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Review Article

AMELIORATIVE PROPERTIES OF NATURAL PRODUCTS AGAINST ANTI-TUBERCULOSIS DRUGS (RIFAMPICIN AND ISONIAZID): A REVIEW

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ABSTRACT

Tuberculosis is a common disease in India (about a quarter of the Global TB Burden) and worldwide and is a major cause of mortality among various infectious diseases. Rifampicin and Isoniazid are among the first line drugs used to treat tuberculosis. These drugs lead to many adverse effects which are one of the major reasons for patients not to choose these drugs which may result in the development of multi drug resistance. To minimize the adverse effects of these drugs, there is a need to supplement them with natural products. The present study was designed to explore all possible data related to the ameliorative properties of a variety of natural products against anti-tuberculosis drugs.

Keywords: Ameliorative, Extract, co-administration, Hepatoprotective, Anti-oxidative

1. INTRODUCTION

Tuberculosis is a leading public health problem worldwide, particularly in developing countries. It is spread through the air by cough, sneeze or by contact with saliva. It is estimated that 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 [1]. Rifampicin and Isoniazid are first line anti-tuberculosis drugs used against Tuberculosis. These first line anti-tuberculosis drugs Isoniazid, Rifampicin continue to be the effective drugs in the treatment of tuberculosis however; the use of these drugs is associated with toxicity in tissues, particularly in the liver, leading to drug induced hepatitis. Many therapeutic inventions have been attempted to improve the therapeutic benefits of the drugs. In several studies, it has been reported that natural products like honey, garlic and various other plant extracts have antioxidant, anti-inflammatory, antibacterial, analgesic and hepatoprotective properties and the same has been summed up in this study.

2. REVIEW

The leaf extract of *Ocimum sanctum* has hepatoprotective action against isoniazid, rifampicin and pyrazinamide. Adult albino rats treated with these anti-tuberculosis drugs show significant fall in serum protein level and rise in the levels of bilirubin, ALT, AST and ALP. When leaf extract of tulsi is administered with the antitubercular drugs, the abnormal biochemical levels are reverted. Furthermore, the histology of liver of anti-tuberculosis drugs treated rats reveal that changes of degeneration, necrosis and fibrosis are brought to normal condition in rats co-administered with tulsi extract. Ursolic acid, key constituents of *Ocimum sanctum,* is responsible for inhibition of lipid peroxidation [2].

Garlic has protective effect on INH+RIF induced liver injury in rats. Higher levels of glutathione and low levels of LPO are observed as compared to INH+RIF treated group. Garlic prevents the initiation of histopathological injuries in INH+RIF co-treated Wistar rats [3].

Cimetidine prevents increase in AST and ALT levels in the liver of experimental rabbits as well as attenuates histological changes like portal inflammation, necrosis, fatty changes and ballooning degeneration associated with isoniazid (50mg/kg) and rifampicin (100mg/kg) combination after seven days of treatment in liver which are due to inhibition of toxic reactive metabolites [4].

Vitamin E detoxifies harmful free radicals formed during isoniazid and rifampicin induced toxicity. When high dose of tocopherol (100mg/kg) is given half an hour prior to anti-tuberculosis drugs, the level of alanine transaminase (ALT) and arginine succinic acid lyase (ASAL) remains near normal. Both the reversible

and irreversible changes in the histology of liver are prevented with tocopherol as well as cimetidine pretreatment. Tocopherol is more effective than cimetidine in the studies [5].

Silymarin regenerates and protects liver in case of toxicity caused by first line anti-tuberculosis drugs isoniazid, rifampicin and pyrazinamide in male Wistar albino rats. Serum biochemical tests for liver function show increased levels of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin in anti-tuberculosis drug treated animals. Also, the increased levels of albumin and total protein are recorded in these animals. Histopathological changes are noticed in liver of these animals. Simultaneous administration of *Silymarin* significantly brings the biochemical and histological changes induced by the drugs to near normal [6].

Carotenoids show hepatoprotective effect against isoniazid and rifampicin induced toxicity. Treatment with carotenoids along with anti-tuberculosis drugs partially reverses lipid peroxidation, thiols, catalase and SOD in the liver and blood of rats. There is reduced degree of necrosis and inflammation, thereby indicating protection of carotenoids against liver injury [7].

Methanolic extract of leaves of *Pisonia aculeate* has hepatoprotective and antioxidant activity against rifampicin and isoniazid induced hepatotoxicity. Treatment of male Wistar rats and Swiss albino mice with drugs and plant extract significantly alters serum marker enzymes and antioxidant levels to near normal. Also the plant extract is effective against drug metabolizing enzymes such as Cytochrome P450, NADPH Cytochrome C reductase and glutathione S transferase thereby indicating the hepatoprotective activity against the hepatotoxicity induced by the combination of two antitubercular drugs [8].

Ranitidine and Vitamin E are both potent protectors against rifampicin induced hepatotoxicity. Treatment with ranitidine alone or vitamin E alone slightly improves serum marker enzymes, antioxidant activities and cytochrome P-450 content while the protection by the combination of ranitidine and vitamin E shows additive effect. Study shows that the inhibition of cytochrome P-450 by ranitidine and vitamin E against rifampicin induced hepatic injury is the cause behind hepatoprotective activity [9].

The hydro alcoholic extract of *Cissampelos pareira* has protective action against hepatotoxicity caused by intraperitoneal injection of isoniazid and rifampicin in Wistar albino rats. Serum biochemical tests show the protective effects of extract of *Cissampelos pareira* on SGPT, SGOT, ALP, total protein, albumin and total bilirubin compared to control and rifampicin and isoniazid induced hepatotoxicity in a dose related manner [10].

Pretreatment with *Daucus carota* extract and co-administration of aqueous extract of *Daucus carota* root with isoniazid and rifampicin in Wistar albino rats significantly reduces biochemical parameters like serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) alkaline phosphatase (ALP) activities and unconjugated bilirubin (uBIL). Carrots being an excellent source of vitamin A and C and rich in carotenoids, minerals (Mn, S, Cu, Fe, Mb, P, Cl) and antioxidants (falcarinol, dicaffeoylquinnic acid) act as hepatoprotective agent against drug toxicity [11].

The aqueous extract of *Piper longum* and piperine shows hepatoprotective effect against toxicity induced by ethambutol, rifampicin, isoniazid and pyrazinamide anti-tubercular drugs. Increased level of GSH and decreased level of LPO is noticed when aqueous extract of *Piper longum* and piperine is fed along with anti-tuberculosis drugs [12].

Isoniazid hepatotoxicity in its mild form shows moderate elevation in liver enzymes and in severe form causes hepatic damage, especially hepatic necrosis. *Nigella sativa* at the dose of 1 g/kg/day possesses antioxidant, anti-inflammatory, and anti-angiogenesis properties which play important protective role against isoniazid induced toxicity in rabbits. Treatment with plant extract before isoniazid significantly reduces serum AST, liver homogenate AST, serum ALT level, liver homogenate ALT, serum MDA, liver homogenate MDA and bilirubin. In histological studies the liver of treatment group with herb extract and anti-tuberculosis drug together show normal architecture with mild inflammation [13].

Solanum xanthocarpum fruit extract shows hepatoprotective effect against isoniazid, rifampicin and pyrazinamide drug-induced liver toxicity. Biochemical parameters like AST, ALP, total bilirubin, albumin, total protein, LPO, cholesterol, GSH, SOD and Catalase show abnormal results with anti-tuberculosis drugs and hence, indicated their hepatotoxic nature. When the experimental groups were supplemented with *S. xanthocarpum* significant changes are observed and the levels are near normal. *S. xanthocarpum* also attenuates the hepatocellular necrosis in liver and

reduces the inflammatory cells infiltration, thereby providing protection against liver injury [14].

The administration of *Camellia sinensis* (aqueous extract of green tea) partly prevents hepatotoxicity due to isoniazid and rifampicin induced toxicity through anti-oxidative and anti-inflammatory mechanisms. Pretreatment with aqueous extract of green tea to drug intoxicated male Wistar rats, shows remarkable reduction in AST, ALT, ALP, LDH and bilirubin level of liver. Homogenized liver tissue activities of SOD, catalase and MDA are also brought to near normal level by green tea extract. Histology of liver of treatment group with isoniazid, rifampicin and green tea extract also shows remarkable reduction in necrosis and fatty changes with pyknotic nuclei [15].

Bee pollen showed the modulatory effect against damage and oxidative stress induced by antituberculosis drugs (rifampicin and isoniazid) in rat testis [16].

Asteracantha longifolia plays important role against first line anti-tuberculosis drugs isoniazid rifampicin in protecting toxic reactions in tissues, particularly liver of male Sprague-Dawley rats. Treatment of rats with anti-tuberculosis drugs induced hepatotoxicity is evidenced by elevated levels of ALT, AST and ALP and total bilirubin while the levels of albumin and total protein are decreased. Treatment of rats with plant extract causes a significant reduction in the levels of biochemical markers and leads to a reversal of hepatotoxicity. The histological architecture of drug treated liver sections shows massive hepatic necrosis with dilated blood vessels. The *Asteracantha longifolia* treated groups along with drugs show regeneration of hepatocytes, normalization of fatty changes and necrosis of the liver [17].

Garlic has protective role against toxicity induced by first line tuberculosis drugs (isoniazid, rifampicin, pyrazinamide and ethambutol). As the garlic concentration increases, the levels of AST and ALT are found to decrease. Histological slides also support the hepatoprotective role of garlic against the toxicity caused by anti-tuberculosis drugs [18].

The methanolic extract of *Ficus benghalensis* has protective effect on isoniazid-rifampicin (100mg/kg each) induced hepatotoxicity in rats. Administration of methanolic extracts of *F. benghalensis* prevents isoniazid-rifampicin-induced elevation in the levels of total bilirubin, albumin, SGOT, SGPT, ALP. Moreover, total protein and GSH are significantly increased in treatment group. From the biochemical and histological profiles (minimal inflammation with moderate portal triditis and normal lobular architecture), the protective efficacy of the methanolic extract of *F. benghalensis* is concluded [19].

The ethanolic extract of *Cnidoscolus chayamansa* leaves show ameliorative effects on drug (rifampicin and isoniazid) induced hepatitis in rats. There is increase in serum AST, ALT, ALP, total protein and total bilirubin levels in drug treated animals. Administration of ethanolic extracts of *Cnidoscolus chayamansa* significantly prohibits rifampicin-isoniazid-induced elevation in the levels of serum diagnostic liver marker enzymes [20].

The ethanolic extract of *Ziziphus oenoplia* root has hepatoprotective potential against isoniazid and rifampicin induced liver damage in Wistar albino rats. The levels of SGOT, SGPT, ALP, bilirubin, SOD, catalase, GST, GPx and LPO which become abnormal post drug administration, are restored with the help of root extract of plant. The biochemical observations supplemented with histopathological examination of rat liver sections prove its hepatoprotective potential [21].

The over consumption of antibiotics might nullify their benefits and leads to side effects. Treatment of rats with rifampicin causes a significant increase in the total cholesterol, triglycerides and LDL-cholesterol levels, serum AST, ALT, bilirubin and urea, while HDL-cholesterol level, total protein, albumin and alpha 1-globulin show a significant decrease. Histological examination of the liver and kidney in the rifampicin-treated rats indicates that the liver pathology includes necrosis of hepatocytes, cytoplasmic vacuolation, and distended sinusoids with some lymphatic aggregations. In the kidney, the glomeruli increases in size, the mesangial matrix is expanded and the renal tubules are degenerated [22].

Methanol extract of *Cissus quadrangulari s*has hepatoprotective activity against rifampicin induced toxicity in Wistar albino rats. Treatment with *Cissus quadrangularis* and *Silymarin* significantly brings down the elevated levels of AST, ALT, ALP and bilirubin (total and direct) with anti-tuberculosis drugs. Decreased level of MDA and increased level of GSH, SOD and catalase is seen in animals treated with rifampicin and plant extract. Histology of animals treated with rifampicin exhibit focal haemorrhage, inflammation and necrosis which are significantly reduced when *Cissus quadrangularis* or *Silymarin* is given to them [23].

The aqueous extract of leaves of *Carica papaya* show effective protection against isoniazid and rifampicin toxicity. Significant reduction in the levels of ALT, AST, ALP and total bilirubin is noticed when plant extract is administered with anti-tuberculosis drugs.

Moreover, rise in the levels of SOD, GSH and total protein and fall in the level of TBARS is seen. *Silymarin* administration at the dose of 200mg/kg also shows similar results when fed along with rifampicin and isoniazid, thereby, supporting the protective effect of aqueous extract leaves of *Carica papaya* and *Silymarin* against hepatotoxicity caused by drugs. Histology of liver hepatocytes show minimal microcellular fatty changes with little vascular congestion in groups treated with leaves of *Carica papaya* and anti-tuberculosis drugs, confirming its regenerative and protective nature [24].

Honey when administered with isoniazid, rifampicin and pyrazinamide shows prophylactic and therapeutic potential. Various biochemical parameters like ALT, AST, serum total protein, LPO and SOD and histopathological examination of liver performed to find the toxicity caused by anti- tuberculosis drugs and the protective effect of honey show that honey significantly prevents and reverses the toxicity caused by the drugs. Changes of degeneration, necrosis and fibrosis in liver caused by the drugs are prevented or reversed by administration of honey [25].

The ethanolic extract of *Mirabilis jalapa* leaves has protective effect on isoniazid, rifampicin, pyrazinamide and ethambutol induced hepatotoxicity. When anti-tuberculosis drugs are administered along with ethanolic extract of *Mirabilis jalapa* Linn leaves, significantly reduced liver biomarker enzymes are seen. Even the antioxidant parameters like SOD, CAT, GSH, GPx and GR are decreased and elevated TBARs levels in drug treated animals are restored on co-treatment of ethanolic extract of *Mirabilis jalapa* and anti-tuberculosis drugs. Liver histology of drug treated animals shows hepatocyte necrosis and inflammation in the centrilobular region with portal triaditis. Administration of extract of *Mirabilis jalapa* leaves one hour prior to administration of anti-tubercular drugs reveal minimal inflammation of hepatocytes with moderate portal triaditis and normal lobular architecture. The treatment of *Mirabilis jalapa* leaf extract shows inhibitory effect on mitochondrial enzymes which are responsible for the metabolism of anti-tubercular drugs and thereby restores the level of bilirubin to near normal [26].

Metallothionein is a potent antioxidant to protect against isoniazid and rifampicin and the combination of both drugs induced hepatic oxidative stress in mice wild type (MT+/+) and MT-null (MT2/2). It is evident from biochemical and histological findings that expression of metallothionein in wild type (MT+/+) provides protection against hepatotoxicity and MT-null (MT2/2) mice remains more sensitive to drugs. Furthermore, the protein expression of hepatic CYP2E1 is increased by isoniazid while the expression of hepatic CYP1A2 declines due to both drugs administered alone or in combination [27].

The methanolic extract of *Ficus religiosa* with the help of its chemical constituents like flavonoids and phenolic compounds, produces protective action against the hepatotoxicity induced by isoniazid + rifampicin and thereby acts as prophylactic as well as curative drug in treating hepatotoxic conditions[28].

Kaempferol has protective effects against INH/RIF-induced hepatotoxicity. Significantly increased level of hepatic glutathione and decreased MDA formation are recorded with kaempferol administration in mice. It is also observed that kaempferol does not interfere with the anti-TB effects of INH/RIF on the contrary; it inhibits CYP2E1 activity by 60-88% and thereby weakens INH/RIF-induced hepatotoxicity in mice [29].

The alcoholic extract of whole herb *Lucas cephalotes* shows antioxidant and hepatoprotective potential on isoniazid and rifampicin induced hepatotoxicity in Sprague Dawley rats due to the presence of flavones and luteolin. Herb treated animals with anti-tuberculosis drugs show significantly lower ($P<0.01$) level of SGOT, SGPT, ALP and bilirubin as compared to rifampicin and isoniazid treated groups. In *Lucas cephalotes* extract treated animals, level of LPO is significantly lower while level of SOD, GSH, and catalase is significantly raised as compared to toxicity induced group. Histology of liver at 200 mg/kg dose of *Lucas cephalotes* shows mild signs of inflammation while at 400 mg/kg of herb the liver retains normal architecture when administered with anti-tuberculosis drugs [30].

Pretreatment with ethanolic extract of propolis shows hepatoprotection against isoniazid (INH) induced hepatotoxicity in male albino mice. On assessing liver functions biochemically using enzymatic markers ALT, AST, ALP and total serum bilirubin, their values are raised significantly in INH treated group, confirming isoniazid as hepatotoxic drug. The values of the test come down significantly in EEP pretreated groups followed by 30 days treatment with INH, showing its hepatoprotective effect [31].

Centella asiatica extract and *Silymarin* have hepatoprotective role on rifampicin and isoniazid induced hepatotoxicity. Treatment with *Centella asiatica* attenuates the anti-TB drugs induced elevated levels of SGOT, SGPT, ALP. The treatment groups with herb extract and anti-tuberculosis drugs shows elevated

mitochondrial enzyme complex I (NADH Dehydrogenase activity), II (Succinate Dehydrogenase) and IV (Cytochrome oxidase) activity and MTT ((3-(4, 5-dimethylthiazol-2-yl)-2,5- diphenyltetrazolinium-bromide mitochondrial redox) activity in liver as compared to drugs alone. When compared with rifampicin and isoniazid treated groups, *Centella asiatica* (40 mg/kg) treatment group shows less denaturation with small amount of inflammatory cell. The ability of *Centellaasiatica* to suppress various antioxidant and apoptotic pathways is responsible for its hepatoprotective role [32].

The alcoholic extract of *Bauhinia variegate* and reference drug *Silymarin* show hepatoprotective potential against isoniazid, rifampicin induced oxidative stress. Treatment with *Bauhinia variegata* decreases the elevated levels of SGOT, SGPT, ALP, GGT, LDH, CHO and triglycerides and increases the albumin and total protein levels. In anti-tuberculosis drugs treated group, moderate to heavy lobular inflammation, hepatocytes degradation and necrosis is noticed. Treatment with *Silymarin* shows recovery from liver toxicity. Treatment with *Bauhinia variegata* shows amelioration of liver injury which isdue to direct scavenging effect of biflavone on free radical released during hepatotoxicity [33].

Quercetin has hepatoprotective effects against isoniazid and rifampicin induced hepatotoxicity in rats. When quercetin or N-acetylcysteine is administered along with anti-tuberculosis drugs, reduction in AST, ALP and ALT activities and increase in total antioxidant status (TAS) are seen. In histology, evident reduction of eosinophils in lobular parenchyma and perivenular zone with minimal Kupffer cell hyperplasia are noticed when compared with liver from rats that receives anti-tuberculosis drugs alone. Qquercetin performs its activity by scavenging the reactive metabolites and hydroxyl radicals [34].

The methanolic extract of *Mussaenda philippica* shows hepatoprotective effects on isoniazid and rifampicin intoxicated Wistar albino rats. Increased level of SGOT, SGPT, ALP and total bilirubin and decreased level of total protein by anti-tuberculosis drugs are reverted by the treatment of methanolic extract of *Mussaenda*. Maximum therapeutic efficacy is noticed with 400 mg/kg dose of extract. Histopathological analysis of liver in animals treated with anti-tuberculosis drugs shows centrilobular necrosis, fatty infiltration, lymphocytes infiltration, inflammation. Methanolic extract of *Mussaenda philippica* treated group at different doses shows minimal inflammation with moderate portal triaditis and the lobular architecture is normal, thereby indicating hepatoprotective role [35].

Treatment with efavirenz, isoniazid and efavirenz-Isoniazid combination have toxicological effects. Effects produced by co-treatment with EFV-INH on absolute liver weight, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, conjugated and total bilirubin are insignificant when compared to effects produced by treatment with individual doses of EFV and INH. Vascular congestion, inflammation of parenchyma and hepatocyte degeneration is seen in liver of animals treated with drug combination [36].

Prunus armeniaca leaves extract has protective effects-against isoniazid and rifampicin induced nephrotoxicity in rats. Anti-tuberculosis drugs induced nephrotoxicity is supported by significant increase in serum urea, creatinine and uric acid. These rats also exhibit a significant increase in serum tumor necrosis factor alpha and renal lipid peroxidation levels and decrease in the level of reduced glutathione content, and activity of superoxide dismutase and glutathione peroxidase. The presence of glycosides, tannins, flavonoids, coumarins and triterpenes in the leaves extract of *Prunus armeniaca* modulates the isoniazid and rifampicin induced renal injury through abolishment of oxidative stress and potentiation of the antioxidant defense system [37].

Flavonoid hesperidin has protective effects on isoniazid, rifampicin and pyrazinamide induced hepatotoxicity and oxidative stress. Antituberculosis drugs cause increase in levels of ALT, AST, ALP, gamma glutamyl transferase, lactate dehydrogenase, and lipidperoxidative products such as lipid hydroperoxides, conjugated dienes and malondialdehyde. Decreased level of antioxidant enzymes SOD, catalase, GR, GSH, GST, Gpx, vitamin C and E are recorded in the toxicity induced experimental rats. These biochemical parameters are modulated to normal with the administration of hesperidin administered along with anti-tuberculosis drugs. Histological alterations in drug treated liver like changes in hepatocytes, bridging necrosis, congestion of central vein, inflammation and widening sinusoids are changed to normal hepatocyte morphology with mild sinusoidal congestion in liver treated with hesperidin and anti TB drugs, thereby supplementing its hepatoprotective significance [38].

The ethanolic extract of *Canthium dicoccum* and *Silymarin* show hepatoprotective activity against isoniazid and rifampicin induced hepatotoxicity. Ethanolic extract of *Canthium dicoccum* reduces the anti-tuberculosis drugs

induced elevated serum levels of SGPT, SGOT, ALP, and T-CHO. The plant extract at 300mg/kg dose when compared to standard *Silymarin* is found to be more active than *Silymarin* in normalizing the serum levels [39].

Ruta graveolens leaves extract has protective effects on isoniazid and rifampicin induced nephrotoxicity. Isoniazid/rifampicin induced kidney injury is evidenced by increase in serum creatinine, urea and uric acid, serum tumor necrosis factor alpha, renal lipid peroxidation and nitric oxide levels. On the other hand, reduced glutathione level, and activity of superoxide dismutase and glutathione peroxidase are markedly declined in kidney of isoniazid/rifampicin-treated rats. Supplementation with *Ruta graveolens* leaves extract helps these biochemical and histopathological alterations to revert to near normal [40].

The ethanolic leaf extract of *Trigonella foenum graecum* and *Curcuma zeoderia* have hepatoprotective and therapeutic effects against isoniazid, rifampicin and pyrazinamide induced liver injury in albino rats. Rats treated with leaf extracts of *Trigonell afoenum graecum* and *Curcuma zeoderia* normalize the increased levels of AST, ALT, ALP, GGTP, LDH, and CPK due to anti TB drugs. Similarly leaf extract decreases the raised level of blood urea, serum creatinine, serum cholesterol, serum triglycerides caused due to anti tuberculosis drugs. Anti TB drugs also reduce the level of vitamin C, GSH, vitamin E, SOD, GPx and catalase and increase the LPO which are restored to normal level by leaf extract of *Trigonella foenum graecum* and *Curcuma zeoderia*. Liver histology of animals treated with leaf extracts and anti TB drugs show normal cellular architecture with no infiltration of inflammatory cells in the tissue [41].

The levels of GPx, GRD, SOD, CAT, GSH decrease while sharp increase is noticed in lipid peroxide after RIF + INH (50 mg/kg) treatment. The administration of different doses, *viz,* the low dose (50 mg/kg), moderate dose (100mg/kg and250mg/kg), and high dose (500mg/kg) of fruit extract of *Cucumis melo* decline the level of LPO and elevate the levels of GPx, GRD, SOD, CAT, GSH. Among the three different doses, 500 mg/kg dose shows better activity than the standard drug, *Silymarin* (2.5mg/kg), in the case of LPO and GRD. Histological studies further strengthen the protective effect of *Cucumis melo* at the dose of 500mg/kg in normalizing the liver damage like disarrangement of normal hepatic cells, vacuolization, loss of cell boundaries, space formation and centrilobular hepatic necrosis caused by rifampicin and isoniazid treatment [42].

Aloe vera extract in combination with isoniazid and rifampicin is efficient in preventing increase in the levels of enzymes like AST, ALT, ALP, and ACP, bilirubin total protein, total albumin and total globulin leading to a significant reversal of hepatotoxicity in male Wistar rats after 30 days of treatment [43].

Bee propolis supplementation (200 mg/kg body weight) showed increased level of hemoglobin with respect to rifampicin (15.45%), isoniazid (11.34%), and rifampicin plus isoniazid (5.04%) administered groups after 30 days of treatment. The decreased level of red bloodcell count and white blood cell count by anti-TB drugs rifampicin, isoniazid, and rifampicin plus isoniazid together was also elevated in treatment group with bee propolis [44].

Drastic decrease in haemoglobin count, RBC count and WBC count was noted when animals were treated with Rifampicin, Isoniazid and Rifampicin and Isoniazid in combination. On supplementing bee pollen with antituberculosis drugs significant increase in the level of haemoglobin, RBC count and WBC count was recorded [45].

3. CONCLUSION

Reason for development of anti-TB drug toxicity is mainly hepatotoxicity, oxidative stress and cell damage. As reviewed, various natural products like leaf extract of *Ocimum sanctum,* Garlic, Cimetidine, Vitamin E, *Silymarin,* Carotenoids, methanolic extract of leaves of *Pisonia aculeate,* Ranitidine, hydro alcoholic extract of *Cissampelos pareira, Daucus carota* extract, aqueous extract of *Piper longum* and piperine, *Nigella sativa, Solanum xanthocarpum* fruit extract, *Camellia sinensis, Asteracantha longifolia,* methanolic extract of *Ficus benghalensis,* ethanolic extract of *Cnidoscolus chayamansa* leaves, *Ziziphus oenoplia* root, methanolic extract of *Cissus quadrangularis,* aqueous extract of leaves of *Carica papaya,* honey, ethanolic extract of *Mirabilis jalapa,* metallothionein, methanolic extract of *Ficus religiosa,* Kaempferol, alcoholic extract of whole herb *Lucas cephalotes,* ethanolic extract of propolis, *Centella asiatica* extract and *Silymarin,* alcoholic extract of *Bauhinia variegate,* Quercetin, methanolic extract of *Mussaenda philippica,* efavirenz, *Prunus armeniaca* leaves extract, Flavonoid hesperidin, ethanolic extract of *Canthium dicoccum, Ruta graveolens* leaves extract, ethanolic leaf extract of *Trigonella foenum graecum* and *Curcuma zeoderia, Cucumis melo, Aloe vera* extract have hepatoprotective,

anti-oxidative, anti-inflammatory and anti-analgesic properties, co-administration of which can prevent the development of adverse reactions during tuberculosis therapy which is a milestone in the area of human health if used aptly.

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