reduced serum levels of AST, ALT, and ALP as well as serum MDA, an indicator of lipid peroxidation. Furthermore, the extract was able to enhance GSH, SOD, CAT, glutathione s-transferase (GST), glutathione peroxidase (GPx), and interleukin (IL)-10 levels, indicating an improvement in antioxidant status.[44] Bacoside-A is a bioactive compound present in the plant and has been proven to protect against D-GaIN-induced hepatotoxicity in rats.[103]

Bombax ceiba

Methanolic extract of *B. ceiba* (450 mg/kg bw) was reported to prevent RIF/INH-induced hepatotoxicity by boosting GSH levels, and preventing lipid peroxidation as evident in decreased hepatic TBARS in Wistar rats.[45] Furthermore, the hepatoprotection was evident in reduced serum levels of AST, ALT, ALP, and total bilirubin. The presence of flavonoids (kaempferol, quercetin, vitexin, and rutin) and terpenoids (sesquiterpenoids) that are known to be potent free radical scavengers are believed to be responsible for the hepatoprotective capacity of *B. ceiba* extract.[46]

Cassia auriculata Linn

The hepatoprotective effects of methanolic root extract of *C. auriculata* against liver damage caused by a combination therapy of RIF, INH, and PZA were investigated in Wistar rats. The extract (600 mg/kg bw po) lowered serum levels of ALT, AST, ALP, total bilirubin, cholesterol, and the lipid peroxidation index (MDA) while increasing the activity of endogenous antioxidant systems (CAT, SOD, and GSH).[47] Histopathological findings corroborated the aforementioned results.

Cassia fistula

Ethanolic leaf extract of *C. fistula* (400 mg/kg po) was reported to protect Wistar albino rats against liver damage caused by RIF and INH (50 mg/kg bw each). The elevated serum levels of hepatic enzymes (AST, ALT, and ALP) and bilirubin caused by the ATDs were remarkably reduced by the extract treatment. Substantial hepatic recovery was also evidenced from histological assessment. The presence of flavonoids and anthraquinones, which have antioxidant capabilities, have been implicated in hepatoprotection.[48]

Centella asiatica

The hepatoprotective potential of *C. asiatica* leaf extract (40 mg/kg bw) was studied in Wistar rats challenged with RIF and INH (50 mg/kg bw each). Relative to silymarin (50 mg/kg bw), *C. asiatica* leaf extract (40 mg/kg bw) restored normal serum levels of hepatic enzymes (ALP, AST, and ALT) and markedly improved the antioxidant capacity (CAT, GSH, and SOD) of the liver. These positive effects were attributed to the presence of flavonoids (quercetin and kaempferol derivatives), which are known to mitigate oxidative stress in hepatocytes.[49]

Cissampelos pareira Linn

Ethanolic extract of *C. pareira* was studied for its ability to protect against hepatotoxicity caused by ATDs (RIF/INH, 50 mg/kg bw, po each) in Sprague-Dawley rats.[50] The extract (400 mg/kg bw, po) effectively restored the serum levels of hepatic enzymes (ALT, AST, and ALP). The total protein and albumin levels increased as well. These findings were similar to that of silymarin.[50]

Citrus sinensis L. Osbeck

The ethanolic dried peel extract of *Citrus sinensis L. Osbeck* was found to provide hepatoprotection against liver injury induced by a combination of RIF and INH (50 mg/kg bw) in Wistar rats. The extract (600 mg/kg po) restored serum levels of hepatic enzymes (ALT and AST). Phytochemical analysis revealed the presence of several beneficial bioactive components in the extract (phenols, coumarin, flavonoids, and kaempferol), which may help to minimize oxidative stress.[51]

Cnidoscolus chayamansa

Two studies reported hepatoprotective effects of *C. chayamansa* against ATD-induced liver injury in mice and rats. The first study demonstrated a dose-dependent alleviation of hepatotoxicity in male BALB/c mice using chloroform-methanol extract (200 or 400 mg/kg bw) of *C. chayamansa* leaves/stems.[52] Histological assessments showed fewer amounts of steatosis present within diseased liver regions exhibiting lower levels of inflammation. The second study showed that ethanolic leaf extract of *C. chayamansa* protected Wistar rats from hepatic injury caused by RIF/INH.[53] The extract reduced the serum levels of AST, ALT, and ALP while increasing the levels of total protein and albumin. The hepatoprotective effects in both studies have been attributed to the presence of high concentrations of flavonoids and derivatives (amentoflavone, astragalin, and kaempferol-3-O-rutinoside), which are known to exhibit antioxidant properties.

Crocus sativus Linn

Ethanolic extract of *C. sativus L*. petals exhibited hepatoprotective effects against RIF/INH drug-induced liver injury in Wistar rats.[54] The extract significantly modulates biochemical hepatic damage indices, including decreased ALT, AST, ALP, MDA, and tumor

necrosis factor-alpha (TNF-α), while increasing the antioxidant enzyme (CAT and SOD). Flavonoids and fatty acids were found to be components present in the plant.[54]

Cucumis trigonus Roxb

The ethanolic fruit extract of *C. trigonus Roxb* (50 mg/kg ip) demonstrated hepatoprotective properties against ATD-induced hepatotoxicity in rats. The hepatoprotective effects were evident by decreased serum levels of ALT, AST, ALP, GGT, total bilirubin, and MDA. Interestingly, the extract treatment causes a significant increase in indices of antioxidant systems (GSH, GPx, glutathione reductase [GR], SOD, and CAT), which contributed to the overall favorable benefits. Cucurbitacin, phenolic chemicals, and vitamins were present in the plant extract.[55]

Curcuma longa

Two studies evaluated the hepatoprotective properties of *C. longa* extract. The first study looked at the hepatoprotective effects of *C. longa* extract (200 mg/kg bw) in Duncan Hartley Guinea pigs treated with a combination of RIF (50 mg/kg bw), INH (100 mg/kg bw), and PZA (300 mg/kg bw). The extract effectively restored serum levels of liver enzymes following an increase caused by the ATDs.[56] The second study examined the hepatoprotective effects of *C. longa* extract in Sprague-Dawley rats that had liver damage caused by a combination of RIF (100 mg/kg) and INH (50 mg/kg). Serum levels of AST, ALT, ALP, total bilirubin, lipid peroxidation index (MDA), TNF-α, and caspase were reduced by the extract. In addition, the extract improved the levels of various antioxidant components, including GSH, SOD, and GPx.[57] Curcumin, the main component of *C. longa*, has been shown to lower oxidative stress.[104–106]

Embelia tsjeriam-cottam

A study evaluated the hepatoprotective effect of both aqueous and alcoholic extracts of *E. tsjeriam-cottam* against INH-induced liver damage in Wistar rats.[58] The liver damage caused by INH (50 mg/kg bw, po) was reversed by administration of 200 mg/kg bw extract and 5 mL/kg bw drug Liv-52. The serum levels of liver marker enzymes (ALT and AST) were found to be lower, whereas antioxidant systems (GSH, SOD, and CAT) were enhanced thereby resulting in lipid peroxidation reduction. The histology result revealed the restoration of normal liver architecture by the extract treatment.[58] Quercetin, rutin, and hyperin are prominent among the several antioxidant phytochemicals identified in the plant extract.

Emlica officinalis

The extract of *E. officinalis* has been shown to have hepatoprotective properties against ATD-induced liver damage. The extract (50 mg/kg bw) was found to restore the plasma levels of various liver enzymes, including AST, ALT, ALP, and bilirubin, which had been raised by the drugs. There was also an improvement in antioxidant status (GSH, GPx and CAT) and a reduction in lipid peroxidation.[59]

Erythrina indica Lam

The methanolic leaf extract of *E. indica* (200 mg/kg bw, po) was reported to exhibit hepatoprotective properties against liver damage caused by RIF/INH (50 mg/kg each) in Sprague-Dawley rats. Relative to silymarin, the extract showed comparable levels of decrease in serum levels of liver function indicators, AST, ALT, ALP, lactate dehydrogenase (LDH), and total bilirubin, while improving antioxidant status (GSH, SOD, and CAT) with an attendant decrease in lipid peroxide.[60] Furthermore, histological data revealed a reduction in hepatocellular necrosis, repairs, and improved cell regeneration. Isoflavones (indicanines D and E) and flavonoids (apigenin, genkwanin, isovitexin, swertisin, and saponarin) are the key phytochemicals present in the plant that could provide protection.

Euclea natalensis ADC

Ethanolic (95%) shoot extract of *E. natalensis* was reported to elicit hepatoprotective effects against liver injury caused by a combination of RIF and INH (50 mg/kg bw) in Sprague-Dawley rats.[61] The extract has been shown to protect the liver by lowering serum ALT and IL-10 levels while elevating TNF-α, IL-12, and IL-2 levels. Silymarin was utilized as a reference drug in the study.[61] The presence of lupeol 2 and β-sitosterol in the plant may contribute to the reported hepatoprotection.

Fiscus religiosa

The methanolic leaf extract of *F. religiosa* considerably reduced the elevated levels of serum ALT, AST, and total bilirubin caused by ATD-induced hepatotoxicity in Wistar rats. In addition, the extract enhanced serum levels of GSH and lowered TBARS to normal levels when compared to the positive control group that received Liv 52 (100 mg/kg bw, po). The histological pattern was consistent with the observed biochemical changes.[62] The hepatoprotective benefits of *F. religiosa* have been attributed to the high flavonoid and phenolic content of the plant.

Hibiscus vitifolius Linn

Hibiscus vitifolius Linn root extracts in methanol, chloroform, petroleum, and water were reported to elicit hepatoprotective effect against RIF/INH/PZA (10/7.5/35mg/kg bw)-induced liver damage in Wistar rats.[64] The extracts were able to reduce TBARS levels, implying decreased lipid peroxidation while strengthening the antioxidant system. The hepatoprotective effect was found to be similar to that of silymarin. The plant phytochemicals that are believed to elicit hepatoprotective action include gossypin, hibifolin, and vitiquinolone.

Lasianthera Africana

The study assessed the hepatoprotective effects of a hot aqueous leaf extract of *L. africana* against hepatic oxidative damage caused by RIF and INH (100 mg/kg bw each) in the Wistar rat model. The aqueous leaf extract restored the elevated serum levels of AST, ALT, ALP, and total bilirubin to normal serum levels. The extract also enhanced GSH, GPx, CAT, and SOD with a resultant decrease in MDA level. The antioxidant activity of the plant may be attributed to the presence of quercetin, gallic acid, kaempferol, and isoquercitrin.[65] The findings were comparable to those of the standard, silymarin.

Lawsonia inermis

The study investigated the hepatoprotective effect of aqueous Na_2CO_3 leaf extract of *L. inermis* (lawsone) against RIF/INH-induced hepatotoxicity in Wistar rats. The extract significantly reduced the RIF/INH-induced increase in serum ALP, ALT, AST, LDH, total bilirubin, and MDA levels. The extract also reversed the severe centrilobular necrosis, hepatocyte ballooning, and inflammatory tissue infiltration caused by RIF/INH administration. The findings were comparable to those obtained with silymarin. The plant contains flavonoids and phenolic substances such as apigenin, kaemperol, and quercetin, which may be responsible for the hepatoprotective effects of the leaf extract.[66]

Leucas cephalotes

The study examined the hepatoprotective effects of methanolic whole plant extract (400 mg/kg bw) of *L. cephalotes* against RIF-induced hepatotoxicity in Wistar rats. The hepatoprotective efficacy was evident from restored serum levels of AST, ALT, ALP, bilirubin, and MDA. Furthermore, the extract improved the antioxidant status of rats challenged with RIF. However, the hepatoprotective efficacy of the extract was lower when compared with silymarin.[67]

Luffa acutangula

The study assessed the hepatoprotective efficacy of the hydroalcoholic fruit extract of *L. acutangula* (400 mg/kg bw, po) against RIF-induced hepatotoxicity in Wistar rats.[68] The extract exhibited considerable hepatoprotection by reducing serum levels of marker enzymes (ALT, AST, ALP, and LDH) and increasing total protein concentration. The extract enhanced the enzymatic antioxidant activity (CAT and SOD) with an attendant significant reduction in MDA and restored liver histoarchitecture. The observed hepatoprotective capability of the extract was attributable to its flavonoid content, which is known to increase endogenous antioxidants and mitigate lipid peroxidation.[68]

Maytenus royleans

The hydromethanolic leaf extract of *Maytenus royleans* (400 mg/kg bw) was investigated for its hepatoprotective potential against RIF/INH/PZA/ETM-induced liver injury in BALB/c mice.[69] The extract offered protection by restoring serum levels of AST, ALT, ALP, and LDH to normal levels. Antioxidant status (CAT, SOD, POD, GPx, GST, GSH reductase, GGT, and GSH) was significantly enhanced and lipid peroxidation alleviated. The biochemical findings were corroborated by restored histology. The plant extract is rich in flavonoids and phenolics (quercetin, gallic acid, luteolin, vitextin, apigenin, kaempferol, and myricetin), which have been implicated in the enhancement of antioxidant defense system.[69]

Mentha piperita

The hepatoprotective potential of ethanolic leaf extract of *M. piperita* (100 mg/kg bw) on ATD-induced liver damage in Sprague-Dawley rats was investigated. The extract reduced the serum levels of hepatic enzymes, total bilirubin, and MDA while improving total antioxidant capacity and GSH levels. These observed hepatoprotective benefits of the extract were comparable to that of silymarin (100 mg/kg bw).[70]

***Millettia pulchra* (Benth.) Kurz var *Laxior* (Dunn) Z. Wei**

Dong *et al*. studied the hepatoprotective efficacy of aqueous root extract (400 mg/kg bw) of *M. pulchra* (Yulangsan) against ATD-induced liver injury in Kunming mice.[71] The extract reduced serum levels of ALT and AST that were elevated by the ATD. The extract improved the mice's antioxidant system by augmenting SOD, CAT, GPx, and GSH levels while decreasing MDA levels. The results were compared to a positive control of dimethyl bicarbonate.

Mirabilis jalopa Linn

The study investigated the hepatoprotective effect of the ethanolic leaf extract (500 mg/kg bw) of *M. jalopa L* against ATDs-induced liver toxicity in Wistar rats.[72] The extract displayed hepatoprotective effects by decreasing serum levels of liver enzymes (AST, ALT, and ALP), augmenting antioxidant levels, and minimizing hepatocellular necrosis. Flavonoids are present in the extract and substantially contribute to its antioxidant properties.

Monotheca buxifolia

Two studies reported on the hepatoprotective effects of *M. buxifolia* against ATD-induced hepatotoxicity. Ullah *et al*.[73] assessed the hepatoprotective effects of hydroethanolic fruit extract (300 mg/kg bw) of *M. buxifolia* in Sprague-Dawley rats while Javed *et al*.[107] examined the hepatoprotective effects of the methanolic aerial parts (stem and leaf) extract (500 mg/kg bw) in albino mice. The extract used in both studies significantly reversed the ATD-induced increase in the serum levels of AST, ALT, ALP, and total bilirubin. This hepatoprotection was evident in the restored hepatic histological architecture. Based on their experimental findings, Javed *et al*.[107] reported a high free radical scavenging activity of the extract and concluded that the hepatoprotective effect of the extract is not unconnected with the presence of bioactive phytochemicals (total phenolics and flavonoids; isoquercetin, and oleanolic acid).

Moringa oleifera

The hepatoprotective effect of hydroethanolic leaf extract (250 mg/kg bw po) of *M. oleifera* against ATD-induced hepatotoxicity was assessed in Wistar rats. Evidently, the extract caused a decrease in the serum levels of AST, ALT, ALP, and bilirubin. Additionally, indices of antioxidant status (SOD, CAT, GPx, GST, and GSH) increased significantly with a considerable decrease in lipid peroxidation. The histological findings in the liver supported the observed recovery from ATD-induced liver injury.[74] The leaves of *M. oleifera* contain antioxidative substances (gallic acid, myricetin, kaempferol, lutein, rutin, and beta carotene), which strengthen its hepatoprotective activity. The leaves of *M. oleifera* are rich in beta carotene, which is more effective than silymarin against liver injury caused by ATDs.

Mucuna pruriens

In a comparative study with silymarin (50 mg/kg bw), the hepatoprotective potential of hydroethanolic leaf extract of *M. pruriens* (400 mg/kg bw, po) against RIF/INH-induced liver injury in Wistar rats was evaluated. The extract significantly reversed the increase in ALT, AST, ALP, and bilirubin levels in serum caused by the ATD. The extract markedly enhanced the antioxidant status (SOD, CAT, GPx, and GSH) with a resultant decrease in lipid peroxidation. The authors reported the presence of gallic acid, β-sitosterol and phenols in the plant, which have been shown to contribute to hepatoprotection.[75]

Nigella sativa

The aqueous extract of *N. sativa* (black seeds) was studied in rabbits for its hepatoprotective efficacy against INH-induced hepatotoxicity. The extract caused a decrease in serum levels of AST, ALT, ALP, and MDA. Another study that utilized hydroethanolic extract at a concentration of 500 mg/kg bw found that it suppressed ATD injury. Furthermore, a study on Sprague-Dawley rats discovered that a dose of 200 mg/kg bw of the extract protected the liver from RIF/INH injury.[57,76,77]

Nymphae alba Linn

Nasiruddin *et al*.[78] investigated the hepatoprotective effect of hydroethanolic flower extract of *N. alba* (400 mg/kg bw) on liver enzymes, antioxidants, and histology following INH administration (50 mg/kg bw) in Wistar rats. The extract significantly reduced the INH-induced elevated serum levels of liver marker enzymes (AST, ALT, and ALP). The extract also ameliorated antioxidant biomarkers (CAT and GSH) and suppressed lipid peroxidation.

These findings were corroborated by histological restoration of the liver and were comparable to silymarin. The presence of flavonoids and phenolic compounds in the plant may be responsible for the observed antioxidant activity.[78]

Ocimum sanctum

A study on Duncan Hartlay guinea pigs examined the use of *O. sanctum* extract (200 mg/kg bw) for the management of ATD-induced liver damage. The extract was found to restore serum normal levels of hepatic enzymes (AST, ALT, and ALP) in the study. Phytochemicals found in the plant included eugenol, linalool, cirumaritin, apigenin, rosameric acid, and orientin.[56]

Origanum vulgare

The hepatoprotective efficacy of hydroethanolic leaf extract of *O. vulgare* (100 mg/kg bw po) against ATD-induced liver injury was examined in Sprague-Dawley rats. The extract protected the liver from the detrimental effects of the RIF/INH/PZA/ETM combination by considerably lowering the serum levels of AST, ALT, ALP, total bilirubin, and MDA. Also, the extract augmented the antioxidant status (total antioxidant capacity and reduced GSH). The observed hepatoprotection of the extract was attributed to the presence of polyphenols, rutin, quercetin, and quercitrin.[70]

Pergularia daemia

The hepatoprotective effect of hydroethanolic extract of *P. daemia* against liver damage caused by ATDs (RIF/INH/PZA/ETM)-induced liver damage in Wistar rats was investigated and reported.[79] The extract of *P. daemia* restored the elevated serum biochemical parameters (AST, ALT, ALP, bilirubin, cholesterol, triacylglycerol) as well as improved serum antioxidant biomarkers (GSH, SOD, CAT, and glucose-6- phosphate dehydrogenase) while reducing TBARS. These findings were confirmed by histological evidence. The plant contains phytochemicals (quercetin, β-sitosterol, isorhamnetin, betaine, and naringenin), which may contribute to the extract's mechanism of hepatoprotection.[79]

Phyllanthus debilis

The study examined the hepatoprotective effect of hydroethanolic whole plant extract of *P. debilis* (400 mg/kg bw, po) against ATD-induced hepatotoxicity in Wistar rats. The extract exerted a modest hepatoprotective effect with no appreciable restoration in serum levels of hepatic MDA and thiols.[80]

Picrorrhiza kurroa

The authors investigated the hepatoprotective effect of ethanolic roots and rhizome extract of *P. kurroa* (50 mg/kg bw) against RIF/INH (200 mg/kg bw) induced liver damage in Wistar rats. The study showed that *P. Kurroa* significantly augmented the antioxidant status (GSH, SOD, CAT, GPx, and GST) and thus suppressed ATD-induced changes.[81]

Pimpinella anisum

The study examined the hepatoprotective potential of hydroethanolic leaf extract of *P. anisum* (100 mg/kg bw, po) against ATDs (RIF/INH/PAZ/ETM)-induced liver damage in Sprague-Dawley rats. The extract was found to be beneficial in preventing liver damage by increasing LDH, total protein, total antioxidant capacity, and GSH levels. Furthermore, the extract restored serum levels of AST, ALT, ALP, total bilirubin, and diminished lipid peroxidation. The plant extract was reported to contain quercetin-3-glucuronide, rutin, isovitexin, and isoorientin.[70]

Pisonia aculeate

Anbarasu *et al*.[82] demonstrated the hepatoprotective potential of *P. aculeate* against hepatotoxicity caused by RIF/INH in Wistar rats. The administration of *P. aculeate* extract reduced liver injury by lowering serum levels of AST, ALT, ALP, MDA, cytochrome P450, and nicotinamide adenine dinucleotide phosphate cytochrome C reductase. Furthermore, the extract enhanced antioxidant systems (GSH, GPx, GR, GST, SOD, and CAT), thereby providing protection. The authors suggested that the hepatoprotective properties of the extract were due to the major flavonoids present.[82]

Punica granatum

The protective potential of hydroacetone fruit extract of *P. granatum* (400 mg/kg bw, po) against RIF/INH (50 mg/kg bw, ip each)-induced liver damage was investigated in Wistar rats. The fruit extract considerably reduced the elevated serum levels of hepatic enzymes (AST, ALT, ALP, LDH) and histological abnormalities. The extract augmented the antioxidant defense (SOD, CAT, GSH, GPx, GST, vitamins C, and E and decreased lipid peroxides. The plant contains antioxidant phytochemicals, which may have antioxidant effects.[83]

Saccharum officinarum

The stem juice extract (15 mL/kg/day) of *S. officinarum L* has been shown to protect mice against INH-induced liver injury.[84] The hepatoprotective effect of the extract was evidenced by lower serum levels of AST, ALT, ALP, and total bilirubin. Furthermore, the histological investigation revealed significant improvement in histological structure. The plant phytochemicals, particularly flavonoids, caffeic acid, coumaric acid, and luteolin derivatives, are known to have high antioxidant capacity, thereby providing hepatoprotection against oxidative liver damage caused by INH co-administration.[84]

Sagittaria sagittifolia

Aqueous root tuber extract of *S. sagittifolia L* polysaccharide (80 mg/kg bw) has been shown to elicit hepatoprotective effect against RIF/INH (100 mg/kg/day each)-induced liver injury in BALB/c mice. The extract considerably reduced liver damage, evidenced by decreased serum levels of ALT, AST, and LDH, and a lower concentration of MDA in the liver. In addition, there was an increase in GSH content and activity of SOD and CAT in the liver.[85] The extract reduced pathological tissue damage and inhibited the gene expression of cytochrome P_{450} (CYP2E1 and CYP3A4), while inducing the gene expression of nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1, and glutamate-cysteine ligase. The presence of chrysin, quercetin, rutin, and catechol could be responsible for the enhanced antioxidant activities of the extract.[85]

Solanum xanthocarpum

Ethanolic fruit extract of *S. xanthocarpum* (400 mg/kg bw po) was evaluated for its hepatoprotective potential in Wistar rats against RIF/INH/PZA-induced hepatotoxicity. The extract elicited its hepatoprotective effects by lowering serum levels of ALT, AST, and ALP. The extract treatment augmented the levels of antioxidant status (SOD, CAT, and GSH) while diminishing lipid peroxidation. The protection was comparable to that of silymarin. Phytochemical investigation revealed the presence of solanacarpine, solanacarpidine, aesculentin, diosgenin, and campesterol.[86]

Spirulina fusiformis

Oral administration of saline solution of commercially available *S. fusiformis* (800 mg/kg bw) reduced liver damage caused by RIF/INH (50 mg/kg bw, each) in Wistar rats. The extract caused a reduction in serum levels of ALT, AST, ALP, and total bilirubin while augmenting reduced GSH, SOD, CAT, GPx, and GST. Histological findings confirmed this hepatoprotective function. These findings were similar to those of silymarin.[87] The extract has been shown to contain a variety of antioxidant chemicals, including vitamins E and C, phenols, beta carotene, phycocyanin, and aocyanin.[87]

Spirulina maxima

The hepatoprotective potential of *S. maxima* whole plant extract (500 mg/kg bw, po) against RIF/INH-induced liver damage in Wistar rats was investigated in this study. Pretreatment with the extract significantly reduced the serum levels of hepatic enzymes (ALT, AST, and ALP) and oxidative stress marker TBARS, while increasing the levels of the antioxidant enzymes (SOD and CAT), nonenzymatic protein (reduced GSH), and other protective factors. The results were comparable to those from the silymarin. The plant is reported to contain beta carotene, vitamin E, and lutein.[88]

Tamarindus indica Linn

The hepatoprotective activity of aqueous fruit extract of *T. indica* (500 mg/kg bw, po) against liver damage caused by INH (100 mg/kg bw ip) and RIF (50 mg/kg bw ip) was evaluated in Wistar rats. The extract reduced the serum levels of hepatic enzymes (ALT, AST, and ALP) and bilirubin. Additionally, the extract reduced lipid peroxidation (TBARS) and enhanced antioxidant defense systems (SOD, CAT, and GSH). The histology outcomes were comparable to those of the silymarin standard. In another investigation, hydroethanolic stem bark extract of *T. indica* (200 mg/kg bw) protected Sprague-Dawley rats from hepatotoxicity instigated by RIF/INH (50 mg/kg bw po, each). The extract reduced bilirubin, cholesterol, LDH, and serum levels of hepatic enzymes (ALP, ALT, and AST) that were elevated by ATDs. Serum levels of total protein and albumin were also elevated. The authors identified some of the phytochemicals in *T. indica;* lupeol, apigenin, and procyanidin.[89,90]

Tamarix gallica

According to Amir *et al*.,[89] aqueous fruit extract of *T. gallica* (200 mg/kg bw) had a significant hepatoprotective effect against liver damage caused by RIF (100 mg/kg bw, ip.) and INH (50 mg/kg bw, ip.) in rats. The fruit extract decreased serum levels of ALT, AST, ALP, cholesterol, and TBARS while enhancing antioxidant status (SOD, CAT, and GSH). The observed histological changes paralleled these biochemical changes.[89] Another study by Meena *et al*. investigated the hepatoprotective potential of ethanolic stem bark extract of *T. gallica* (200 mg/kg bw) against hepatotoxicity caused by RIF/INH (50 mg/kg bw po, each) in Sprague-Dawley rats. The stem bark extract reduced the serum levels of ALP, ALT, AST, and LDH that were elevated by ATDs.[90]

Telfairia occidentalis

The hepatoprotective activity of aqueous fruit pulp extract of *T. occidentalis* (500 mg/kg bw) against RIF/INH (100 mg/kg bw, po, each) was investigated in Wistar rats. Liver damage caused by oral administration was restored by the extract. This was evident in the serum level of hepatic enzymes (AST, ALT, and ALP) and bilirubin. Furthermore, the RIF/INH-induced depletion of SOD, CAT, GPx, and GR levels was significantly improved with a concomitant reduction in MDA. The authors identified bioactive phytochemicals (coumarins, kaempferol, flavonoids, and phenols) that are known to elicit antioxidant effects.[92]

Terminalia chebula

Ethanolic fruit extract of *T. chebula* (200 mg/kg bw, po) showed a significant hepatoprotective effect against liver damage caused by a combined administration of (RIF 250 mg/kg/INH 50 mg/kg /PZA 100 mg/kg, po) in Wistar rats. Serum levels of AST, ALT, ALP, bilirubin, and lipid peroxide were reduced after treatment with extract. More so, the extract elicited a considerable increase in the antioxidant parameters (GSH, GPx, and CAT). The presence of phytochemicals such as gallic acid, chebulic acid, terflavin, rutin, quercetin, luteolin, β-sitosterol, and daucosterol was also reported in the study.[93]

Tinospora cordifolia

A study showed that a combination of RIF (100 mg/kg bw), INH (50 mg/kg bw), and PZA (300 mg/kg bw) produced liver damage in Dunkin-Hartley guinea pigs. However, *T. cordifolia* extract (200 mg/kg, bw) reversed the hepatotoxic damage evident in the restored serum level of ALT, AST, and ALP. The histology results revealed that the extract-treated group recovered from necrosis, steatosis, and inflammation caused by ATDs.[56]

Trapa natans

According to one study, hydroethanolic fruit peel extract of *T. natans* (400 mg/kg bw, po) exhibited hepatoprotective potential against liver damage caused by ATDs in Wistar rats.[79] The extract reduced serum levels of cholesterol, bilirubin, and liver enzymes (ALT, AST, ALP, and LDH). The extract also reduced lipid peroxidation while increasing antioxidant enzyme activities (CAT and SOD) and GSH levels. The observed effect was comparable to that of silymarin.[94]

Vitex negundo

The hepatoprotective effect of hydroethanolic leaf extract of *V. negundo* (500 mg/kg bw, po) against liver injury caused by RIF/INH/PZA treatment was investigated in Wistar rats.[95] By lowering serum levels of ALT, AST, ALP, and bilirubin, the extract demonstrated its hepatoprotective potential against liver damage caused by ATDs. This report was comparable to an Lv 52-positive standard. The plant was shown to contain important phytochemicals such as vitexin, viridifol, luteolin, caffeic acid, and β-sitosterol.[95]

Ziziphus mauritiana

The hepatoprotective potential of *Z. mauritiana* extract (200 mg/kg bw) against hepatotoxicity caused by a combination of RIF (100 mg/kg bw), INH (50 mg/kg bw), and PZA (300 mg/kg bw) was investigated in Dunkin-Hartley guinea pigs.[43] The extract treatment restored AST, ALT, and ALP levels to normal levels.[56]

Ziziphus oenoplia

The hepatoprotective effect of methanolic (50%) root extract of *Z. oenoplia (L.) Mill* (30 mg/kg bw, po) against liver damage caused by ATD (RIF/INH, 50 mg/kg bw each, po) was investigated in Wistar rats.[96] The extract reduced serum levels of liver enzymes (ALT, AST, ALP), as well as bilirubin, like silymarin (100 mg/kg bw, po). The plant extract was found to contain ziziphine and phenols.

Discussion

Summary of hepatoprotective mechanisms of plant extract

The exact hepatoprotective mechanism of plant extracts against liver damage caused by ATDs is not well known but it is thought to be multifactorial. The multifactorial mechanism reflects the complex nature of hepatotoxicity which may have emanated from the liver's susceptibility to various mechanisms of toxicity. Hence, the need for a comprehensive approach and understanding. The presence of antioxidant and antiinflammatory phytochemicals in these studied plants is thought to have a role in this multifactorial mechanism of hepatoprotection. Thus, there is a generally acceptable mechanism that the hepatoprotective properties involve (1) the upregulation of the endogenous antioxidant defense system and its ability to repair liver cell membrane integrity, consequently lowering hepatocellular enzyme leakage into the bloodstream; (2) Some of the phytochemicals present in the studied plant extracts have the capacity to scavenge free radicals, protect the liver from oxidative insults and in effect spare the depletion of endogenous antioxidant compounds. Based on the findings of the studies taken into account in this review, the following are some potential mechanisms (Fig. 1).

Antioxidant activity and/or anti-inflammatory activity

ATD metabolism produces a buildup of ROS, which can lead to oxidative stress in the liver. Antioxidants phytochemicals present in plant extracts can scavenge ROS and protect the liver from oxidative insults. In this instance, the antioxidant phytochemicals play the crucial role of trapping ROS and preventing lipid peroxidation as well as sparing the consumption of endogenous antioxidant compounds. For instance, *Trapa natans* fruit peel extract was discovered to lessen the rat hepatotoxicity caused by INH/RIF.[94,108] Based on phytochemical screening, *T. natans* has been shown to contain flavonoids, steroidal alkaloids, triterpenes, and glycosides. It is recognized that these phytochemical molecules have inherent antioxidant properties.[95] Similarly, the hydroalcoholic extract of *Maytenus royleanus* leaves was found to protect against antituberculosis drug-induced liver injury in mice by reducing oxidative stress.[69] The protection provided by the extract may be due to the presence of quercetin and luteolin.[109] Evidently, quercetin employs multiple pathways to elicit its hepatoprotective effect against ATD-induced liver damage. These include modulating oxidative stress which involves the inhibition of ROS released and subsequent ROS-mediated mitochondrial damage, improvement of mitochondrial function via modulation of Nrf2/antioxidant response element signaling pathway. More so, it lowers apoptosis and enhances cell survival by blocking ROS/Caspase-3, ROS/ C-jun N-terminal kinase, and silent information regulator 1/extracellular kinase apoptosis pathways. Additionally, quercetin can also inhibit NLRP3 inflammatory bodies and decrease the inflammatory response.[110–114]

Beside the aforementioned, some phytochemicals are capable of inducing antioxidant defense systems while others may inhibit pathways that generate free radicals. A typical example is a polysaccharide present in the aqueous extract of *Sagittaria sagittifolia L*. The hepatoprotective ability of *S. sagittifolia* against ATD-induced liver damage is largely dependent on its polysaccharide ability to boost the body's antioxidant capacity by actuating the compensatory Nrf2/antioxidant response element antioxidant stress system, inhibiting CYP2E1 and CYP3A4, reducing hepatotoxicity, inhibiting hepatocyte apoptosis (with attendant increase in cell survival rate), regulate metabolic pathway, and restore homeostasis.[85,115,116] The authors proposed that the activation of Nrf2 and its target antioxidant enzymes, as well as suppression of cytochrome P_{450} production, could partly explain the mechanism of hepatoprotection.

Another noteworthy example is sulfated polysaccharides derived from *Prunella vulgaris*. Sulfated polysaccharides from *P. vulgaris* have been reported to exhibit hepatoprotective properties against ATD-induced liver damage.[117] The plant's hepatoprotective ability is achieved via the enhancement of the antioxidant system (especially SOD) and inhibition of the expression (genes and proteins) of inflammatory factors (IL-6 and TNF-α), culminating in a decrease in inflammatory cell infiltration and the regeneration of hepatocytes. Also, Yulangsan polysaccharide from *Millettia pulchra* has been shown to elicit hepatoprotective effects against ATD-induced toxicity in the liver. The hepatoprotection is mediated via free radical scavenging action and enhanced antioxidant status.[71]

Antiinflammatory properties

Inflammation is one of the mechanisms by which drugs can cause liver damage. Antiinflammatory plant extracts help lower inflammation and protect the liver from injury. For instance, polyphenols extracted from *Crocus sativus L.* have been shown to offer hepatoprotection against ATD-induced toxicity via a decrease in the serum levels of hepatic enzyme and proinflammatory cytokines markers.[54] Different bioactive phytochemicals belonging mainly to flavonol, a derivative of flavonoids have been found to be present in *C. sativus*. Fisetin, morin, quercetin, and rutin are the predominant component present in this extract that has been shown to mitigate hepatotoxic damage caused by INH-RIF. Flavonoid compounds are extremely important plant metabolites because of their free radical scavenging ability due to their hydroxyl groups. Therefore, the flavonoid content of plants may directly contribute specifically to their antioxidant and hepatoprotective activity.[118]

Total flavonoids from *Polygonum perfoliatum L* have been reported to elicit hepatoprotection against ATD-induced liver injury via modulation of antioxidant system (increased SOD activity), inflammatory response (inhibition of nuclear factor-κB signaling pathway) and apoptotic pathway (inhibition of the C-jun N-terminal kinase/bcl-2-associated X protein pathway).[119] Thus, it relieves ATD-induced oxidative stress and apoptosis via the activation of the compensatory Nrf2/ARE signaling pathway and inhibition of bcl-2-associated X protein expression.[120]

Depletion of protoporphyrin IX (PPIX)

The accumulation of PPIX, an endogenous hepatotoxin, has been reported to be involved in ATD-induced liver toxicity. Ferrochelatase and breast cancer resistance protein have been reported to play crucial roles in the metabolism and transport of PPIX respectively. He *et al.* revealed that curcumin, a bioactive polyphenolic component of *Curcuma longa,* relieved INH/RIF-induced liver injury by causing depletion of PPIX levels via induction of Ferrochelatase and breast cancer resistance protein expression resulting in accelerated efflux of PPIX from hepatocytes.[121] Thus the depletion of PPIX accumulation is involved in the protective effect of curcumin on INH/RIF-induced liver injury.

Future perspective

The utilization of traditional medicinal herbs has the potential to significantly improve treatment outcomes. The future holds promising prospects as hepatoprotective potentials of TMP against the ravages of ATDs are being assessed using contemporary scientific research. Below are some potential future scenarios that could influence how this dynamic field unfolds.

1. Advanced Research and Discovery: Future research using

genomics, metabolomics, and proteomics can uncover novel bioactive compounds in TMP, aiding in the development of targeted therapies.
2. Precision Medicine: Precision medicine focuses on personalized treatments based on genetic, environmental, and lifestyle factors, using TMP to address unique drug-induced liver injury susceptibility.
3. Herbal Combinations: Synergistic herbal combinations guided by both traditional knowledge and scientific evidence, combining complementary medicinal plants with hepatoprotective properties, could be a key component in tuberculosis treatment.
4. Standardization and Quality Control: Rigorous standards for medicinal plant cultivation, processing, and quality control are crucial for ensuring consistent potency and safety across herbal products, making them more reliable for clinical use.
5. Clinical Validation: Clinical trials are crucial for scientific progress in herbal interventions, requiring large-scale, multicenter studies to investigate efficacy and safety in diverse patient populations.
6. Pharmacovigilance: The utilization of TMP in clinical practice necessitates robust pharmacovigilance systems for monitoring adverse events, and ensuring safety for healthcare providers, regulators, and patients.

Conclusions

The use of TMP in the protection against ATD-induced liver injury represents a fascinating journey connecting the wisdom of folkloric medicine with the exactness of modern medicine. There is a wealth of botanical remedies that have gained popularity as prominent hepatoprotectors. This review has uncovered both amazing potential and remarkable challenges in the search for hepatoprotective herbs against ATD-induced liver injury. Several extracts of some of these botanical remedies have been assessed for their hepatoprotective potentials and, they no doubt contain bioactive phytochemicals that are capable of protecting the liver against hepatotoxicity caused by ATDs.

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Conflict of interest

The authors declare they have no real or potential conflict of interests related to this paper.

Author contributions

Conceived the idea and wrote the initial draft (CEU), and performed the literature search and data collection (MSS). Both authors proofread the final manuscript.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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