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REVIEW ARTICLE

BENEFICIAL ROLE OF HERBAL HEPATOPROTECTANTS: A NOVEL APPROACH TO PREVENT HEPATOTOXICITY DUE TO ANTITUBERCULOSIS TREATMENT

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ABSTRACT

The first line antituberculosis drugs, isoniazid, rifampicin and pyrazinamide continue to be the effective in the treatment of tuberculosis; however, their use is associated with toxic reactions in tissues, particularly in the liver, leading to hepatitis. Hepatotoxicity has been reported in Indian patients at a high risk (up to 11.5%) than in their western counterpart (up to 4.3%). Since all the drugs used in the treatment of tuberculosis are shown to have hepatotoxic effects, studies have been performed to prevent or reduce the toxicity by the use of natural herbal drugs without interfering with the therapeutic actions of the drugs. Management of liver disease is still a challenge to the modern medicine. In the absence of reliable liver-protective drugs in the allopathic medical practices, herbs play a vital role in the management of liver disorders. In traditional medicine, the plants have been used to cure jaundice. In Indian ayurvedic medicine, the oral administration of extracts of dried rhizomes and roots are claimed as a cure for human viral hepatitis. The present review summarizes the list of plants/herbal formulations studied for their hepatoprotective activity in antitubercular drugs-induced hepatitis. However, despite extensive positive research data from experimental studies for herbal drugs in antitubercular drugs-induced hepatitis, and a clinical study, large scale clinical trials are needed to explore the hepotoprotective potential of herbal medicines in antitubercular drugs-induced hepatotoxicity.

KEY WORDS: Tuberculosis, herbal drugs, hepatotoxicity, antitubercular drugs

INTRODUCTION:

Tuberculosis (TB) is a deadly infectious disease caused by mycobacteria, mainly *Mycobacterium tuberculosis*. TB mostly attacks the lungs (as pulmonary TB) but can also affect the central nervous system, the lymphatic system, the circulatory system, the genitourinary system, bones, joints and even the skin. Other mycobacteria such as *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium canetti*, and *Mycobacterium microti* are also responsible to cause tuberculosis, but these species do not usually infect healthy adults [1]. In 2007 there were an estimated 13.7 million chronic active cases, and according to the World Health Organization (WHO), in 2010, 8.8 million individuals became ill with TB, and 1.45 million died, mostly in developing countries. In addition, a rising number of people in the developed world are contracting tuberculosis because their immune systems are compromised by immunosuppressive drugs, substance abuse, or HIV/AIDS [2].

Combination chemotherapy containing isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), with or without ethambutol, for an initial 2 months followed by continuation phase of 4-6 months of INH+RIF is the preferred regimen for successful treatment, which prevents acquired resistance and enhances efficacy [3]. The poor patient compliance is partly due to adverse effects, especially gastrointestinal upset, which are relatively common in the first few weeks of antituberculosis therapy (ATT). Drug-induced hepatotoxicity is a potentially serious adverse effect of antituberculosis or anti-Koch's treatment (AKT) regimens containing INH, RIF and PZA [4]. A high risk of hepatotoxicity has been reported in Indian patients (up to 11.5%) than in their Western counterpart (up to 4.3%). A meta-analysis of studies involving several anti-tuberculosis drug regimens estimates the incidence of liver toxicity is 2.6% with co-administered isoniazid and rifampicin, 1.6% with isoniazid alone, and 1.1% with rifampicin alone [5]. In a group of European patients, the incidence of ATT-induced hepatotoxicity was found to be 18.2% in group having risk factors like, old age, extensive TB, malnutrition, alcoholism,

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HIV and chronic viral hepatitis B and C infections, as against 5.8% in group without risk factors indicating the significance of risk factors [6].

ATT induced hepatotoxicity can be managed in clinical cases by stopping the offending agents, once there is an evidence of liver damage and reintroducing the same after normalization of liver enzymes [7, 8]. To reduce the incidence of hepatotoxicity in latent TB patients, recommendations for drugs and patients selection criteria have been revised several times by organizations such as the Center for Disease Control, American Thoracic Society, Joint Tuberculosis Committee of British Thoracic Society and Hong Kong Tuberculosis Service but until today no drug has been developed for the prevention of hepatotoxicity [9].

Only a few modern drugs are available for treating liver diseases. Drugs such as tricholine citrate, trithioparamethoxy phenyl propene, and essential phospholipids, combination of L-ornithine L-aspartate and pancreatin, silymarin and ursodesoxy cholic acid are generally prescribed for hepatitis, cirrhosis and other liver diseases. However, these modern medical treatments are still far from satisfactory. Management of liver disease is still a challenge to the modern medicine. In the absence of reliable liver-protective drugs in the allopathic medical practices, herbs play a vital role in the management of liver disorders. Many indigenous plants are used for the treatment of liver disorders [10]. The interest in herbal drugs also stems from the fact that modern medicine does not have a suitable answer for many conditions such as liver disorders, heart diseases and for chronic conditions such as arthritis, asthma and many skin conditions [11].

Traditional systems of medicine remain the major source of health care for more than two thirds of the world's population and impressive progress has been made in certain developing countries like China through integration of traditional systems with western systems and the application of modern science and technology to the promotion and development of traditional medicine. Ayurveda, practiced in India, perhaps is the only organized science in the world that deals with the ecological development, cultivation of medicinal plants, harvesting specific parts of plants, processing and preserving them and diagnosing and treating the condition. Several Indian medicinal plants have been extensively used in the Indian traditional system of medicine for the management of liver disorder as hepatoprotectant. The present review article suggests a novel approach of concurrent administration of herbal drugs with antituberculosis agents to prevent their hepatotoxicity justified by preclinical and clinical trials.

PATHOGENESIS OF HEPATOTOXICITY BY ANTITUBERCULAR DRUGS:

The pathogenesis of hepatotoxicity is not clearly known, but one of the possible mechanisms for the hepatotoxicity of isoniazid and rifampicin is through liver enzyme induction in the hydrolase system enhancing the toxicity of some of the isoniazid metabolites. Antituberculosis drug-induced hepatitis has also been found to be associated with acetylator phenotypes and other genetic polymorphisms, including cytochrome P450 2E1 and glutathione S-transferase M1, and certain Major Histocompatibility Complex Class II associated HLA-DQ alleles. Antituberculosis drugs act as inducers of hepatic cytochrome P450 enzymes. For example, rifampicin is a potent inducer of CYP2D6 and CYP3A4, and isoniazid induces CYP2E1 [12]. The induction of cytochrome P450 enzymes is known to take part in increased drug disposition and development of multi-drug resistance. Xenobiotics, including anti-tuberculosis drugs, undergo biotransformation in the liver catalyzed by microsomal enzyme systems. The major isozyme of cytochrome P450 enzymes in bioactivation is CYP2E1, which is also involved in hepatic toxicity of carbon tetrachloride, ethanol and acetaminophen.

Oxidative stress is also one of the mechanisms with a central role involved in the pathogenesis of antitubercular drugs-induced hepatitis. INH and RIF induced damage may involve oxidative stress [13], lipid peroxidation (LPO) [14], choline deficiency leading to lowering of phospholipids, and protein synthesis with alteration in cell wall configuration [15], reduced glutathione level [16]. It is the result of excessive production of oxidant species and/or depletion of intracellular antioxidant defenses, leading to an imbalance in the redox status of the hepatic cells [17].

The effects of oxidative stress can be evidenced by cellular accumulation of lipid peroxides. The oral administration of anti-tubercular drugs caused elevation in the level of lipid peroxidation with concomitant decline in the level of reduced glutathione (GSH) and the activities of glutathione-dependent antioxidant enzymes glutathione peroxidase (GPx) and glutathione-S-transferase (GST) and antiperoxidative enzymes catalses (CAT) and superoxide dismutase (SOD) in liver mitochondria. In accordance with earlier reported investigations [17, 18], lack of antioxidant defense might have resulted in increased lipid peroxidation and subsequent deleterious effects on hepatocellular membranes in anti-tubercular drugs-induced hepatitis.

THERAPEUTIC IMPLICATIONS OF HERBAL DRUGS:

A review of available literature suggests that reduction in lipid peroxide content in tissue and increase in

SOD, CAT, GSH, GST and GPx activities should help to maintain liver cell integrity and control the increase in level of liver enzymes. It is well known that some herbs are having opposite activities in the form of membrane stabilizing, anti-oxidative and cytochrome P450 2E1 inhibitory effects [19]. It is of importance to note that the inhibition of CYP450 2E1 and antioxidant actions seem to be the common mechanism of action of herbal drugs [20, 21].

PLANT REMEDIES FOR LIVER DISEASES:

Liver disease is still a worldwide health problem. Unfortunately, conventional or synthetic drugs used in the treatment of liver diseases are inadequate and sometimes can have serious side effects [22]. In the absence of a reliable liver protective drug in modern medicine, there are a number of medicinal preparations in Ayurveda recommended for the treatment of liver disorders [23]. In allopathic medicinal practices reliable liver protective drugs are not available but herbs play an important role in management of liver disorders [24]. In view of severe undesirable side effects of synthetic agents, there is growing focus to follow systematic research methodology and to evaluate the scientific basis for the traditional herbal medicines that are claimed to possess hepatoprotective activity [25].

The practitioners of Ayurveda and other traditional medicine have claimed for centuries that extracts from plants can be effectively used for the alleviation of different types of liver diseases. Most of the claims, however, are anecdotal and very few have received adequate medical or scientific evaluation. Except for the use of an appropriate vaccine for the treatment of hepatitis caused by viral infection, very few effective treatments are available today to cure liver diseases. It is not surprising, therefore, that a considerable interest has been taken by researchers to examine these numerous traditional plant remedies, used for treating liver disorders. In recent years, investigations have been carried out to provide experimental evidence, confirming that many of these plants do indeed have hepatoprotective properties. Recent progress in the study of such plants has resulted in the isolation of about 170 different phytoconstituents from plants belonging to about 55 families, which are claimed to exhibit hepatoprotective activity [26]. Numerical medicinal plants are used for the same purpose in ethnomedical practices and in traditional system of medicines in India. Many herbs were found in India as well as in tropical and sub tropical regions of the world. Table 1 summarizes plants and the part of the plants used for hepatoprotective activity.

PLANTS/HERBS WITH HEPATOPROTECTIVE ACTIVITY AGAINST ANTITUBERCULAR DRUGS-INDUCED HEPATOTOXICITY:

The available literature shows that the extracts obtained from several plants have hepatoprotective activities against the toxicity induced by xenobiotics, including those that are used in the treatment of tuberculosis [27]. Table 2 summerizes the list of plants/herbal formulations studied for hepatoprotective activity against anti-tubercular drugs-induced hepatotoxicity.

Garlic (*Allium sativum* L. Alliaceae), has been found to have an important dietary and medicinal role for centuries. Hepatoprotective effect of garlic (garlic bulb) was evaluated on isoniazid and rifampicin-induced hepatic injury in Wistar rats. Garlic along with INH+RIF significantly lowered the elevated serum ALT, AST and bilirubin levels. Garlic with INH+RIF prevented the induction of histopathological injuries and showed higher levels of glutathione and low levels of LPO as compared to the INH+RIF treated group [28]. Thiosulfinates and other secondary metabolites of garlic, including steroids, terpenoids, flavonoids and other phenols, may be responsible for reported therapeutic effects of garlic. Garlic also increases the antiinflammatory monocyte IL-10 production and decreases that of proinflammatory cytokines such as TNF-α, IL-1ß, IL-6, IL-8, T cell interferon gamma, IL-2 [29]. Garlic, a natural substance, has also been shown to inhibit LPO [30]. Phytochemicals from plant rich diets (including garlic) provide an important additional protection against oxidative damage [31]. Organic sulfur compounds from garlic and related compounds have antioxidant, detoxifying and other properties. These detoxifying effects are related to their ability to inhibit phase I enzymes and induce phase II enzymes or bind to exogenous toxins through sulfhydryl groups [32]. A hepatoprotective role of garlic has been documented in acetaminophen-induced hepatotoxicity [33]. Aged garlic extract increases cellular glutathione in a variety of cells including those in normal liver and mammary tissue [34].

Turmeric (*Curcuma longa* Linn. Zingiberaceae), a common Indian dietary pigment and spice have been shown to possess a wide range of therapeutic utilities in the traditional medicine. Curcumin has free radical scavenging and hepatoprotective activities tested *in vitro* [35]. Turmeric powder was used as hepatoprotectant in INH+RIF+PZA induced hepatotoxicity in guinea pigs. It suppresses the production of superoxide by macrophages, has a potent anti-inflammatory action that inhibits the production of tumor necrosis factor alpha (TNF-α), interleukin (IL) 1- β and the activation of NFκ- B in human monocytic derived cells [36]. It also has a strong

antioxidant property and it inhibits lipid peroxidation in rat liver microsomes, erythrocytes membrane and brain homogenates, by maintaining the activity of SOD, catalase and glutathione peroxidase at a higher level [37]. These properties clearly explain the hepatoprotective potential of *C. longa* in the experimental study.

Ocimum sanctum Linn. (Labiateae), commonly known as *Tulsi* in India, is known to have adaptogenic activity [38]. It has numerous pharmacological activities, such as hypoglycemic, antistress, immunomodulatory, analgesic, antipyretic, antiinflammatory, antiulcerogenic, antihypertensive, CNS depressant, hepatoprotective, chemopreventive, radioprotective, antitumor and antibacterial activities [39, 40]. A fine powder of shade dried leaves of Tulsi was tested as hepatoprotectant in INH+RIF+PZA induced hepatotoxicity in guinea pigs. *O. sanctum* in mice decreases hepatic lipid peroxidation (LPO) and glucose-6-phosphatase (G-6-P) activity, while the activities of endogenous antioxidant enzymes, SOD and CAT were increased [41].

Tinospora cordifolia (Wild) Miers ex Hook F and Thomas (Menispermaceae) is popularly known as *Giloya* in Hindi. It is an effective immunostimulant [42]. *Giloya* powder of aerial roots was tested as hepatoprotectant in INH+RIF+PZA induced hepatotoxicity in guinea pigs. *Tinospora cordifolia* induces enzymes of drug metabolism and the antioxidant system and inhibits lipid peroxidation in mice. Cytochrome P450, GST, SOD and CAT are enhanced. These effects improve liver function, protect against toxic assaults and increase protein synthesis by the liver [43].

Zizyphus mauritiana Lam. (Rhamnaceae), commonly known as *Ber* in India. The biological active compounds, such as triterpenes, cyclopeptide alkaloids and flavonoids have been shown to have inhibitory effects on histamine release, hippocampal formation, and cycolo-oxygenase-1 and 2 [44]. It also has cytotoxic, immunological adjuvant and hepatoprotective activities [45]. A fine powder of seeds of *Ber* was tested as hepatoprotectant in INH+RIF+PZA induced hepatotoxicity in guinea pigs.

Picrorhiza kurroa Royle ex Benth. (Scrophulariaceae) is commonly known as, *Kutki* in India. In traditional medicine, the plant has also been used to cure heart ailments, abdominal pain, stomach disorders, anaemia, jaundice, and for promoting bile secretion [46]. The antihepatotoxic effects of ethanol extract of rhizomes and roots of *Picrorhiza kurroa* on liver mitochondrial antioxidant defense system in anti-tubercular drugs (isoniazid and rifampicin)-induced hepatitis in rats had been investigated [47]. Co-administration of *P. kurroa* with INH+RIF increases the activities of the antioxidant enzymes. The administration of ethanol extract of *P. kurroa* protects liver mitochondrial membranes against D-galactosamine-induced hepatotoxicity by its membrane-stabilizing and antioxidant properties [48]. The ethanol extract of the plant has protective property against CCl_4-induced liver damage in rats [49]. Picroliv, an iridoid glycoside mixture of picroside I and kutoside from *Picrorhiza kurroa* (roots and rhizomes) offers protection against thioacetamide induced hepatic damage in rats [50]. It has been reported that picroliv protects against alcohol induced chronic hepatotoxicity [51]. The unpaired electron present in the hydroxyl free radical generated during antitubercular drugs-induced hepatitis might have been trapped and dismuted by the electrophilic substances such as picroside I, picroside II and kutkoside, which are present in rich quantities in the roots and rhizomes of *P. Kurroa* [46].

Oral treatment with an ethanolic extract of roots of *Hemidesmus indicus* (L.) R.Br. (Asclepiadaceae) (100 mg/kg, for 15 days) significantly prevented rifampicin and isoniazid-induced hepatotoxicity in rats [52]. An extract of this plant is reported to possess antiinflammatory, antipyretic, antioxidant and antiulcerogenic properties [53]. *H. indicus* extract is also found to inhibit lipid peroxidation and scavenge hydroxide radicals *in vitro* [54].

Azadirachta indica Juss (Meliaceae), popularly known as *Neem*, is known to possess antiinflammatory, antipyretic, antimicrobial, antidiabetic and diverse pharmacological properties. Co-administration of *A. indica* aqueous leaf extract along with the anti-tubercular drugs significantly prevented all the biochemical and histological alterations caused by the anti-tubercular drugs [55]. *A. indica* leaves have been shown to prevent hepatic damage induced by paracetamol in rats [56].

Moringa oleifera Lam. (Moringaceae), commonly known as *Drumstick*, is used in Indian folk medicine for the treatment of various illnesses. The hepatoprotective effect of an ethanolic extract of *Moringa oleifera* leaves was evaluated on liver damage induced by antitubercular drugs (INH, RIF and PZA) in Wistar rats. Oral administration of the extract showed a significant protective action evident by decreasing the levels of ALT, AST, ALP and bilirubin in the serum; liver LPO, and enhancing antioxidants in liver [10].

Vitex negundo Linn. (Verbenaceae), has been claimed to possess many medicinal properties [57]. Fresh leaves *Vitex negundo* of have been suggested to possess anti-inflammatory and pain suppressing activities possibly mediated via prostaglandin (PG) synthesis inhibition, antihistaminic, membrane stabilizing and antioxidant activities [58]. Hepatoprotective activity of *Vitex negundo* leaf ethanolic extract was investigated against

hepatotoxicity produced by administering a combination of three antitubercular drugs INH, RIF and PZA [59].

The hepatoprotective property of a 50% hydroalcoholic extract of the fruits of *Emblica officinalis* Gaertn. (Euphorbiaceae) (fruit) (EO-50) has been evaluated against antituberculosis drugs-induced hepatic injury. The hepatoprotective activity of EO-50 was found to be due to its membrane stabilizing, anti-oxidative and CYP 2E1 inhibitory effects [19].

Terminalia chebula Retz. (Combetraceae) is an important herbal drug in Ayurvedic Pharmacopoeia [60]. 95% ethanolic extract of *Terminalia chebula* (fruit) prevents the hepatotoxicity caused by the administration of rifampicin (RIF), isoniazid (INH) and pyrazinamide (PZA) (in combination) in a sub-chronic mode (12 weeks). The hepatoprotective effect of *Terminalia chebula* extract could be attributed to its prominent anti-oxidative and membrane stabilizing activities [61].

Silymarin has been used as a dietary supplement for hepatoprotection for over 2000 years. Silymarin, commercially available as Milk Thistle, is an extract from the seeds of *Silybum marianum* (L.) Gaerth (Asteraceae). Silybines (A and B isomers), isosilybines (A and B), silychristine and silydianine are active flavonoids found in silymarin extract [62]. Biochemical manifestations of liver toxicity caused by antiTB drugs are reversed by co-administration of Silymarin [63]. It has been reported that the administration of silymarin together with INH+RIF or INH+RIF+PZA decreases hepatotoxicity of drugs as judged from liver function tests [64]. Silymarin decreased serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP), levels of bilirubin, LPO and increased GSH content, GPx and CAT activities in liver.

Rhinax, (a polyherbal formulation from Hindustan Antibiotics Ltd., Pimpri, Pune, India.) exhibited hepatoprotective function against anti-tubercular drug-induced hepatotoxicity in Wistar rats. This herbal formulation consists of water extracts of medicinal plants, namely *Withania somnifera*, *Asparagus racemosus*, *Mucuna prurience*, *Phyllanthus emblica*, *Terminalia chebula*, *Myristica fragrance*, and *Glycyrrhiza glabra*. *Rhinax* affords hepatoprotection by inhibiting lipid peroxidation and, as a result, the animals showed improved antioxidant status [18].

Liv 52 (a polyherbal Ayurvedic formulation from Himalaya Drug Company, Bangalore, India.), exhibited hepatoprotective activity when tested against chronically antitubercular drug treated rats. Liv 52 is prepared from *Capparis spinosa*, *Cichorium intybus, Solanum nigrum, Cassia occidentalis, Terminalia arjuna, Achillea millefolium, Tamarix gallica* and *Mandur bhasma* (It is prepared from ferric oxide, triturated in the juices of many hepatic stimulants and cholagogues). Liv 52 affords hepatoprotection by improved antioxidant status and inhibiting lipid peroxide production [65].

The influence of Liv 100 (a polyherbal Ayurvedic formulation from Himalaya Drug Company, Bangalore, India), on the hepatotoxicity of antituberculosis drugs (INH, RIF, PZA) was studied in male Wistar albino rats. Liv 100 is an improvised and indigenous preparation of Liv 52 which contains extracts of *Cichorium intybus, Solanum nigrum, Phyllanthus amarus, Piccorhiza kurroa and Embelica oficinalis* [66]. Liv 100 is a scavenger of free radicals and it exhibits dose and time dependant protective response against hydrogen peroxide-induced lipid peroxidation [67]. Oral Liv 100 co-administration with antituberculosis drugs modulate the alterations in the xenobiotic metabolizing system and microsomal lipid peroxidation in experimental animals [68].

The number of people being prescribed liver protection drugs worldwide is not known, but it is generally agreed that it is almost universal for TB patients in China [69]. These drugs are either given to all patients on antituberculosis treatment, or those with some liver function test abnormalities. Clinicians and TB specialists in China are convinced that the herbal preparations may have a protective effect on the liver in people taking anti-TB treatment. For many years, the concept of classical phytotherapy using herbal drug combinations with superior efficacy and lesser side effects in comparison with single isolated constituents o plant extracts has been repeatedly assessed clinically as well as pharmacologically [70].

In a preliminary preclinical study, *Curcuma longa* (CL) and *Tinospora cordifolia* (TC) were found to offer protection in guinea pig model of ATT-induced hepatotoxicity [71]. Both these herbs have an excellent safe toxicological profile. In a randomized controlled clinical trial, CL and TC were given as an adjuvant to standard ATT to any kind of TB patients prevented hepatotoxicity very significantly in terms of incidence, duration and severity [9].

Tuberculosis is a leading public health problem world wide, particularly in developing countries. About one third of world's population has latent tuberculosis and approximately 9 million cases of active tuberculosis emerge annually resulting in 2–3 million deaths [71]. Out of 1.86 billion people estimated to be infected with the TB, an estimated 1.3 billion infected people reported to be in developing countries, such as India and China [27]. In view of the seriousness of the problem, World Health Organization (WHO) declared it to be a global emergency in 1993. Active tuberculosis kills about two out of every three

people, if untreated. RIF, INH, PZA with or without ethambutol are still widely used in most anti-tubercular chemotherapeutic regimens. However, these drugs are also well known as hepatotoxic agents [68, 72]. Oxidative stress is one of the mechanism with central role involved in the pathogenesis of antitubercular drugs (INH and RIF)-induced hepatitis [13]. A review of the available literature suggests that a reduction in the lipid peroxide content of tissue and an increase in superoxide dismutase, catalase, glutathione, glutathione-S-transferase and glutathione peroxidase activities should help to maintain liver cell integrity and control the increased level of serum AST, ALT and ALP. The rate of hepatotoxicity is much higher in developing countries like India (8%–30%) as compared to that in advanced countries [73].

In view of the lack of definitive recommendation or alternative safe agents for treating latent or active tuberculosis, it is imperative to evaluate the ability of well known herbs to offer hepatoprotection in animal model of AKT-induced hepatotoxicity. Selection of an animal model is important, if the results of the experiment are to be extrapolated to a human population. The available literature shows that rhinax [18], garlic [28], Liv 52 [54], *Emblica officinalis* [19] and *Terminalia chebula* [60] have demonstrated hepatoprotective activities in experimental animal models of AKT-induced hepatotoxicity in the rat via cellular antioxidant support.

Accumulated data shows that these herbal drugs inhibit several isoforms of CYT P450 enzymes [74], potentiate the antioxidant capacity of the liver [71] and act as a scavenger of oxygen free radicals [75].

As latent TB cases on different preventive regimens have to be at a greater risk for developing hepatotoxicity, the efficacy of these herbs may also be tested in TB patients showing increased liver enzymes detected due to ATT. It remains to be done to exploit the full potential of the hepatoprotective ability of these herbs in cost-effective manner with defined recommendations for different subclasses of patients including latent TB cases and different high risk groups of clinical cases [9]. Yet clinicians and TB specialists convinced that these pharmaceutical and herbal drugs/formulations may have protective effects on the liver in people taking anti-TB treatment. However, it is unclear how the effects, and safety, of these drugs are being evaluated in TB patients. It is suggested that conventional randomized controlled and blinded trials design might be performed. The summary indicates that the evidence base for the use of liver protective drugs in TB patients comprises mainly small, poorly conducted studies that do not reach the standards of trials used in reliable systematic reviews [69]. Hence, large scale clinical trials are needed to explore the hepatoprotective potential of herbal medicines in antitubercular drugs-induced hepatotoxicity.

Table 1: Plants Parts Used For Hepatoprotective Activity

Botanical name (Family)	**Parts Used**
Allium cepa (Alliaceae)	Bulbs
Allium sativum (Alliaceae)	Bulbs
Aphanamixis polystachya (Meliaceae)	Stem, Root bark, Seeds
Apium graveolens (Apiaceae]	Seeds
Arbutus unedo (Ericaceae)	Leaves, Stem Bark.
Areca catechu Linn (Arecaceae)	Inflorescence
Argemone mexicana (Papaveraceae)	Yellow juice
Arenga wightii Griff (Arecaceae)	Inflorescence and fruit husk
Aristolochia indica Linn (Aristolochiaceae)	Roots (tender)
Aspargus officinalis (Liliaceae)	Roots
Asparagus racemosus Willd (Liliaceae)	Roots
Azadirachta indica A. Juss (Meliaceae)	Root Bark, Leaves
Boerhaavia diffusa (Nyctaginaceae)	Whole plant with root
Calotropis gigantean (Asclepiadaceae)	Leaves
Carica papaya (Caricaceae)	Milky juice
Centella asiatica (Apiaceae)	Whole plant with root
Centella asiatica Urban (Apiaceae)	Whole Plant
Ceratopteris siliquosa (L) Copel (Ceratoptendaceae)	Whole Plant
Cichorium intybus (Asteraceae)	Leaves and roots
Cuminum cyminum Linn (Apiaceae)	Fruits
Curcuma domestica Val (Zingiberaceae)	Fresh rhizome

Cynara scolymus (Asteraceae)	Leaves and roots
Daucus carota (Apiaceae)	Fruit and root
Desmodium biflorum Linn (Fabaceae)	Whole plant
Eclipta prostrata (Asteraceae)	Whole plant
Elettaria cardamomum Maton (Zingiberaceae)	Seeds
Ficus glomerata Roxb (Moraceae)	Fruits
Ficus racemosa Linn (Moraceae)	Tender root
Foeniculum vulgare (Apiaceae)	Seeds
Fumaria officinalis (Fumiriaceae)	Whole plant
Fumaria parviflora (Fumaricaceae)	Whole plant
Glycosmis pentaphylla (Rutaceae)	Leaves
Hibiscus lampas Cav. (Malvaceae)	Fresh root
Impatiens henslowiana Arn (Balsaminaceae)	Flowers and leaves
Iris germanica (Iridaceae)	Rhizomes
Ixora coccinea Linn (Rubiaceae)	Fresh root
Lobelia inflate (Lobeliaceae)	Whole plant
Lycopodium clavatum (Lycopodiaceae)	Plant and spores
Momordica subangulata Bl. (Cucurbitaceae)	Fruits (tenders)
Moringa oleifera Lam (Moringaceae)	Stem bark
Moringa pterygosperma (Moringaceae)	Leaves, stem, root and gum
Myristica fragrans (Myristicaceae)	Fruits
Myrtus communis (Myrtaceae)	Leaves
Naregamia alata W & A (Meliaceae)	Whole plant
Phyllanthus emblica (Euphorbiaceae)	Roots
Phyllanthus fratenus Webst. (Euphorbiaceae)	Whole plant
Piper longum Linn (Piperaceae)	Stem
Primula obconica (Primulaceae)	Whole plant
Raphanus sativus (Brassicaceae)	Whole plant
Ricinus communis Linn (Euphorbiaceae)	Tender Leaves
Ruscus aculeatus (Ruscaceae)	Whole plant with root
Santolina chamaecyparissus (Asteraceae)	Whole plant
Sarothamnus scoparius (Papilionaceae)	Roots
Silibum marianum (Asteraceae)	Seeds
Solanum nigrum (Solanaceae)	Leaves
Taraxacum officinale (Asteraceae)	Roots
Terminalia chebula (Combretaceae)	Fruits
Tinospora cordifolia (Menispermaceae)	Fresh stem
Trigonella foenum graecum (Papilionaceae)	Leaves and seeds
Viola odorata (Violaceae)	Whole plant
Zingiber officinale (Zingiberaceae)	Rhizomes

Table 2: Plants Studied For Hepatoprotective Potential In Antitubercular Drugs – Induced Hepatitis In Experimental And Clinical Trials

Name of herb/formulation	Component / part used	Dose	Model	Therapeutic uses reported	Parameters estimated	Inference	Reference
Allium sativum L.	Fresh homogenate of Garlic bulb	0.25g/kg orally	Isoniazid and rifampicin-induced hepatic injury in rats	Anticancer, antioxidant, immunomodulatory, anti-inflammatory,	Body weight, liver weight, ALT, AST, Bilirubin, Lipid peroxidation, Histological	Reduction in ALT, AST bilirubin level, Increase in body weight, liver	[28]

				hypoglycaemic and as antibiotic	analysis of liver	weight and reduced lipid peroxidation	
Curcuma longa Linn., *Ocimum sanctum* Linn., *Tinospora cardiofolia* (Willd.) Miers ex Hook. F. and Thoms and *Zizyphus mauritiana* Lam.	Powder from dried rhizomes of C. longa, fine powder of shade dried leaves of O. sanctum, powder of aerial roots of T. cardifolia and fine powder from seeds of Z. mauritiana	200 mg/kg orally	Effects on isoniazid, rifampicin and pyrazinamide - induced hepatic injury and immunosuppression in guinea pigs	Anti-inflammatory, antioxidant, antimutagenic, antitumor, antifungal, antiviral, antibacterial, antispasmodic and hepatoprotective (*C. longa*); Adaptogenic activities, hypoglycaemic, antistress, immunomodulatory, analgesic, antipyretic, anti-inflammatory, antiulcerogenic, antihypertensive, CNS depressant, hepatoprotective, chemopreventive, radioprotective, antitumor and antibacterial (*O. sanctum*); Debility, digestive disturbances, loss of appetite, fever and immunostimulant (*T. cardifolia*); Cytotoxic, immunological adjuvant and hepatoprotective (*Z. mauritiana*)	Serum AST, ALT, ALP, total bilirubin and Liver histology	Recovery of liver enzymes e.q. AST, ALT ALP, decrease in hepatic lipid peroxidation	[71]
Picrorhiza kurroa Royle ex Benth.	Crude ethanolic extracts of Picrorhiza kurroa(dried rhizomes and roots)	50 mg/kg orally	Antihepatotoxic effect on mitochondrial defense system in antitubercular drugs (isoniazid and rifampicin)-induced	Heart ailments, abdominal pain, stomach disorders, anaemaia, jaundice, and for promoting bile secretion	Lipid peroxides, GSH, GPx, GST, SOD, CAT	Increase the activities of antioxidant enzymes, to counteract the free radicals	[47]

			hepatitis in rats				
Hemidesmus indicus (L.) R.Br.	Ehanolic extract of Hemidesmus indicus (roots)	100 mg/kg/ p.o.	Rifampicin and isoniazid-induced hepatotoxicity in rats	Antidiarrhoeal, Antioxidant, Hypoglycaemic, Renoprotective, Antnociceptive, Hepatoprotective activity	Serum ALT, AST, ALP, Bilirubin, and Lipid peroxidation, SOD, CAT,	Decrease in AST, ALT, ALP and bilirubin level, reduction in lipid peroxidation	[52]
Azadirachta indica Juss	Aqueous extract of Azadirachta indica (Leaves)	1 g/kg orally	Antitubercular drugs-induced hepatotoxicity in albino rats.	Anti-inflammatory, antipyretic, antimicrobial, anti diabetic, hepatoprotective	ALT, AST, ALP and histology of liver	Decrease in ALP, AST, ALT	[55]
Moringa oleifera Lam.	Ethanolic extract of Moringa oleifera (Leaves)	500 mg/kg p.o.	Hepatoprotective activity on antitubercular drugs-induced liver damage in rats	Cardioprotective, Antioxidant, Anti-inflammatory, Antipyretic, Wound healing, Hepatoprotective activity	Serum AST, ALT, ALP, Bilirubin, Lipid peroxidation in liver	Decrease in AST, ALT, ALP and bilirubin level, reduction in lipid peroxidation	[10]
Vitex negundo Linn.	Ethanolic extract of Vitex negundo (Leaves)	250 and 500 mg/ kg orally	Hepatoprotective activity against anti-tubercular drugs induced hepatotoxicity	Anti-inflammatory, antihistaminic, membrane stabilizing and antioxidant activities, hepatoprotective activity	Serum AST, ALT and ALP levels; Histology of the liver	Decrease in serum AST, ALT and ALP levels	[59]
Emblica officinalis Gaerth	Hydroalcoholic extract of Embelica officinalis (Fruits)		Protective effect against anti-tuberculosis drugs - induced liver toxicity	Antiplatelet activity, hypolipidemic, haematinic, antiulcer, hepatoprotective, antiaging activity	GSH, GR, GPx, GST SOD, CAT	Improved antioxidant status, membrane stablizing activities and Inhibition of CYP 2E1	[19]
Terminalia chebula Gertn.	Ethanolic extract of Terminalia chebula (Fruits)	200 mg/kg orally	Prevention of liver toxicity caused by sub-chronic administration of rifampicin, isoniazid and pyrazinamide in combination	Antibacterial, Antifungal, Antioxidant, Antiviral, Antimutagenic, Anticarcinogenic, Urogenital activity, Hypolipidemic, Cardioprotective and Antidiabetic ,Hepatoprotective activity	GSH, GR, GPx, GST SOD, CAT	Improved antioxidant status, membrane stablizing activities and histological changes in liver	[61]
Silybum marianum (L.) Gaerth	Extracts from Silybum	200 mg/kg intra-	Liver protection against toxic	Antioxidant, Anti-inflammatory,	Serum ALT, AST , ALP, Serum albumin, serum	Reduction in ALT, AST, ALP level, increase	[64]

	marianum (Seeds)	gastric administration	effects of anti-tuberculosis drugs in experimental animals	Anticancer and hepatoprotective	total bilirubin	in serum albumin protein and decrease in total bilirubin level, decreased frequency of both steatosis and patchy necrosis in liver	
Rhinax	Polyherbal formulation	160 mg/kg p.o.	Hepatoprotective effect on antitubercular drugs-induced hepatotoxicity in rats	Antioxidant, Anti-ulcer activity, Hepatoprotective activity	GSH, GR, GPx, GST SOD, CAT and Cytochrome P-450 content	Inhibition of lipid peroxidation, improved antioxidant status, decrease in cytochrome P-450 contents	[18]
Liv 52	Polyherbal Ayurvedic formulation	500 mg/kg, p.o.	Antitubercular Drugs-induced Hepatotoxicity in Rats	Hepatoprotective	GSH, GST, GPx, SOD, CAT and LPO	Inhibition of lipid peroxidation, improved antioxidant status	[65]
Liv 100	Polyherbal Ayurvedic formulation	400 mg/kg, orally	Rifampicin, isoniazid and pyrazinamide-induced hepatotoxicity in rats	Hepatoprotective	Drug metabolizing enzyme Cytochrome P-450, LPO	Decrease in LPO, and cytochrome P-450	[68]
Curcuma longa Linn., *Tinospora cordifolia* (Willd.) Miers ex Hook. F. Thoms	Herbal formulation of Curcuma longa Tinospora cordifolia	1 gm each divided into two doses orally	Prevention of hepatotoxicity due to antituberculosis treatment in TB patients	Anti-inflammatory, antioxidant, antimutagenic, antitumor, antifungal, antiviral, antibacterial, antispasmodic and hepatoprotective (C. longa); Debility, digestive disturbances, loss of appetite, fever and immunostimulant (T. cardifolia);	Serum bilirubin and liver enzymes (e.g. AST, ALT, ALP)	Decrease in bilirubin, ALT, AST and ALP levels	[9]

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