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Review Article

Exploring Hepatoprotective Potential of Medicinal Plants and Bioactive Compounds against Liver Damage Induced by Antituberculosis Drugs: A Comprehensive Review

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ABSTRACT

Tuberculosis is one of the major leading causes of infectious diseases worldwide; liver toxicity is one of the common side effects causing treatment failure. Many cases of hepatotoxicity and relapse were reported in various clinical research studies. However, research advances have shown many strategies to protect the liver from antituberculosis drug damage. This review will highlight the apport of some medicinal plants and active molecules against antituberculosis drugs causing liver injuries. We performed a literature review of the existing reported literature.

Keywords: Tuberculosis; Medicinal plant; Bioactive compound; Hepatoprotective; Liver damage; Drug

INTRODUCTION

Mycobacterium tuberculosis complex organisms are the cause of the airborne infectious disease known as Tuberculosis (TB). Although M. *tuberculosis* is primarily a pulmonary pathogen, it can infect practically any area of the body and lead to disease. The progression of tuberculosis can go from a condition of containment in the host, where the bacteria are isolated within granulomas (latent TB infection), to a contagious state, where the patient will exhibit symptoms such as coughing up blood, having a fever, sweating excessively at night, and losing weight. Contagious pulmonary TB is the only active kind.

Isoniazid, rifampicin, pyrazinamide, and ethambutol are known as first-line drugs for the standard treatment of tuberculosis. Treatment for most forms of pulmonary and extrapulmonary TB consists of a 6-month short-course chemotherapy regimen with Isoniazid (INH), Rifampicin (RMP), Pyrazinamide (PZA), and Ethambutol (EMB) for 2 months followed by INH and RMP for the next 4 months, and normal plasma concentrations for TB drugs have been defined as 3-6 µg/ml for 300 mg/kg of isoniazid daily in normal adults, 8-24 µg/mg for 600 mg/kg of rifampicin, 20-60 µg/ml for 25-35 mg/kg of pyrazinamide daily and 2-6 µg/mg for 25 mg/kg of Ethambutol daily.

Moreover, High plasma concentrations of anti-TB drugs have been associated with many ADRs induced by anti-TB therapy and some Adverse Drug Reactions (ADRs) may compromise the effectiveness of the treatment and induce severe complications that increase morbidity and mortality.

Medicinal plants have been used for a decade to treat various diseases and remain until now a source of medicine in many developing countries where over 80 of the population rely on folk medicine and as described in the world pharmacopeia. Recent experimental studies reported on medicinal plants demonstrated satisfactory hepatoprotective effects against antituberculosis drug liver injury.

In addition, some active molecules have produced excellent results in various research studies also conducted for the same purpose.

As a result, this study aims to provide an overview of existing evidence on the hepatoprotective effect of medicinal plants and some natural and synthetic molecules against anti-tuberculosis drug-induced liver injuries.

LITERATURE REVIEW

Mechanism of antituberculosis drug hepatotoxicity

Aerosol Transmissible Diseases (ATDs) may produce hazardous intermediates during drug metabolism, such as phase-I bioactivation/toxification reactions and phase-II detoxification

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events, which may lead to hepatotoxicity. INH, RMP, and PAZ are the primary medications that cause hepatotoxicity among first-line ATDs. The accumulation of hazardous intermediates from its metabolism is thought to be the mechanism of INH-induced liver injury. INH is first converted to acetyl isoniazid in the hepatocyte using N-Acetyl Transferase (NAT), and then it is hydrolyzed into acetyl hydrazine and isonicotinic acid. Direct hydrolysis of INH into hazardous hydrazine and subsequent acetylation into acetyl hydrazine constitute another metabolic route. Glutathione S-Transferases (GSTs) can detoxify acetyl hydrazine by oxidizing it into hepatotoxins. Uncertainty surrounds the mechanism underlying the hepatotoxicity caused by RMP/PZA. RMP occasionally results in hyperbilirubinemia or increased serum transferase levels when administered alone. When used in conjunction, it may also cause INH to emit hydrazine and increase INH's hepatotoxicity. PZA causes hepatotoxicity that is dose-dependent, which points to a direct toxic action on liver cells. Additionally, PZA and INH co-administration during anti-TB medication may raise the risk of hepatotoxicity in patients [1].

Medicinal plant hepatoprotective effect against antituberculosis drug

Experimental studies evaluate the hepatoprotective effect of garlic on liver injury induced by Isoniazid (INH) and Rifampicin (RIF). In this experiment, rats were treated with INH+RIF (50 mg/kg per day each) induced hepatotoxicity. Serum Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and bilirubin were estimated in all the rats. A histological investigation was done to determine the extent of the liver damage. In liver homogenate, Lipid Peroxidation (LPO), a sign of oxidative stress, and non-protein thiols (glutathione), a sign of antioxidant levels, were assessed. In all treated animals as judged by elevated serum ALT, AST, and bilirubin levels, presence of focal hepatocytic necrosis, and portal triaditis. However, garlic administrated simultaneously at a dose of 0.25 g/kg per day prevented the induction of histopathological injuries in INH+RIF cotreated animals with higher levels of glutathione and low levels of LPO compared to the INH+RIF treated group [2].

Lasianthera africana (Icacianacaeae), evaluated against isoniazid and rifampicin-induced liver damage in rats, where hematological indices and antioxidant levels were decreased ($P<0.001$) and increased the levels of livers marker enzymes ($P<0.001$) when treated with Isoniazid and rifampicin alone. However, pretreatment with hala extract and silymarin provoked a significant elevation of hematological indices. Histopathological evaluation supports the hepatoprotective activity [3].

In other studies, the hepatoprotective properties of *Solanum xanthocarpum* (*S. xanthocarpum*) fruit extract against antitubercular drug-induced liver damage in experimental animals were examined. Commonly referred to as yellow-berried nightshade (synonym: kantakari), *Solanum xanthocarpum* (*S. xanthocarpum*) Schrad. and Wendl. (Family: Solanaceae) is a prickly, diffuse, bright green perennial herb, woody at the base, and 2-3 m tall, found throughout India, mostly in dry places as a weed on roadside and wastelands. The 1.3 cm-diameter berries have yellow or white veins and are enclosed by an expanded calyx. Several biochemical markers, including Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), Total Bilirubin (TBL), Albumin (ALB), Total Protein (TP), Lactate Dehydrogenase (LDH), and serum Cholesterol (CHL), were used to evaluate the hepatoprotective effect. In the meantime, rat liver homogenate was used to test *in vivo* antioxidant activities such as Lipid Peroxidation (LPO), reduced Glutathione (GSH), Superoxide Dismutase (SOD), and Catalase (CAT). When three antituberculosis drugs, namely rifampicin, isoniazid, and pyrazinamide were administered daily for 35 days. The biochemical observations were supported by histopathological examination results that demonstrated a preventive effect. Serum hepatic enzyme levels increased, LPO levels in the liver tissue decreased, and the activities of the antioxidant defense enzymes GSH, SOD, and CAT returned to normal levels. An analysis of the liver's histopathology revealed [4].

Nigella Sativa Linn, known for its antioxidant activity estimated with a 1,1-Diphenyl-2-Picrylhydrazyl (DPPH) assay and by analyzing total phenolic contents. ATD-induced adverse effects were associated with a sharp elevation in levels of serum transaminases, albumin, cholesterol, urea, uric acid, creatinine, and Blood Urea Nitrogen (BUN). ATDs significantly increased Lipid Peroxidation (LPO) and decreased enzyme activities (Superoxide Dismutase (SOD), Catalase (CAT), Adenosine Triphosphatase (ATPase), and Glucose-6-Phosphatase (G6Pase)) in the liver, indicating oxidative stress. Conjoint treatment with NS reverses the serological biochemistry and inhibits oxidative stress by suppressing LPO and augmenting antioxidant enzyme activity toward that of the control in this experimental animal model treated with ATDs and followed by NS for two weeks [5].

Other plants, like *Emblica officinalis* (fruits), have also a hepatoprotective properties. Recently published paper on 50% ethanol extract of *Emblica officinalis* against antituberculosis drugs-induced hepatic injuries was performed. *In vitro*, acute toxicity study of combined EO-50 and anti-TB drugs (alone or used with EO-50), The biochemical markers evaluated were cell viability, GSH content (cells), and the release of Alanine aminotransferase (ALT) in the medium and the sub-acute toxicity in an experimental animal model where the biochemical assays for the determination of Aspartate aminotransferase (AST) and ALT activities, Lipid Peroxidation (LPO), reduced Glutathione (GSH) and antioxidant activity. After 30 sub-acute treatments (once daily, p.o.), with both these combinations, a significant increase in the serum toxicity markers compared with the control rats. In the group, ALT was increased by 220% and AST was increased by 148%. ALP activity was enhanced by 101% and bilirubin by 96% was recorded. In this group the liver LPO increased by 122% while the GSH loss was recorded to be 47%. The effect of EO-50 was investigated in a dose-dependent manner (50, 100, and 200 mg/kg). A dose of 100 mg/kg (once daily, p.o. for 30 days) was found to produce an optimum reversal of serum toxicity. The protection recorded at this dose of EO-50 was 88% and 95% in the serum enzymes, ALT and AST, respectively. ALP was suppressed by 77% and bilirubin by 85%. The hepatoprotective activity of EO-50 was found to be due to its membrane stabilizing, antioxidative, and *CYP2E1* inhibitory effects [6]. Known for its popular edible seeds produced by the gourd have high nutritive value and are rich in fats and proteins, *Telfaira occidentalis* (Cucurbitaceae) is a tropical climbing plant cultivated in West Africa, its leaves are commonly eaten. In addition to its local uses in food, the seeds and leaves of the plant have been the subject of investigations

for their chemical composition and pharmacological activities, including antioxidant, antimicrobial, hepatoprotective, anti-inflammatory, immunomodulatory, anticancer, and hypoglycemic. By intoxicating Wistar rats with RIF and INH for 60 days, an induced hepatotoxicity model of oxidative stress was used to test *T. occidentalis* pulp extract and silymarin. Markers indicating oxidative stress and hepatic damage such as Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and Alkaline Phosphatase (ALP) were assessed. Biomarkers of antioxidant status, including catalase, glutathione reductase, glutathione peroxidase, superoxide dismutase, and marker of lipid peroxidation, Malondialdehyde (MDA), were assayed using standard procedures. In addition, the histopathological analysis, lipid profile, serum indicators for renal function, and hematological profile were evaluated. RIF and INH intoxication considerably decreased the hematological indices and increased the biochemical enzyme markers (AST, ALT, and ALP, P 0.001) and lipid profile (P 0.001), while MDA was enhanced and antioxidant biomarkers were severely (P 0.01) depressed. This change was dramatically (P 0.001) reduced and the antioxidant potential was maintained by pretreatment with TOPE. The histopathological morphology supports the biochemical evidence of hepatoprotection confirming the benefit of the plant [7].

The hepatoprotective effects of *Crocus sativus L.* (CS), also known as saffron and cultivated in nations like Iran, Spain, Italy, etc., were investigated in an experimental animal model against Rifampicin Isoniazid (RIF-INH) drug-induced liver injury. The CS's chemical structure varies depending on the place, the season, and the local vegetation. CS contains various secondary metabolites that are responsible for different pharmacological activities. After 14 days of administering RIF-INH varying doses, CSP was administered as a standard dose. By modifying oxidative stress and anti-inflammatory responses to this drug-induced liver injury, the CSP treatment at both doses effectively regulated all regulating biochemical hepatic injury indicators and resulted in the mitigation of overall INH-RIF damage. The results demonstrated that administration of the INH-RIF combination to rats increased their hepatic biomarker concentrations of ALT (p 0.05), AST (p 0.001), and ALP (p 0.01) and decreased their TP (p 0.05) as compared to the control group. Rats were given CSP at dosages of 100 mg/kg, 200 mg/kg between, and silymarin at doses of 10 mg/kg between showed hepatoprotective action of CSP by demonstrating lesser regulation of hepatic biomarkers (ALT, AST, and ALP) and higher regulation of TP levels. Hepatotoxicity-stressed INH-RIF was used to gauge the effectiveness of CSP's defense against oxidative stress. The results revealed a statistically significant rise in malondialdehyde and a statistically significant decrease in Catalase (CAT) and Superoxide Dismutase (SOD) concentrations in the hazardous group. The rats administrated with 100 mg/kg, 200 mg/kg between, and silymarin at 10 mg/kg between of CSP prevented this induction, and CAT, SOD, and MDA levels were normalized to their control values. The effect of CSP and INH-RIF treatment on (Tumor Necrosis Factor-Alpha) TNF-α and Cyclooxygenase-2 (COX-2) inflammatory mediators was analyzed. There was an increase in TNF-α and COX-2 levels in the toxic group when compared with Group-I ($p<0.001$), However, rats groups administrated with CSP and silymarin exhibited significantly and dose-dependently reduced levels of COX-2 and TNF-α [8].

Solanum Lycopersicum L. (tomato), effect against rifampicin and isoniazid-induced liver injury have been reported. A group of Brazilian researchers investigated its potential on experimental animals (wisters rats), intoxicated by isoniazid+rifampicin administration. Five groups of animals were formed. The first one was kept as a control group while the other groups (II, III, IV, and V) received RIF+INH administration for hepatotoxicity inducing for seven days. Rats of Group-III were then treated with silymarin while Group-IV and V were treated with *Solanum Lycopersicum L.* (tomato). INH+RIF induced liver damage caused considerable increase in the serum levels of the hepatic enzymes Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), and total bilirubin while significantly lowering albumin levels. At an 80 mg/kg dose, *Solanum lycopersicum* considerably decreased the levels of the liver enzymes AST, ALT, ALP, and bilirubin while significantly raising albumin levels [9].

Otherwise, some plant formulations were assessed for their hepatoprotective effect against antituberculosis drug-induced hepatotoxicity. Here it's the case of Liv.100, Ayurvedic formulations tested against Isoniazid (INH), Rifampicin (RIP), and Pyrazinamid (PZA) induced hepatotoxicity. Using intragastric administration, antituberculosis médications were administered to rats every day for six weeks. Cytochrome P-450 and cytochrome b5 levels were increased by taking antituberculosis medications together. Following the administration of an antitubercular medication, a considerable rise in the levels of NADPH-cytochrome P-450 reductase and NADH-cytochrome-b5 reductases was seen. As part of the antitubercular medication therapy, a considerable decline in the activity of glucose-6-phosphatase when compared to healthy control animals, the level of lipid peroxides caused by NADPH and ascorbic acid during antitubercular medication treatment was significantly higher. The changes in the xenobiotic metabolizing system and microsomal lipid peroxidation in experimental mice were controlled by oral Liv.100 co-administration during the same period [10].

A deciduous tree known as the Natal gwarri or Natal ebony (*Euclea natalensis* A.DC.) is widely distributed in southern Africa, particularly in Kwazulu-Natal and the southern coast. The ethanolic extract of the *E. natalensis* shoots' antimycobacterial, antioxidant, hepatoprotective, immunomodulatory, and cytotoxic properties were assessed *in vitro*. The extract's hepatoprotective efficacy (50-150 mg/kg) was investigated in a rat model of isoniazid and rifampicin (50 mg/kg; i.p.) caused liver damage. At 50 and 150 mg/kg, the extract was able to lower toxicity by 15% and 40%, respectively. The treatment of HepG2 cells with D-galactosamine (30 mM) resulted in a considerable decrease in cell viability. At a concentration of 12.5 g/ml, *Euclea natalensis* demonstrated considerable protection (505.9% protection) against the cell toxicity of D-Galactosamine when performing *in vitro* studies. The current study validates the plant's historical use in treating tuberculosis symptoms [11].

DISCUSSION

Bioactive molecule potential against antituberculosis drugs causing liver injury

In a study with 47 white outbred male rats, runihol and S-adenosyl-L-methionine (ade methionine) were used to imitate liver

impairment brought on by reserve antituberculosis medications (Para-AminoSalicylic acid (PAS), prothionamide, and cycloserine). In this experimental study, the drugs demonstrate their potential to correct functional and structural disorders. The signs of structural and functional liver abnormalities brought on by reserve antituberculosis medications were reduced by runihol and ade methionine, respectively. The test medications improved recovery of the liver parenchyma and reduced signs of hepatocyte dystrophy to the same level, without necrobiotic processes or mononuclear infiltration [12].

N-acetylcysteine was tested through a randomized clinical trial conducted on 60 new TB patients who were aged 60 years or more. Two groups of patients were randomly assigned. The medication regimen for Group-I (n=32) includes isoniazid, rifampicin, pyrazinamide, and ethambutol in daily dosages. Patients in Group-II (n=28) received the same therapy as well as NAC. At baseline, after 1 and 2 weeks of medication, and anytime the patients displayed clinical symptoms of hepatotoxicity, liver enzymes, and bilirubins were assessed. After 1 and 2 weeks of treatment, the mean SD values of aspartate aminotransferase and alanine aminotransferase in Group-I were substantially higher than in Group-II, proving the hepatoprotective of N-acetylcysteine [13].

Immunity and inflammation are tightly controlled by nuclear Factor B (nF-B). According to studies, Pyrrolidine dithiocarbamate (PdTc), an inhibitor of nF-B, protects the liver from both acute and long-term damage. Experimental studies reported on this molecule, have studied the INH/RIF producing protective effect and PDTC mechanisms on liver injury. InH (50 mg/kg/day) and riF (50 mg/kg/day) were given intragastrically to rats every day for 28 days. To compare liver biochemical indicators in the serum, histopathological damage, nF-B activity, oxidative stress, hepatic mRNA expression of Tumor Necrosis Factor (TNF), Bile Salt export Pump (BSeP), and protein expression of BSeP, PdTc (50 mg/kg/day) was intraperitoneally injected 2 hours after the co-administration of inH and riF. It was discovered that PdTc therapy inhibited nF-B activation, which in turn reduced oxidative stress and TnF-mRNA levels and prevented reductions in BSeP mRNA and protein expression brought on by the concurrent administration of inH and riF. Overall, the data presented suggested that activation of nF-B is necessary for inH/riF-induced liver damage PDTC worked [14].

Experimental studies on kaemferol's protective effect against Isoniazid (INH) and Rifampicin (RIF) induced liver injuries have been conducted. In This work, *CYP2E1* inhibitors were identified *in vitro* and determined whether the chosen substance might avert INH/RIF-induced hepatotoxicity in mice. Kaemferol is a flavonoid, which is the most abundant type of secondary plant metabolite. Plants employ these low-molecular-weight polyphenolic chemicals to control and boost their growth as well as for defense [15]. The first-line antituberculosis (anti-TB) chemotherapeutic medications are Isoniazid (INH) and Rifampicin (RIF). 27% of patients receiving INH and RIF therapies and 19% of patients receiving INH alone have abnormal levels of the blood transaminases Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT). When ethanol, carbon tetrachloride, and INH are processed by cytochrome P450 2E1 (*CYP2E1*), it damages the liver. In mice, kaempferol decreased *CYP2E1* activity by 0.31 to 0.48 fold (p 0.005). When kaempferol was administered, the serum levels of AST and ALT as well as the GSP value in the mice with INH/RIF-induced hepatotoxicity were significantly abnormal (p 0.005). In mice, kaempferol dramatically decreased the loss of hepatic glutathione and stopped the rise in MDA production. Additionally, kaempferol had no impact on INH/RIF's anti-TB actions [16].

Bacoside is an active compound derived from *Bacopa monnieri* plant found throughout India. It has been utilized as a free radical scavenger, antioxidant, and nerve tonic. In recently reported studies, bacoside is effective against liver damage triggered by Isoniazid (INH) and Rifampicin (RIF). Bacoside was experimentally tested against INH and RIF-induced toxicity in the livers of Wistar albino rats. It is well established that preserving the integrity of the rat hepatocyte membrane can counteract the combination of INH-RIF-induced hepatotoxicity. The studies were carried out on body weight, liver enzyme markers, liver antioxidants, and liver histology in four experimental groups of rats. Rats given INH and RIF had aberrant liver indicators, which Bacoside was able to normalize. This appears to be comparable to the normal control and Silymarin-treated groups [17].

CONCLUSION

Medical professionals, pathologists, and microbiologists are still faced with numerous challenges related to tuberculosis, and problems with early detection and treatment of all forms of the disease still exist. To reach the WHO END TB strategy's goal of a 95% decrease in the overall number of tuberculosis deaths by 2035, a complete understanding of tuberculosis is required, as well as systemic filling of treatment and detection gaps. The conflict is based on actual information, and humanity is equipped with modern weapons and wisdom from the past to defeat this ancient opponent in all of its manifestations. Additionally, A practical approach that can assist us in achieving the WHO's 2035 goals is hepatoprotective methods against antituberculosis drug-induced liver damage. Considering the various research efforts that have been documented and have had positive outcomes.

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