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A Review on Hepatoprotective Plants used against Antituberculosis drug (Isoniazid and Rifampicin) Induced Toxicity

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ABSTRACT

Objective The present study aimed to provide the information regarding the hepatoprotective plants used against antituburculosis drugs (Isoniazid and Rifampicin).

Material and Methods In this study, online databases including Web of Science, PubMed, Scopus, and Science Direct were searched for papers published from January 1970 to March 2018. Search terms consisted of medicinal plants, traditional medicine, hepatoprotective, India, liver, antioxidants, Isoniazid and Rifampicin.

Results Punica granatum L., Ficus carica, Daucus carota L., Curcuma longa, Tinospora cordifolia, Picrorhiza kurroa, Cissus quadrangularis, Anisochilus Carnosus, Cassia fistula, Coldenia procumbens Linn., Ziziphus oenoplia, Andrographis paniculata, Cnidoscolus chayamansa, Allium sativum, Piper longum, Carica papaya, Cissampelos pareira, Adenanthera pavonina, Plectranthus amboinicus, Andrographis lineata Nees, Allamanda cathartica Linn, Butea monosperma, Lucas cephalotes, Calotropis procera, Chelidonium majus, Rhynchosia beddomei, solanum xanthocarpum, Hugonia mystax, Berberis Lycium Royale, Canthium dicoccum, Macrotyloma uniflorum, Polygonum glabrum, Nigella sativa, Trigonella foenum graecum, Curcuma zeoderia, Phyllanthus longiflorus, Brassica oleracea, Cucumis melo linn, Crocus sativus and Ziziphus jujube etc are some of the medicinal plants that have been used for the treatment of liver disorders.

Conclusion This review article contributes to the knowledge of reported hepatoprotective plants, which are prevalent for prevention and treatment of liver disorders.

Keywords: Hepatoprotective plants, Isoniazid, Liver, Rifampicin.

I. INTRODUCTION

Liver, the key organ of metabolism and excretion in the body is always capable to perform the task of detoxification. The hepatotoxicants including viruses, fungal products, bacterial metabolites, minerals,

environmental pollutants and chemotherapeutic agents, can provoke various disorders of the organ **(**Tao *et al*., 2008 [1]**).** It plays role in the maintenance, performance and regulating homeostasis of the body. It is involved in almost all the biochemical pathways to growth, fight against disease, nutrient supply, energy provision and reproduction. It also helps in metabolism of carbohydrate, protein and fat, detoxification, secretion of bile and storage of vitamins (Ward *et al*., 1999 [2]).

Liver diseases afflicts over 10% of the world population. This constitutes hepatitis, cirrhosis, fibrosis, hepatic steatosis, alcoholic liver disease and drug induced liver diseases (Zhang *et al*., 2013 [3]). Liver diseases have become one of the major causes of morbidity and mortality in humans and animals all over globe and hepatotoxicity due to drugs appears to be the most common contributing factor (Nadeem *et al*., 1997 [4]). Therefore, strengthening liver function is a fundamental step to achieving or maintaining perfect liver health (Shanmugasundaram and Venkataraman, 2006 [5]).

Only a few modern drugs are available for treating liver diseases. However, these modern medical treatments are still far from satisfactory results. Management of liver disease is still a challenge to the modern medicine. In absence of reliable liver-protective drugs, herbs play a vital role in the management of liver disorders. Many plants are used for the treatment of liver disorders (Pari and Kumar, 2002 [6]).

About 80% of the world population rely on the use of traditional medicine which is predominantly based on plant materials. Medicinal plants play a key role in maintaining the human health (WHO, 1993 [7]).

Liver protective plants contain a variety of chemical constituents like phenols, coumarins, lignans, essential oil, monoterpenes, carotinoids, glycosides, flavanoids, organic acids, lipids, alkaloids and xanthenes (Sharma *et al*., 2002 [8]).

The use of natural remedies for the treatment of liver diseases has a long history, starting with the Ayurvedic treatment, and extending to the Chinese, European and other systems of traditional medicines. The 21st century has seen a paradigm shift towards therapeutic evaluation of herbal products in liver disease models by carefully synergizing the strengths of the traditional systems of medicine with that of the modern concept of evidence based medicinal evaluation, standardization and randomized placebo controlled clinical trials to support clinical efficacy (Thyagarajan *et al*., 2002 [9]).

II. HEPATOPROTECTIVE PLANTS

This review has been presented to enumerate some medicinal plants that have protective properties against Isoniazid and Rifampicin hepatotoxicity.

2.1, Punica granatum L.

Yogeta *et al*. (2007 [10]) examined Coadministration with 70% acetone extract of *Punica granatum L.* significantly prevented elevation in the level of lipid peroxides, serum hepatic marker enzymes (glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, lactate dehydrogenase, alkaline phosphatase), and decrease in the enzymic antioxidants (superoxide dismutase, catalase, glutathione S-transferase, glutathione

peroxidase) and nonenzymic antioxidants (reduced glutathione, vitamin C, and vitamin E) in isoniazid and rifampicin treated rats. Their study also reveal Cotreatment with extract also preserve the structural integrity of the hepatocellular membrane as evident from the significant reduction in these enzymes, prevent the tissue depletion of reduced glutathione, causes a significant decrease in the levels of thiobarbituric acid reactive substances, which may be attributed to its anti–lipid peroxidative activity.

2.2 Ficus carica

Gond and Khadabad (2008 [11]) assessed antihepatotoxic activity of *Ficus carica* on rats treated with rifampicin orally. They observed significant reduction in SGPT, SGOT levels and liver weight in the group treated with petroleum ether extract of *Ficus carica*. Pentobarbitione sleeping time prolonged in rifampicin treated group were also restored in extract treated group. Their investigation exhibit that liver treated with rifampicin resulted in liver enlargement, pale brown colouration, while as group treated with petroleum ether extract of *Ficus carica* had livers which were similar to that found in the normal rats.

2.3 Daucus carota L.

Shoba *et al*. (2008 [12]) noticed the effect of *Daucus carota L*. extract (DCE) on paracetamol, isoniazid (INH) and alcohol induced hepatotoxicity in different group of Wistar rats. They observed paracetamol, INH and alcohol-induced increased biochemical markers viz. Alanine transaminase (ALT), Aspartate transaminase (AST), bilirubin (both total and direct) and prothrombin time (PT) were significantly lowered by pretreatment with the DCE. They found that pretreatment with DCE restored the hepatic histology to normal in INH and alcohol challenged groups, but in paracetamol challenged animals DCE though significantly lowered these parameters, failed to normalize them, indicating its lower efficacy, as compared to that in INH and alcohol induced hepatotoxicity. The cellular injury of the liver associated with oxygen free radicals were scavenged by the presence of carotenes.

2.4 Curcuma longa and Tinospora cordifolia

Adhvaryu *et al.* (2008 [13]) authenticated the ability of *Curcuma longa* and *Tinospora cordifolia* formulation to prevent anti-tuberculosis treatment (ATT) induced hepatotoxicity. Weight and hemoglobin both increased and ESR reduced significantly on intra group pre- and post- treatment comparison in both the groups proving the efficacy of conventional anti-tuberculosis treatment ATT alone too. They found inter group comparison post treatment showed a significant advantage in weight gain and reduction in ESR, but not in hemoglobin level in trial group suggesting the superiority of ATT plus adjuvant herbs over ATT alone. Incidence and severity of hepatotoxicity was significantly lower in trial group (incidence: 27/192 vs 2/316, $P < 0.0001$). Mean aspartate transaminase (AST) (195.93 ± 108.74 vs 85 ± 4.24, $P < 0.0001$), alanine transaminase (ALT) (75.74 ± 26.54 vs 41 ± 1.41, $P < 0.0001$) and serum bilirubin (5.4 ± 3.38 vs 1.5 ± 0.42, $P < 0.0001$). A lesser sputum positivity ratio at the end of 4 week (10/67 vs 4/137, $P = 0.0068$) and decreased incidence of poorly resolved parenchymal

lesion at the end of the treatment (9/152 vs 2/278, P = 0.0037) was observed. Improved patient compliance was indicated by nil drop-out in trial vs 10/192 in control group (P < 0.0001).

2.5 Picrorhiza kurroa

Jeyakumar *et al.* (2008 [14]) assayed the antihepatotoxic effect of the ethanol extract of *Picrorhiza kurroa* rhizomes and roots (PK) on liver mitochondrial antioxidant defense system in isoniazid and rifampicin-induced hepatitis in rats. They calculated that mitochondria of antitubercular drugs administered rats, showed significant elevation in the level of lipid peroxidation with concomitant decline in the level of reduced glutathione and the activities of antioxidant enzymes was observed. Co-administration of PK extract significantly checked these antitubercular drugs-induced alterations and maintained the rats at near normal status, might be ascribable to its hepatocellular membrane-stabilizing action and antioxidant property or to a counteraction of the free radicals by the presence of the electrophilic constituents picroside I, picroside II and kutkoside, which are present in rich quantities in the roots and rhizomes of *Picrorhiza kurroa*.

2.6 Cissus quadrangularis

Swamy *et al.* (2010 [15]) investigated the hepatoprotective activity of methanol extract of *Cissus quadrangularis* (CQ) against isoniazid-induced hepatotoxicity in rats. Elevated levels of aspartate transaminase, alanine transaminase, alkaline posphatase, and bilirubin following isoniazid administration were significantly lowered due to pretreatment with CQ. Pretreatment of rats also with CQ significantly decreased LPO and increased the antioxidant activities such as reduced glutathione, superoxide dismutase, and catalase. Histopathological observation showed that CQ has reduced focal hemorrhage, inflammation, centrilobular degeneration, and necrosis. The aforementioned properties of the CQ is due to the presence of quercetin and kaempferol carotene, and vitamin C.

2.7, Anisochilus Carnosus

Kumar *et al.* (2010 [16]) reported the hepatoprotective activity of alcoholic and aqueous extract of leaves of *Anisochilus Carnosus* against Rifampicin induced hepato toxicity in rats. During hepatic damage the enzyme levels such as SGOT, SGPT, ALP, ALT changes in serum, also alteration occurs in the metabolic activity of hepatocytes such as macrovascicular fatty changes, inflammation, fatty degeneration, evidence of inflammation etc. However aqueous extract exhibited significant dose dependent hepatoprotective activity in comparison to alcoholic extract against liver injury induced by rifampicin.

2.8, Cassia fistula

Jehagir *et al.* (2010 [17]) appraised the effect of ethanolic extract of *Cassia fistula* leaves in experimentally induced drug hepatitis in rodents. The antituberculous (ATT) group of rats showed variable increase in serum ALT, AST, ALP and total bilirubin levels. They viewed that the treatment with 400 and 500 mg/kg of body weight of *Cassia fistula* decreased the level of these parameters in rats. Morphologically, the group which

recieve low dose of *Cassia fistula* showed partial recovery of liver changes. While as the group which receive high dose of *Cassia fistula* showed a significant recovery towards normal liver.

2.9 *Coldenia procumbens* Linn.

Purnima *et al*. (2011 [18]) tested the in vitro hepatoprotective effect of ethanolic extract of *Coldenia procumbens* Linn. using antitubercular drugs as toxicant and silymarin as standard drug by MTT assay. The CTC50 of anti tubercular drugs and galactosamine HCl, used as hepatotoxicants to assess the hepatoprotective effect of the plant extracts were found to be 500µg/ml and 40µg/ml respectively against BRL-3 A cell lines. The ethanolic extract of *Coldenia procumbens Linn* showed over 80 % protection for both the toxicants. Silymarin at the concentration of 250µg/ml showed highest protection (96.47%). *Coldenia procumbens Linn* at 1000µg/ml showed 86.93% protection followed by 125µg/ml which showed least protection i.e. 55.40%.

2.10 *Ziziphus oenoplia*

Roa *et al*. (2012 [19]) validated the hepatoprotective potential of ethanolic (50%) extract of *Ziziphus oenoplia* root against isoniazid (INH) and rifampicin (RIF) induced liver damage in animal models. They calculated the elevated serum enzymatic activities of glutamic oxaloacetic transaminase, glutamate pyruvate transaminase, alkaline phosphatase and bilirubin due to INH + RIF treatment were restored towards normal in a dose dependent manner after the treatment with ethanolic extract of *Ziziphus oenoplia* roots. Meanwhile, the decreased activities of superoxide dismutase, catalase, glutathione S-transferase and glutathione peroxidase were also restored towards normal dose dependently. In addition, ethanolic extract also significantly prevented the elevation of hepatic melondialdehyde formation, hepatocellular disintegrate and the inflammation in the liver in the centrilobular region by INH + RIF treated groups in a dose dependent manner.

2.11 *Andrographis paniculata*

The ameliorative potential of *Andrographis paniculata* on liver damage was evaluated by rifampicin induced hepatotoxicity in rats. Treatment with *Andrographis paniculata* or silymarin could significantly decrease the ALT, AST, ALP, cholesterol and bilirubin whereas protein levels in serum increased when compared with rifampicin alone treated rats. The normalcy of values of liver marker enzymes is an indication of stabilization of plasma membrane as well as repair of hepatic tissue damage caused by rifampicin (Muthulingam. 2012 [20]).

2.12 *Cnidoscolus chayamansa*

Pillai *et al*. (2012 [21]) studied the effect of ethanolic extract of *Cnidoscolus chayamansa* leaves in experimentally drug induced hepatitis in rats. They noticed significant elevation in the levels of serum AST, ALT, ALP and significant decrease in level of total protein and total albumin in a group which received Rifampicin (RIF) and Isoniazid (INH) as compared to the group who received normal saline. Co-administration of Silymarin, low & high dose of (200 & 400mg/kg) *Cnidoscolus chayamansa* ethanolic extract with INH and RIF and INH in groups maintained the levels of AST, ALT, ALP, and serum Total Protein and Total Albumin towards status

quo and Showed minimal necrosis, mild inflammation and less steatosis as compared to only drug treated rats. While as Standard Control group showed normal liver architecture and occasional inflammatory cells with no necrosis.

2.13 Allium sativum

Nasiru *et al*. (2012 [22]) substantiated the hepatoprotective effect of garlic homogenate co-administered with anti-tuberculosis drugs on the liver in rats. The investigators observed that the values of AST, ALT and ALP were significantly higher in rats administered with 51.4 mg/kg of first line anti-TB drugs (Isoniazid, Rifampicin, Pyrazinamide and ethambutol) (negative control) when compared with rats co-administered with same anti-TB drugs and 57.1 mg/kg of garlic homogenate. The AST and ALT levels were found to increase progressively as garlic concentration decreases. There were no significant differences obtained in the level of AST and ALT when compared with seven days treatment. Histological studies shows grey areas as signs of oxidative stress due to the combined effect of the first line anti-TB drugs administered and shows decrease in the grey areas as the concentration of garlic increases.

2.14 Piper longum

Gurumurthy *et al*. (2012 [23]) demonstrated the hepatoprotective effect of aqueous extract of *Piper longum* and piperine. Reduced glutathione levels were significantly decreased ($p<0.001$) and lipid peroxidative levels were significantly increased ($p<0.001$) in the group treated with antitubercular drugs compared to controls. Administration of aqueous extract of *Piper longum* and piperine with antitubercular drugs significantly increased the reduced glutathione levels ($p<0.001$) and decreased lipid peroxidation ($p<0.001$). Histopathological studies display on administration of *Piper longum* and piperine with anti TB drugs lowers lipid peroxidation and there by tissue damage and necrosis and thus exerts hepatoprotective effect.

2.15 Carica papaya

Bafna *et al*. (2013 [24]) screened the hepatoprotective effect of *Carica papaya* leaves against ethanol and anti-tubercular drug-induced liver damage in rats, They studied the treatment of rats with aqueous extract of leaves of *Carica papaya* (AECPL) at the dose of 400 mg/kg (p.o.) and silymarin administration in rats at the dose of 200 mg/kg significantly ($P < 0.001$) decreased the levels of ALT, AST, ALP and total bilirubin in the serum in dose-dependent manner. They further analyzed the extract reduce the level of TBARS in the liver tissue and increase the levels of GSH and SOD, revealing the antioxidant nature of the extract. The animals upon treatement with *Carica papaya* or Silymarin, showed restoration of the normal tissue architecture, fatty infiltration, hepatitis and cirrhosis.

2.16 Cissampelos pareira

Verma and Hussain. (2013 [25]) confirmed the effect of 50% ethanolic extract of *Cissampelos pareira* on SGPT, SGOT, SALP, LPO, CAT, SOD, Total protein, Albumin and Total bilirubin against control and RIF + INH

induced hepatotoxicity in rats. They determined in RIF+INH treated group, the level of SGPT, SGOT, SALP, LPO, Total bilirubin increased and CAT, SOD, Total protein, Albumin decreased. In contrast to the groups treated with 50% ethanolic extracts of *Cissampelos pareira* at dose of (100 - 400 mg/kg) and silymarin restore these levels towards normalcy in a dose related manner. Histological design of the *Cissampelos pareira* treated liver samples showed its ability to prevent hepatocellular necrosis.

2.17 Adenanthera pavonina

The elevated serum enzymatic activities of SGOT, SGPT, ALP, bilirubin and LDH due to INH and RIF treatment were restored and also the increased level of total protein and albumin attain normalcy upon treatement with methanolic extract of leaves of *Adenanthera pavonina* in a dose dependent manner. The anti-oxidant studies showed significant increase in the levels of glutathione, catalase and superoxide dismutase were also restored. In addition, extract also significantly prevented the elevation of hepatic malondialdehyde formation in the liver of INH and RIF intoxicated rats in a dose dependent manner. The histology of liver revealed centrilobular necrosis, liver cell proliferation and suppression of anti-oxidant system restored by methanolic extract of leaves of *Adenanthera pavonina* against INH and RIF induced hepatic damage in rats as compared to standard drug silymarin (Mujahid *et al.*, 2013 [26]).

2.18 Plectranthus amboinicus

Amberkar *et al*. (2014 [27]) put forth the hepatoprotective activity of ethanolic extract of leaves of *Plectranthus amboinicus* against antitubercular drug induced hepatotoxicity in rats. It has been observed that serum enzyme levels AST, ALT and ALP were significantly lowered in rats given a combination of antitubercular drugs with either ethanolic extract of *Plectranthus amboinicus* or silymarin as compared to rats treated with hepatotoxic drugs alone. Coadministration of extract of *Plectranthus amboinicus* or silymarin with antitubercular drugs significantly ($p<0.05$) decreased MDA levels but increased ($p<0.05$) GSH levels as compared to antitubercular drugs. In addition, *Plectranthus amboinicus* showed membrane stabilizing effect which could have protected the hepatocytes from damage by antitubercular drugs.

2.19 Andrographis lineata Nees

Administration of ethanolic extract of the stems of *Andrographis lineata* Nees (EEALN) (200 and 400 mg/kg body wt.) significantly maintained the levels of serum marker enzymes like SGOT, SGPT, ALP, Total Protein, Total and Direct Bilirubin against rifampicin induced liver damage, comparable with that of the standard drug Silymarin. The extract stabilizes the biliary dysfunction with concurrent depletion of raised bilirubin level and the normal hepatocytes, prominent central veins, comparable to that of silymarin. While as rifampicin treated group showed extensive infiltration of lymphocytic portal tracts and feathery degeneration of the hepatocytes (Chakravarthy *et al.*, 2014 [28]).

2.20 Allamanda cathartica Linn.

Pothan and Harindran (2014 [29]) undertook the work to evaluate the cytotoxic activity of methanolic and aqueous extracts of flowers and roots of *Allamanda cathartica Linn*. on BRL 3A cell lines using the MTT assay. They noticed the reduction of viability of cell cultures in the presence and absence of the extracts. Cell viability was inhibited to different extents by the extracts. Silymarin at the concentration of 250µg/ml showed highest protection (95.13%). *Allamanda cathartica Linn* flower and root extract at 1000µg/ml showed 83.93% and 89.39% protection followed by 125µg/ml each showed least protection i.e. 53.40% and 57.40 % respectively against antitubercular drugs (Isoniazid, Pyrazinamide, Rifampicin) and D (+)-Galactosamine toxication.

2.21 Butea monosperma

Ganeshpurkar *et al*. (2014 [30]) studied the possible hepatoprotective effect of an ethanol extract of *Butea monosperma* in isoniazid-rifampicin induced hepatotoxicity. Phytoanalytical studies demonstrated that the extract is rich in flavonoids, glycosides and polyphenolics. Treatment with *Butea monosperma* extract restored enzymes ALT, AST, ALP to their respective levels and also restored Cholesterol levels of rats. The extract significantly decreased the production of TBARS, which justifies restoration of cellular integrity in the liver of animals.

2.22 Lucas cephalotes

Bais and Saiju (2014 [31]) verified the ameliorative effect of alcoholic extract of whole herb of *Lucas cephalotes* on isoniazid and rifampicin induced hepatotoxicity in Sprague Dawley rats. Treatement with the extract at both doses, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, bilirubin and lipid peroxidase level was found to be significantly less ($P<0.01$) and superoxide dismutase, glutathione and catalase level was significantly high ($P<0.01$) as compared to intoxicated animals. Extract and silymarin showed sifgnificant protection against signs of inflammatory infiltration, steatosis, and vascular endothelial degeneration due to isoniazid and rifampicin toxicity.

2.23 Calotropis procera

Anti-TB drugs (INH 50 mg/kg and RMP 100 mg/kg) have enhanced the ALT, AST, ALP, bilirubin and bring histological changes in liver of rats, whereas co-administration of anti-TB drugs with hydroethanolic extract of *Calotropis procera* flowers has reduced these levels within the normal range. Which was further evident by the significant ($P < 0.01$) reduction in inflammatory changes around portal triad in liver tissues (Kamil and Imran-ul-Haque 2014 [32]).

2.24 Chelidonium majus

Roy *et al*. (2015 [33]) appraised the hepatoprotective effect of *Chelidonium majus* in rats exposed to Isoniazid and Rifamipicin. The treatment of ethanolic extract of *Chelidonium majus* at the dose of 500 mg/kg/p.o with

antitubercular drugs have significantly reduced liver biomarker enzymes. Antioxidant parameters such as SOD, CAT, GPx were suppressed and an increase in malondialdehyde (MDA) level were observed due to anti-tubercular drugs administration but restored the liver biomarkers and antioxidant levels in the treatment of ethanolic extract of *Chelidonium majus*. The reversal of the liver marker enzymes with extract at a dose of 500mg/kg/p.o can be explained as a result of the stabilization of plasma membrane as well as repair of hepatic tissue damage caused by antitubercular drugs.

2.25 Rhynchosia beddomei

Babu *et al*. (2015 [34]) assessed restorative power of methanolic extract of *Rhynchosia beddomei* (MERB) has hepatoprotective activity by reducing the SGOT, SGPT, ALP, Total protein, Triglycerides, DIT (Direct Bilirubin), BIT (Total Bilirubin) levels in the blood, elevated by rifampicin toxicity in rats. While as Rifampicin treated group shows inflammation in lobules, compared to control. However treatment of MERB 250mg/kg and 500mg/kg shows decrease in inflammation in the lobules and necrosis in hepatocytes when compared to control. The standard drug shows normal architecture of liver.

2.26 Solanum xanthocarpum

Verma *et al*. (2015 [35]) concluded the whole plant extract of *solanum xanthocarpum* at the doses of (125 mg/kg &250 mg/Kg) showed significant liver protective effect by decreasing the enzymatic (serum glutamate oxalate transaminase and serum glutamate pyruvate transaminase (SGOT and SGPT), alkaline phosphatase (ALP), total bilirubin and non enzymatic parameters (GSH, LPO, SOD, CAT) parameters aginst isoniazid and Rifampicin induced hepatotoxicity in rats. Histopathological profile of liver at dose level 125 mg/kg showing hepatic cells with well preserved cytoplasm, prominent nucleus, some of central vein and sinusoids exhibited congestion. While at dose 250 mg/kg showing well brought out central vein, hepatic cell with well preserved cytoplasm, prominent nucleus.

2.27 Hugonia mystax

Ethanol extract of leaves of *Hugonia mystax* (HMEE) (200mg/kg, 400mg/kg) and silymarin 100 mg/kg reduced the elevated levels of physical parameters and biochemical parameters (SGOT, SGPT, ALP, direct and total Bilirubin), LPO levels also get reduced, there by increase the levels of GSH in rifampicin induced hepatotoxicity in albino rats. coadministration of silymarin 100 mg/kg and HMEE 400 mg/kg with rifampicin maintained liver architecture, minimal congestion of sinusoids and fatty changes (Shirode *et al*., 2015 [36]).

2.28 Berberis Lycium Royale

Isoniazid produced severe hepatotoxicity as depicted by raised LFT's and severe steatosis, hepatocytic ballooning & inflammation. In Low dose Aqueous extract of stem bark of *Berberis Lycium Royale* treated group and High dose extract treated group, serum levels of biomarkers were decreased and their liver sections

showed improved histological picture, but the reduction in toxic effects were more prominent in animals treated with high Aqueous group (Rafiq *et al*., 2015 [37]).

2.29 Canthium dicoccum

Vuyyuri *et al*. (2015 [38]) evaluated the hepatoprotective activity of ethanolic extract of *Canthium dicoccum* (ECD) whole plant against the standard Silymarin in isoniazid (INH) and rifampicin (RIF) induced hepatotoxicity. They found that treatment with *Canthium dicoccum* (ECD) significantly attenuated the INH and RIF induced elevated serum levels of SGPT, SGOT, ALP, and Total Cholesterol Also the plant extract significantly improved the serum levels of Total Protein when compared to INH and RIF induced toxic group. The plant extract at 300mg/kg dose level proved to be comparable to the standard silymarin and is considered to be more active than silymarin in reducing the serum elevated SGOT levels and improving the serum Total Protein levels. High dose of ECD and silymarin maintains normal lobular architecture having prominent nucleus, very few inflammatory cells when compared to toxic control group.

2.30 Macrotyloma uniflorum

Macrotyloma uniflorum Seed extract (MUSE) elicited significant hepatoprotective and antioxidant activity by attenuating the anti-tubercular drug (isoniazid, rifampicin and pyrazinamide)–elevated levels of the marker enzymes, bilirubin and malondialdehyde and restored the anti-tubercular drug–depleted levels of albumin, total proteins, reduced glutathione and the antioxidant enzymes comparable to reference drug Liv.52. MUSE treatment group showed minimal centrilobular fatty degeneration with minimal leukocytic infiltrate, absence of necrosis comparable to the standard Liv.52 treatment group (Panda *et al*., 2015 [39]).

2.31 Polygonum glabrum

The hepatotoxicity with isoniazid and rifampicin was significantly prevented by pretreatment with methanolic extract of isolate *Polygonum glabrum* Willd in Albino Wistar rats. The researchers found the decrease in wet liver weight and reduction in biochemical parameters like serum SGOT, SGPT ALP, Total protein bilirubin and increase in reactive oxygen species scavenging enzyme activities such as catalase GSH and LPO after treatment with methanolic extract confirmed the hepatoprotective effect of extract. Restoration of hepatic cells with minor fatty changes and absence of necrosis after treatment with extract indicated its satisfactory hepatoprotection (Ghori *et al.*, 2016 [40]).

2.32 Nigella sativa

Nigella sativa oil acted as antiinflammatory and antinecrotic in isoniazid and rifampicin administered drugs in rats. When *Nigella sativa* was coadminstered with Rifampicin + Isoniazid, it resulted in the decrease of marker enzymes AST, ALT, LDH, ALP and bilirubin and maintained these enzymes at normal levels in the serum of rats compared to the only Rifampicin + Isoniazid administered rats. The group treated with only *Nigella sativa* exhibit no lesions in liver as compared to the *Nigella sativa*+Rifamicin+Isoniazid treated group which showed inflammation and yellowish in portal and lobular area, Necrosis (Wahid *et al.*, 2016 [41]).

2.33 Trigonella foenum graecum and Curcuma zeoderia

Murugan and Padmanabhan (2016 [42]) investigated the hepatoprotective effect of ethanolic leaf extract of *Trigonella foenum graecum* and *Curcuma zeoderia* against anti tuberculosis drugs induced liver injury in albino rats. They visualized the treatement of both extracts restored AST, ALT, ALP, GGTP, LDH, and CPK levels. Similarly elevated values of blood urea, serum creatinine, serum cholesterol, serum triglycerides were also brought to normal, the decreased protein levels are returned to normal. Ascorbic acid (vit.C), GSH, α-tocopherol (vit E) was also revived and Enzymic antioxidants such as catalase, superoxide dismutase (SOD) glutathione peroxidase (GPX) levels were also maintained in rats treated with anti tuberculosis drugs. However in animals treated with leaf extracts and anti-TB drugs, the liver tissues exhibit normal cellular architecture and no infiltration of inflammatory cells.

2.34 Phyllanthus longiflorus

Manju and Muthulakshmi (2016 [43]) validated the modulatory effect of ethanolic extract of *Phyllanthus longiflorus* against isoniazid and rifampicin induced hepatotoxicity in wistar rats. They focused that the Co-administration of Silymarin and dose of (200 & 200mg/kg) *Phyllanthus longiflorus* (EEPL) ethanolic extract with INH and Rifampicin (RIF) and Isoniazid (INH) groups maintained the levels of AST, ALT, ALP, and serum total protein and total albumin towards normalcy as compared to only drug treated group. However, Silymarin showed normal liver architecture and occasional inflammatory cells with no traditis or necrosis while as extract with anti-tuberculusis drug treated group exhibit slight recovery and evidence of regeneration in some hepatocytes.

2.35 Brassica oleracea

Silymarin and ethanolic extract of cauliflower leaf (EELC) 200 and 400 mg/kg when administered to rats exhibited protection against RMP-INH induced hepatotoxicity as manifested by the reduction in toxin mediated rise in serum enzymes (AST, ALT, ALP, bilirubin, cholesterol, triglycerides) and increased total proteins levels. Histopathological findings reveal Silymarin treated group showed normal liver architecture and occasional inflammatory cells with no traditis or necrosis. While as EELC extract (200 mg/kg & 400 mg/kg) treated groups exhibit slight recovery and evidence of regeneration in some hepatocytes (Sreekanth *et al*., 2016 [44]).

2.36 Cucumis melo linn

Patel *et al*. (2016 [45]) appraised the methanolic extract of the fruits of *cucumis melo linn* showed normalization of body weight, biochemical parameters like serum ALT, AST, ALP, Serum total bilirubin, and Serum total proteins as well as the levels of liver homogenates, Lipid peroxidase, glutathione peroxidase, glutathione reductase, superoxide dismutase, catalase and reduced glutathione. They observed that the methanolic extract 500 mg/kg ip dose of *cucumis melo linn* showed significant hepatoprotective activity, comparable with silymarin. They further analysed that RIF + INH and high dose of the methanolic extract of the fruits of

Cucumis melo showed significant recovery when compared with drug treated group viz., absence of necrosis, space formation and vacuoles, while as RIF + INH and silymarin (2.5 mg/kg ip) showed normal liver architecture and occasional inflammatory cells with no traditis or necrosis.

2.37 Tripala (Emblica officinalis, Terminalia bellirica, Terminalia chebula)

The hepatotoxic group showed significant increase in liver enzymes ($P<0.001$) and total and direct bilirubin ($p<0.001$, $p=0.006$ respectively) in murine model of isoniazid and rifampicin induced hepatotoxicity compared to normal control. *Triphala* 250mg, 500mg and Silymarin groups showed statistically significant decrease in liver enzymes and total and direct bilirubin compared to hepatotoxic control ($p<0.001$). There was no statistically significant difference in the total protein and albumin among groups. Histopathological evaluation of liver further conferred the hepatocellular disintegration with periportal and sinusoidal inflammation and interphase hepatitis in the hepatotoxic control group. While as *Triphala* at both doses showed considerable hepatoprotection signified by minimal sinusoidal infiltration and focal cell death. The silymarin treated group showed only focal cell drop out and maintenance of normal liver architecture to a large extent (Shenoy *et al.*, 2016 [46]).

2.38 Crocus sativus, Ziziphus jujuba and Berberis vulgaris

Moossavi *et al*. (2016 [47]) dicovered hepato-protective effects of three medicinal plants, Crocus *sativus* (petal and stigma), *Ziziphus jujuba* and *Berberis vulgaris* in acute drug-induced hepatotoxicity and evaluation of their preventive effects in acetaminophen and rifampicin-induced hepatotoxicity in rat. Their evaluation showed, treatment with medicinal plants decreased liver enzyme levels and improved oxidative stress status in hepatotoxic rats. These plants effectively treated acetaminophen group in comparison with rifampicin group. *Ziziphus jujube* extract at dose of 200 mg/kg showed good protection on hepatocytes and normalized liver enzymes. It is speculated that antioxidant and hepato-protective effects of these extracts are fundamentally linked to their phenol and flavonoid components.

2.39 Tylophora asthmatica

Chandrakapure *et al*. (2016 [48]) evaluated the administration of antitubercular drug combination of isoniazid and rifampicin for 14 days significantly elevated the levels of serum ALT, AST and bilirubin (Total and Direct) and resulted in portal inflammation, ballooning degeneration, fatty change and necrosis in rat liver. *Tylophora asthmatica* treated group had no significant rise in values of Serum ALT, AST, bilirubin (total and direct) and there were no significant changes like portal inflammation, ballooning degeneration, fatty change and necrosis.

2.40 Tinospora crispa

Wahyuningrum *et al*. (2017 [49]) tested to screen extract and fractions of *Tinospora crispa* for activity against Mycobacterium tuberculosis H37Rv using the Microplate Alamar Blue Assay (MABA) method. They found ethanolic extract of *Tinospora crispa* exhibit antituberculosis activity against Mycobacterium tuberculosis H37Rv with minimum inhibition concentration of 12.5 mg/ml. Based on chromatogram, Brotowali ethanolic

extract exhibited a clear seperation using chloroform and methanol as mobile phase, n-hexane soluble fraction contains non-polar compounds dominantly, while as the polar compounds contained in the ethyl acetate non soluble fraction. The growth of Mycobacterium tuberculosis was determined by visual color change, without the use of specialized equipment.

2.41 Brysocarpus coccineus

Andrew *et al*. (2017 [50]) inspected the phytochemicals and ameliorative effects of aqueous extracts of *Brysocarpus coccineus* on serum liver enzymes in isoniazid (INH) induced hepatotoxicity in adult male Wistar rats. Tanins, saponins, alkaloids and flavonoids were quantitatively present at 2.29%, 18.05%, 23.24% and 18.99%, respectively. They found that there was an increase in the serum AST and ALT in the isoniazid treated group, which was reversed by livolin forte and the aqueous extracts at a dose of 200 mg/kg, however the extracts of *Brysocarpus coccineus* increased the serum levels of AST and ALT at higher doses, which was however not significant ($p > 0.05$) when compared to the control. There were no visible indicators of hepatic tissue damage, which include balloon degeneration of hepatocytes, bridging necrosis, sinusoidal dilatation, fatty deposits, or vacuolated cytoplasm in all the extract treated groups, these features are usually seen in hepatitis induced by isoniazid treated group.

2.42 Vernonia amygdalina

Iwo *et al*. (2017 [51]) analyzed antioxidant and hepatoprotective activity of *Vernonia amygdalina* in male Wistar rats exposed to isoniazid (INH) and rifampicin toxicity. They visualized *Vernonia amygdalina* ethanol extract contained alkaloids, flavonoids, saponins, and steroid/triterpenoids which attribute it antioxidant activity. Based on serum albumin concentrations and ALT activity, the high dose extract (100 mg/kg) was more potent as a hepatoprotective agent compared to the extract at a low dose (50mg/kg). The group of rats treated with a high dose extract showed normal liver index compared to the positive control. Liver tissue of the group given 100 mg/kg body weight of extract showed lighter liver damage than the 50 mg/kg bw administered group, but not better than the group given silymarin.

2.43 Caralluma attenuata

Rifampicin treated rats showed an increase in the activities of AST, ALT, ALP, LDH, GGT, bilirubin and decrease in the level of protein when compared with control rats. Oral administration of aqueous extract of *Caralluma attenuata* (125, 250 and 500 mg/kg body wt.) and silymarin to rifampicin treated rats showed an inhibition in the elevated activities of serum AST, ALT, ALP, LDH, GGT, bilirubin and protein level was increased when compared with rifampicin alone treated rats. Oral administration of aqueous extracts of *Caralluma attenuatta* (125, 250 and 500 mg/kg body wt.) and reference drug silymarin to rifampicin treated rats showed gradually reduced histopathological changes viz., necrosis, ruptured hepatocytes, space formation, vacuolization, fatty accumulation, loss of cell boundaries and enlargement of hepatocytes (Muthulingam. 2017 [52]).

III. CONCLUSION

The protective effect of these plant extracts against antituberculosis treatement may be related to polyphenolic compounds, terpenoids, alkaloids, coumarines, phytosterols, flavonoids etc. which protect the liver cells either by increasing the capability of antioxidant enzymes or by acting as antioxidants to overcome the oxidative stress created by reactive oxygen species, generated by drug treatement.

Despite encouraging data on possibility of new discoveries in the near future, evidence on treatment of liver diseases by herbal medications is not ample. Therefore, herbal medications should be suggested within the setting of more finely-conducted clinical trials.

IV. INNOVATIONS AND BREAKTHROUGHS

It is well known that there are many plants that have hepatoprotective action in the world. In the present study, authors have reviewed the hepatoprotective activity of plants against Isoniazid and Rifampicin.

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