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HEPATOPROTECTIVE POTENTIAL OF POLYHERBAL FORMULATION AGAINST ANTITUBERCULAR DRUGS INDUCED HEPATOTOXICITY ON RATS

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ABSTRACT
The first line anti-tuberculosis drugs isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and Ethambutol(ETH)continues to be the effective drugs in the treatment of tuberculosis, however, the use of these drugs is associated with toxic reactions in tissues, particularly in the liver, leading to hepatitis. This is one of the most serious adverse effects of anti-tuberculosis drugs (ATD). Currently, there is no effective treatment against ATD induced hepatic damage. Plants are an important component of the health care system in India and have been found to be effective in the treatment of different diseases. Hence the present study was undertaken to explore the use of Poly herbal formulation as a hepatoprotective formulation against Anti TB drugs induced hepatic adverse effect. The botanical species of *Eclipta prostrata*, *Wedeliac hinensis*, *Centella asiatica*, *Acalypha indica*, *Indigofera tinctoria* and *Sphaeranthus indicus* were collected from rural areas of Thanjavur, Tamil Nadu, India. Obvious hepatic injury was observed after the treatment of rats with the anti-TB drug for 45 days. Polyherbal formulation showed a significant protective effect on anti-TB-induced liver injury. The hepatoprotective action of Polyherbal formulation might be associated with its ability to attenuate oxidative stress. The current evidence from experimental studies demonstrates that supplementation of KKC has potential hepatoprotective and antioxidant activity against anti-tubercular drugs induced hepatotoxicity on rats.

KEYWORDS: Polyherbal medication, Antitubercular drugs, hepatoprotective plants, phytoconstituents, Karisalai Karpa Chooranam.

INTRODUCTION
In India, both *Ayurveda* and *Siddha* are considered as traditional systems of medicine. In both Siddha and Ayurveda single or multiple herbs (polyherbal) are used for various treatments. Scientific literatures suggested that the active phytochemical constituents of individual plants are insufficient to achieve the desirable therapeutic effects. When combining the multiple herbs in a particular ratio, it will give a better therapeutic effect and reduce the toxicity.[1] Drug formulation in traditional Indian systems of medicine (ISM) is based on two principles: use as a single herbal and use of more than one herbal, in which the latter is known as poly herbal formulation. This key traditional therapeutic strategy exploits the combining of several medicinal herbs to achieve extra therapeutic effectiveness, usually known as polypharmacy or polyherbalism.[2] Ethno botanical research have focused for decades mostly on the search for the single 'active principle' in plants, based on the assumption that a plant has one or a few ingredients which determine its therapeutic effects. But traditional systems of medicine like Siddha and Ayurveda generally assumed that a synergy of all ingredients of the plants will bring about the maximum of therapeutic efficacy. This approach has for long been impossible to investigate since adequate methods to standardize complex polyherbal formulation as well as to rationalize the complex mode of actions were lacking.[3]

The recent development in synergy research and variety of analytical techniques such as Ultra violet spectroscopy (UV-Visible), Gas Chromatography (GC), High Performance Liquid Chromatography (HPLC), High Performance Thin Layer Chromatography (HPTLC) Ultra Performance Liquid Chromatography (UPLC), Mass Spectrometry (MS) and omic technologies have opened highly interesting perspectives for a new generation of phytopharmaceuticals. In spite of various techniques available, UV, HPLC, HPTLC and GCMS have become a universal tool for herbal drug analysis and biomedical research.

The drug selected for this study Karisalai Karpa Chooranam (KKC) is a polyherbal formulation

recommended for the treatment for various illness especially age related diseases, immunodeficiency, hepatic disorders and general weakness. The name '*Karisalai'* of this formulation indicated the plant species *Eclipta prostrata* (*Asteraceae*) which is the primary ingredient. '*Karpam'* is one of the unique therapeutic formulations in Siddha system advocated for rejuvenation, longevity and elimination of disease causing factors. '*Chooranam'* means powder form. This formulation consists of plants, namely *Eclipta prostrata* (*Asteraceae*), *Wedelia chinensis* (*Asteraceae*), *Centella asiatica* (*Apiaceae*), *Acalyphaindica* (*Euphorbeaceae*), *Indigoferatinctoria* (*Fabaceae*) and *Sphaeranthusindicus* (*Asteraceae*). This classical formulation said to improve health and youthfulness (*kayakarpam*).[4]

On this ground, because of being a combination of plant materials known to have health promoting effects, this study was designed to provide scientific basis to the efficacy of KKC mentioned in the texts. The method of preparation and therapeutic uses of this formulation is mentioned in ancient text *Bogar 7000*. Another name of *Bogar 7000* is *Bogar Sapthakandam*.[5] Scientific documentation regarding the quality, safety and efficacy of Karisalai Karpa Choornam is inadequate. Therefore the present study designed to evaluate the hepato protective role of polyherbal formulation (KKC) on the hepatotoxicity induced by anti TB drugs.

MATERIALS AND METHODS

Collection of botanical species

The botanical species of *Eclipta prostrata (Asteraceae), Wedeliac hinensis (Asteraceae), Centella asiatica (Apiaceae), Acalypha indica (Euphorbeaceae), Indigofera tinctoria (Fabaceae)* and *Sphaeranthus indicus (Asteraceae)* were collected from rural areas of Thanjavur, Tamil Nadu, India.

Authentication

All of the plant specimens are authenticated by scientist Dr.G.V.S.Murthy, Botanical Survey of India (BSI), Ministry of Environment and Forests, Coimbatore, Tamilnadu, India. Voucher specimens (BSI/SRC/5/ 23/2011-12/Tech-1046, 47, 48, 49, 50, 51) of the same have been deposited in the Department of Pharmacy, PRIST University for future reference.

Preparation of Polyherbal formulation

Karisalai Karpa Chooranam (KKC) is a polyherbal formulation which consists dried whole plant powders of *Eclipta prostrata* (*Asteraceae*), *Wedelia chinensis* (*Asteraceae*), *Centella asiatica* (*Apiaceae*), *Acalypha indica* (*Euphorbeaceae*), *Indigofera tinctoria* (*Fabaceae*) and *Sphaeranthus indicus* (*Asteraceae*). KKC was prepared by the method described in the Siddha literature *'Bogar 7000'*. As mentioned in the text, leaf, stem, root, flower and seeds of each plant were collected. After collection, the raw medicinal plant materials were subjected to proper preliminary processing, including elimination of unwanted materials and contaminants, washing to remove excess soil, sorting and cutting. As per the reference, shade drying was preferred to avoid the loss of active chemical constituents of the herbals. All medicinal plant materials individually spread out in thin layers on drying frames and turned repeatedly. In order to maintain adequate air circulation, the drying frames were placed at a sufficient height above the ground. Efforts were made to achieve uniform drying of medicinal plant materials. After 15 days, each plant was powdered separately and passed through 40# sieve. Finally each plant powder was weighed accurately and mixed together in specific proportions to get moderately coarse powder. Finally it was stored in airtight container and used for further analysis. The composition of KKC was mentioned in Table 1.

Table 1: Composition of Karisalai Karpa Chooranam.

S.No	Botanical name	Family	Parts used	Each 100 gm Contains
1	*Eclipta Prostrata*	*Asteraceae*	Leaf, stem, root, flower and seeds	16.66 gm
2	*Wedelia chinensis*	*Asteraceae*	Leaf, stem, root, flower and seeds	16.66 gm
3	*Acalypha indica*	*Apiaceae*	Leaf, stem, root, flower and seeds	16.66 gm
4	*Centella asciatica*	*Euphorbeaceae*	Leaf, stem, root, flower and seeds	16.66 gm
5	*Indigofera tinctoria*	*Fabaceae*	Leaf, stem, root, flower and seeds	16.66 gm
6	*Sphaeranthus indicus*	*Asteraceae*	Leaf, stem, root, flower and seeds	16.66 gm

High Performance Liquid Chromatography (HPLC) analysis

The HPLC analysis of KKC was carried out with Chromatographic system (Shimadzu Class-VPV6.14SP2, Japan) consist of autosampler and an UV-Visible detector. All chromatographic data were recorded and processed using auto chro-software.

Screening of hepatoprotective and antioxidant activity

Experimental Animals

Healthy adult albino rats of either sex of Wistar strain weighing 200-250 g were used for study. They were kept on standard balanced diet and water *ad libitum*. The care and procedures adopted for the present investigation

were in accordance with the approval of Institutional Animal Ethics Committee.

Housing conditions

The experimental animal room temperature maintained at 22°C (± 3°C). The relative humidity was maintained at 40% - 60%. Feed *ad libitum*, RO water (*ad libitum*).

Drugs preparation

Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA) were purchased from Alkem laboratories, Maharashtra, India. Silymarin was purchased from Micro labs, Bangalore. Isoniazid (7.5 mg/kg) and pyrazinamide (35 mg/kg) were dissolved in sterile distilled water whereas Rifampicin (10 mg/kg) was first dissolved in 0.5 ml of 0.1N HCl and then made up to the required volume with sterile distilled water. Ethanolic extract of KKC was suspended in 5% Tween 80. Silymarin suspension was prepared by suspending the pure sample of Silymarin in sterile distilled water. All drugs including the extracts under study and the standard drug were given orally once daily for 45 days by gastric incubation.

Experimental design

All animals were divided into four groups. Each group consisted of six animals (*n=6*). Group I served as Control,

Group II served as Disease control received only *ATD

Group III served as Drug treated received *ATD along with KKC-180mg/kg/*p.o*

Group IV served as Standard drug treated received *ATD along with Silymarin-200 mg/kg/ *p.o*.

(*Antitubercular drugs (Isoniazid (INH) 7.5-mg/kg/*p.o*, Rifampicin(RIF) -10 mg/kg/ *p.o*, Pyrazinamide (PZA) -35mg/kg/ *p.o).*

Collection of blood samples

On completion of 45th day, animals were anaesthetized with thiopentone sodium (50mg/kg/*i.p*). Whole blood was collected from each animal by retro orbital route. Blood, serum and plasma were collected.

Isolation of liver

After blood collection, all animals were sacrificed by decapitation. liver was dissected out, washed with chilled physiological saline, weighed, homogenized in 0.1M Tris HC1 buffer (pH 7.4) at 4ºC in homogenizer, and then used for the evaluation of Malondialdehyde (MDA) and glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX) , Vitamin C and Vitamin E.

Estimation of various parameters on biological samples enzymatic and non ezymatic markers in plasma, liver and kidney

MDA was estimated by the thiobarbituric acid assay method of Beuge and Aust (1978).[6] SOD was determined by the procedure of Kakkar *et al* (1984).[7] CAT was estimated by the method of Beers and Sizer (1952).[8] GP_X was assayed by the method of Rotruck *et al* (1973).[9] GSH was estimated by method of Moron *et al* (1979).[10] Vitamin C was estimated by the method of Omaye *et al* (1979).[11] Vitamin E was estimated by the method of Baker *et al* (1980).[12]

Estimation of serum SGOT, SGPT, GGT, ALP and Total protein

Serum glutamic-oxaloacetic transaminase (SGOT) was estimated by the method of Reitman and Frankel (1957).[13] Serum glutamic-pyruvic transaminase (SGPT) was estimated by the method of Reitman and Frankel *(*1957).[13] Gamma glutamyl transpeptidase (GGT) was estimated by the method of Naftalin *et al.,* (1969).[14] Serum alkaline phosphatase (ALP) was estimated by the method of Kind and King's (1954).[15] Serum total Protein was estimated by the method of Lowry *et al.* (1951).[16]

Estimation of urea and creatinine

Urea was estimated by the method of Natelson (1957).[17] Creatinine was carried out by alkaline picrate method of Boneses and Taussk (1954).[18]

Statistical Analysis

The results were presented as mean ± SD. Data was statistically analyzed using student "t" test. P values set as less than 0.001,0.01,0.05 were considered as statistically significant.

Histopathology

The tissues of liver was dissected out and washed in physiological saline, cut into pieces of desired size and fixed in 10% buffered neutral formalin fixative for 24 hours. The paraffin sections were prepared and stained with haematoxylin and eosin and examined microscopically for histopathological changes.

Examination of electron microscopy in liver biopsies

Scanning electron microscopy was performed on normal, disease control, drug treated and standard treated rats. The blocks were fixed in 2.5% glutaraldehyde buffered in 0.1-M phosphate overnight at 4℃. The specimens were then washed in a phosphate buffer thrice and osmicated in 1% osmium tetroxide for 2 hours. After the specimens had been washed in buffer and dehydrated in a graded series of ethanol solutions and dried. Specimens were then viewed under a scanning electron microscope (Model VEGA 3, Tescan) operated at 15 kV. Specimens were scanned on a monitor at a magnification of x1000. For each block of tissue, an area with maximum damage was chosen and photographed.

RESULTS AND DISCUSSION

HPLC Analysis

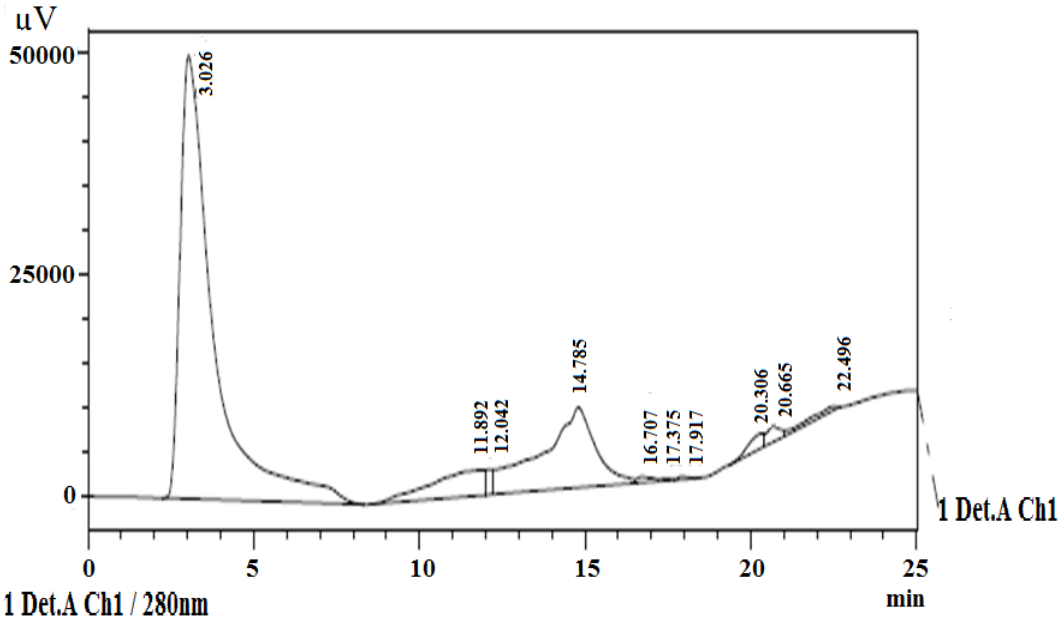


Fig. 1: HPLC Chromatogram of ethanol extract of karisalai karpa chooranam.

Table 2: Identification of bioactive components by using literature.

S. No.	Ret. Time	Area	Height	Area %	Height %	Compounds Identified (by literature)
1	3.026	3486239	50061	68.596	71.580	Quercetin
2	11.892	332671	2851	6.546	4.076	Ellagic acid
3	12.042	37981	2827	0.747	4.043	Resorcinol
4	14.785	1039714	9071	20.458	12.970	Unidentified
5	16.707	20106	659	0.396	0.943	Cyanidin-3-O-glucoside
6	17. 375	5800	255	0.114	0.364	Unidentified
7	17. 917	6161	325	0.121	0.464	Unidentified
8	20.306	57973	1662	1.141	2.377	Naringenin
9	20.665	49889	1776	0.982	2.540	Unidentified
10	22.496	45737	449	0.900	0.642	(-)-Epicatechin
Total		5082271	69936	100.000	100.000	

The HPLC chromatogram of ethanolic extract of karisalai karpa chooranam shown in Fig. 1. The results of HPLC analysis indicated that the presence of Quercetin (flavonoid), Ellagic acid (natural phenol antioxidant), Resorcinol (benzenediol), Cyanidin-3-O-glucoside (anthrocyanin), Naringenin (flavonoid), (-)-Epicatechin (flavonoids) (Table 2). The hepatoprotective effect of the polyherbal formula might be attributed to the presence of unique chemical classes such as polyphenols and flavonoids.

Drug-induced HT is a potentially serious adverse effect of the currently used anti-tubercular chemo-therapeutic regimens containing INH, RIF and PZA.[19] All these drugs are potentially HT independently, when given in combination their toxic effects are enhanced in a synergistic manner. It interrupts the treatment regime and compromises its efficacy, leading to grave consequences. Mitochondria are prominent targets for the hepatotoxicity of many drugs. Dysfunction of these vital cell organelles results in impairment of energy metabolism and oxidative stress with excessive formation of reactive oxygen species and peroxynitrite. In addition to mitochondria, induction of cytochrome P450 isoenzymes such as CYP2E1 also promotes oxidative stress and cell injury. Once hepatocellular function is impaired, accumulation of bile acids causes additional stress and cytotoxicity.[20] The conversion of monoacetyl hydrazine, a metabolite of INH, to a toxic metabolite via cytochrome P450 leads to hepatotoxicity. RIF-induces cytochrome P450 enzyme causing an increased production of toxic metabolites from acetyl hydrazine (AcHz). RIF can also increase the metabolism of INH to isonicotinic acid and hydrazine, both of which were hepatotoxic. The plasma half life of AcHz (metabolite of INH) was shortened by RIF and AcHz is quickly converted to its active metabolites by increasing the oxidative elimination rate of AcHz, which is related to the higher incidence of liver necrosis caused by INH and RIF in combination. In addition to these

mechanisms; oxidative stress induced hepatic injury is one of the important mechanisms in HT produced by anti-tubercular drugs.[21] Rats have been used successfully to investigate INH and RIF-induced hepatotoxicity models.[22-27] Therefore, the authors speculated that rats may be used to study the hepatotoxic effect of antituberculosis drugs and hepatoprotective action of polyherbal formula. Numerous tests have been developed and employed to evaluate liver function or diseases. There were several pathological mechanisms on which these tests are based. Damaged hepatocytes or biliary epithelium may release cell constituents (e.g. enzymes) into blood resulting in increased levels of these analytes. The more commonly measured 'liver' enzymes were alanine aminotransferase (ALT, formerly sGPT), aspartate aminotransferase (AST, formerly known sGOT), Alkaline phosphatase (ALP), sorbitol dehydrogenase (SDH) and gamma-glutamyl transferase (GGT). There were some other tests used less frequently. e.g. ornithine carbamyl transferase, isocitrate dehydrogenase, and arginase. Increased levels of ALT, AST, and SDH were usually associated with damage to hepatocytes.[28-31]

Estimation of Serum SGOT, SGPT, GGT, ALP and Total protein levels

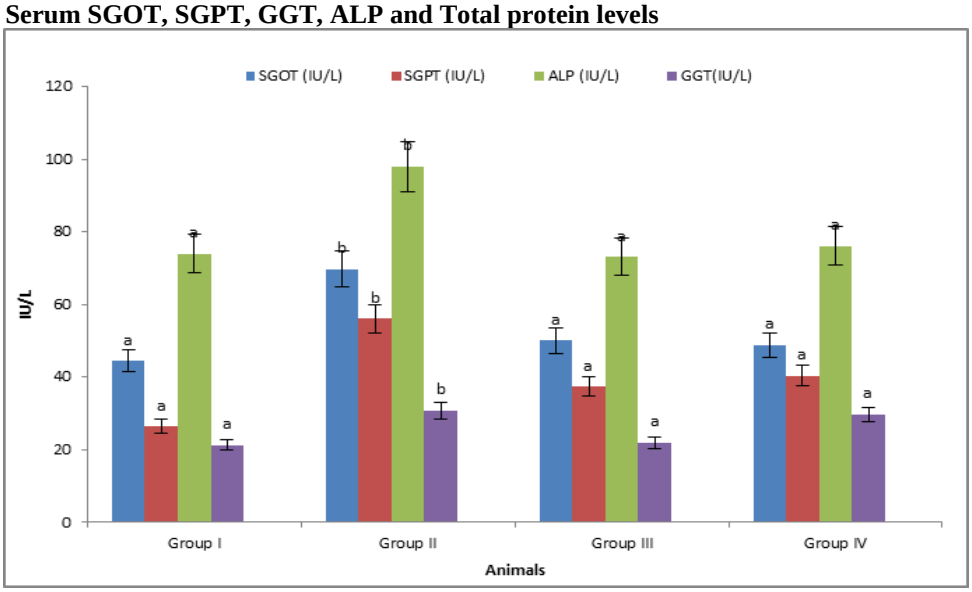


Fig. 2: Effect of KKC on SGOT, SGPT, ALP and GGT activities in experimental rats.

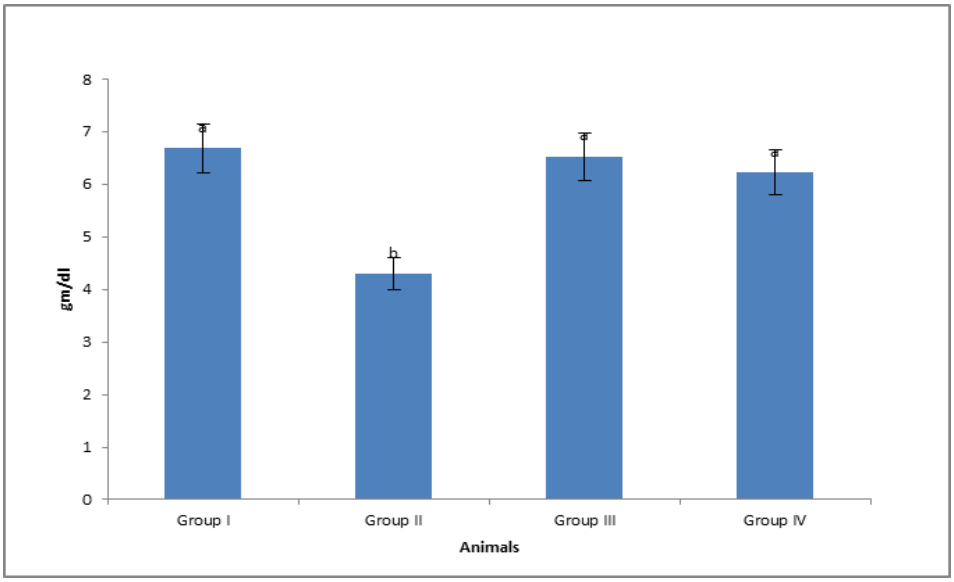


Fig. 3: Effect of KKC on total protein levels.

ap< 0.05 significantly different compared with Group II animals,
bp< 0.001 significantly different compared with Group I, III & IV animals

Group II (disease control) animals which received antitubercular drugs for 45 days showed rise in SGOT, SGPT, GGT and ALP (Fig. 2) significant fall in serum protein level (Fig. 3) as compared to control, drug treated and standard treated group.

In the present study, the hepatic injury induced by Isoniazid, Rifampicin and Pyrazinamide (I+R+P) combination is evident by an increase in the levels of serum enzymes. This is in agreement with the results obtained in other previous investigations.[32,33] Furthermore, Yee et al. also concluded on the basis of survey findings conducted on 430 patients of TB, the drug most likely responsible for the occurrence of hepatitis is PZA.[34] These data support the claim that role of PZA is likely more to raise levels of liver enzymes. The increased levels of AST and ALT are indicative of cellular damage and loss of functional integrity of the cell membrane in the liver.[35] The increase in ALP in liver disease is the result of increased synthesis of the enzyme by cells lining the canaliculi, usually either intra- or extra hepatic, which reflects the pathological alteration in biliary flow.[36] Prior oral administration of KKC extract exhibited significant protection against I+R+P induced hepatotoxicity. The extract-mediated reduction in the levels of these enzymes towards respective normal values is an indication of stabilization of the plasma membrane as well as repair of hepatic damage caused by I+R+P. The histopathological observations suggested the possibility of the polyherbal extract being able to condition the hepatic cells to a state of accelerated regeneration thus decreasing the leakage of ALT, AST and ALP into the circulation. These results also good agreement with the previous study.[37]

Estimation of Blood Urea, Serum Creatinine and Serum Lipid Profile

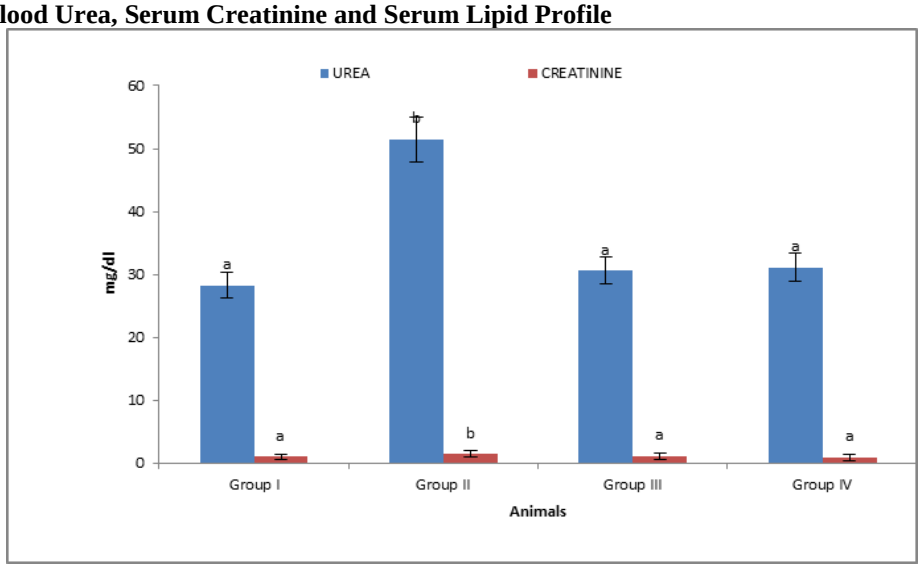
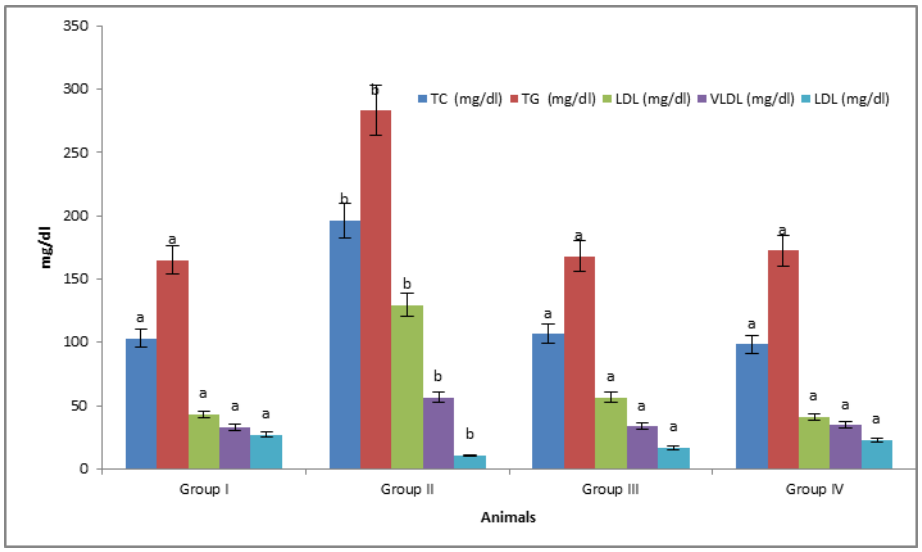


Fig. 4: Effect of KKC blood *on* urea and serum creatinine.



ap< 0.05 significantly different compared with Group II animals; bp< 0.001 significantly different compared with Group I, III & IV animals.

Fig. 5: Effect of KKC on serum lipid profile.

Group II (disease control) animals which received antitubercular drugs for 45 days showed significant raise in blood urea, Serum creatinine levels as compared to control, drug treated and standard treated group (Fig. 4). As a measure of renal function status, serum urea, uric acid and creatinine are often regarded as reliable

markers.[38] Serum creatinine has been used to estimate glomerular filtration rate. Thus, elevations in the serum concentrations of these markers are indicative of renal injury.[39,40] The same was observed after toxicant administration. It may be due to dysfunctional and dystrophic changes in the liver and kidney. Experiment showed significant protective was observed at KKC-180mg/kg/*p.o* indicating normal glomerular filtration rate thereby improved functional status of kidney. These results also agreement with previous reports.[41]

In disease control, raise in TC, TG, LDL, VLDL levels observed when compared to control, drug treated and standard treated group. But significant ($p< 0.001$) fall in HDL level observed in disease control group when compared to control, drug treated and standard treated group (Fig. 5).

Results of the Estimation of Liver Antioxidant Parameters

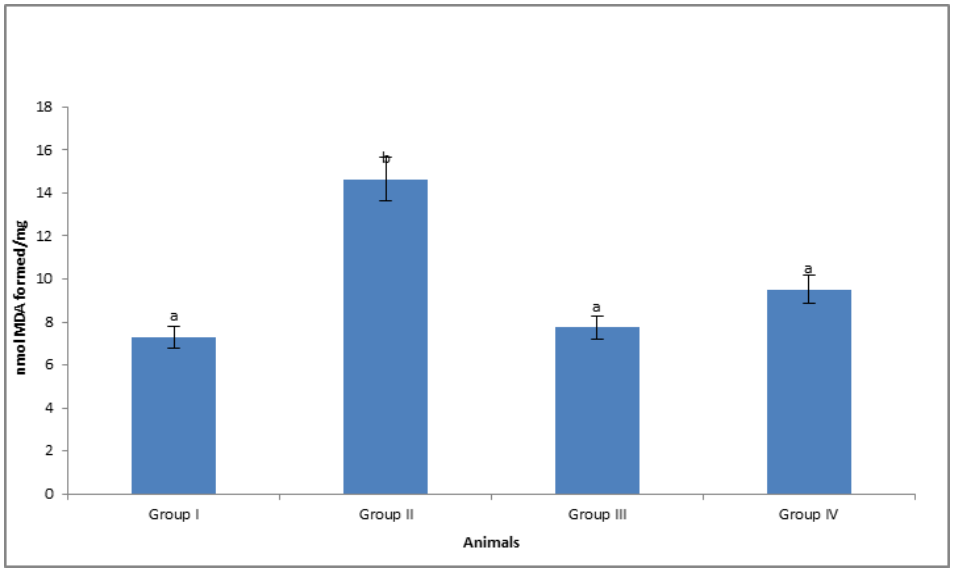


Fig. 6: Effect of KKC on liver MDA in control and experimental rats.

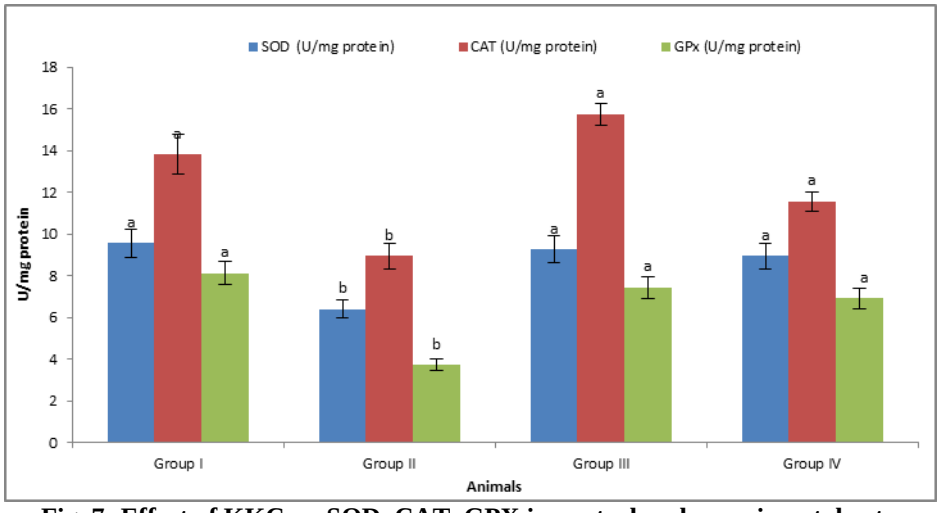
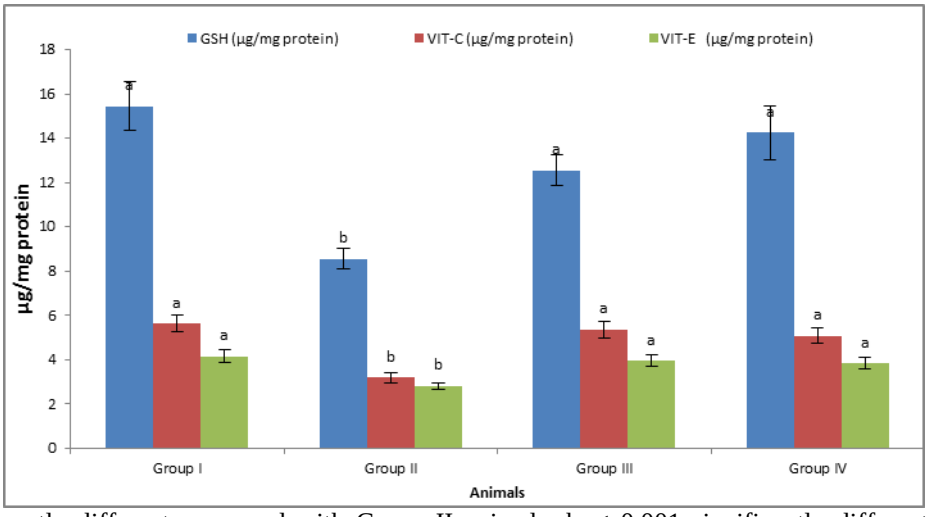


Fig. 7: Effect of KKC on SOD, CAT, GPX in control and experimental rats.



a*p*< 0.05 significantly different compared with Group II animals; b*p*< 0.001 significantly different compared with Group I, III & IV animals.

Fig. 8: Effect of KKC on GSH, Vit C,Vit E in control and experimental rats.

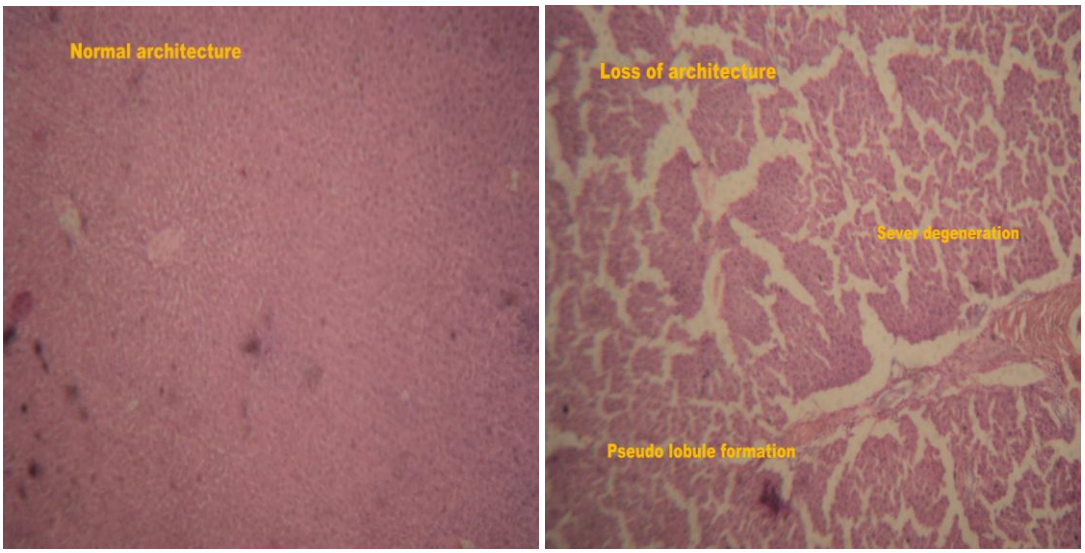
In antitubercular drugs treated (disease control) animals significant raise of MDA was observed when compared to control, drug treated and standard treated group (Fig.6). Significant fall SOD, CAT, GP_X, GSH, Vitamin C and Vitamin E were observed in disease control while compared with control, drug treated and standard treated animals (Fig. 7 & Fig. 8).

Activities of hepatic SOD, CAT and GPx were given in the Fig. 7. SOD and GPx activities were significantly (P<0.05) enhanced after the treatment of KKC + Isoniazid, Rifampicin and Pyrazinamide (I+R+P) treated group. However, the hepatic CAT activity was improved significantly (P<0.05) when compared to the hepatotoxic control. Further the activity of GSH was enhanced and normalized in the KKC+ Isoniazid, Rifampicin and Pyrazinamide (I+R+P) treated (Fig. 8). Hepatic MDA level was significantly (P<0.05) elevated Group II than the normal control group. MDA level was significantly (P<0.05 to P<0.005) reduced by the administration of ATD along with KKC-180mg/kg/*p.o* (Fig. 6). The significant raise of MDA level in drug treated group and the decrease in MDA level in drug treated group supported by the previous studies.[42]

Histopathology and Sem Examination

Histological examination of the liver showed normal architecture in both normal control group and standard supplemented rats. However, cellular damage was obvious in the anti-tuberculosis drug treated (disease control) liver. The liver showed loss of architecture, severe degeneration, vesicular nuclei and prominent nucleoli. It showed nodular arrangement (Pseudo lobule formation) surrounded by lymphocytic infiltrate. In contrast, anti-tuberculosis drug with KKC co-treatment showed near normal hepatocytes with lymphocytic infiltration formed around the central vein without disruption of the liver architecture (Fig. 9).

Control **Disease control**



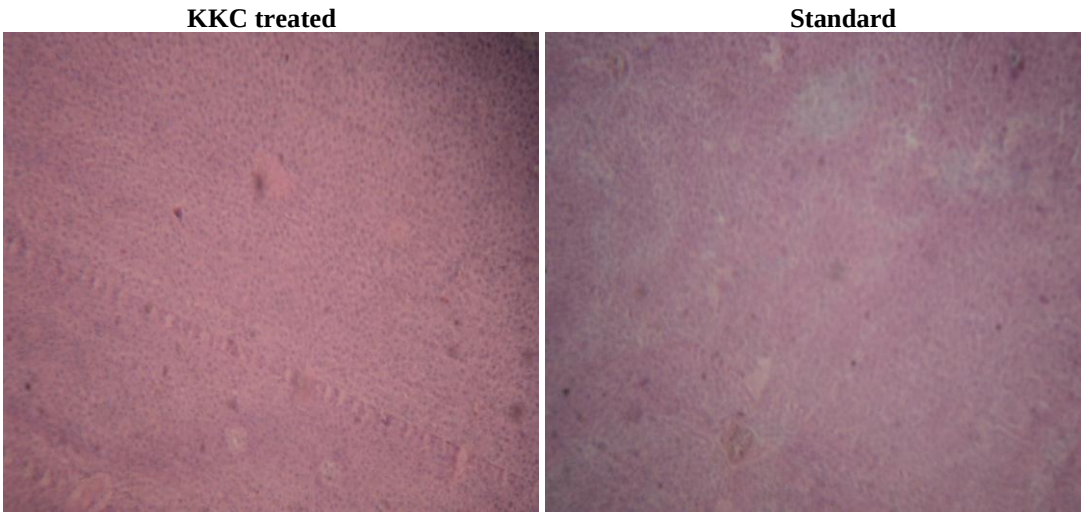


Figure 9: Histopathological analysis of liver in experimental rats.

Scanning electron microscope examination of the liver showed normal extra cellular matrix, normal blood sinusoids with normal hepatocytes in both normal control group and standard silymarin supplemented rats (Fig. 12 & Fig. 13). However, damage of extra cellular matrix components with degenerating hepatocytes having a plenty of lipid droplets was obvious in the anti-tuberculosis drug treated liver (Fig. 10). In contrast, anti-tuberculosis drug with KKC co-treatment showed near normal hepatocytes with normal extra cellular matrix, normal blood sinusoids (Fig. 11).

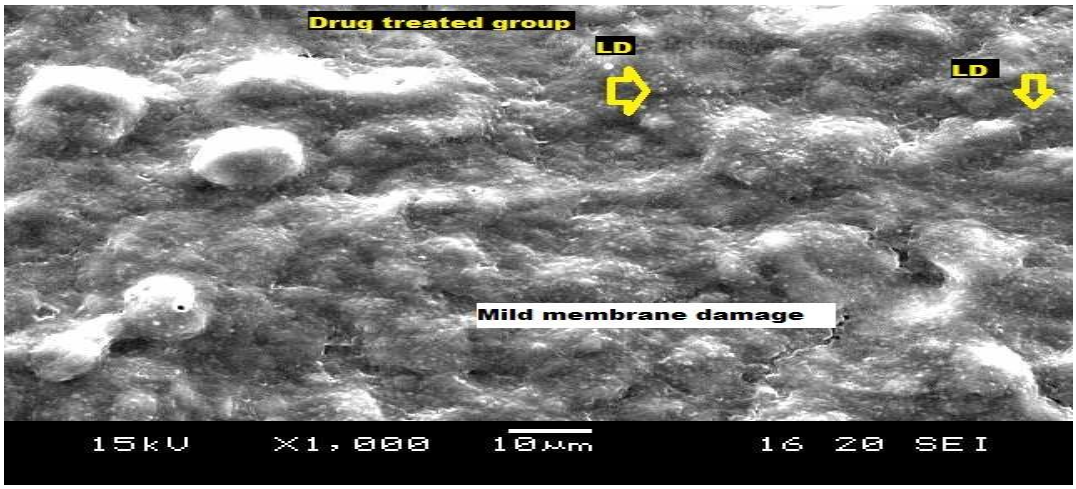


Figure 10: SEM image showing mild membrane damage observed in drug treated group. Near normal hepatocytes with normal extra cellular matrix, normal blood sinusoids observed.

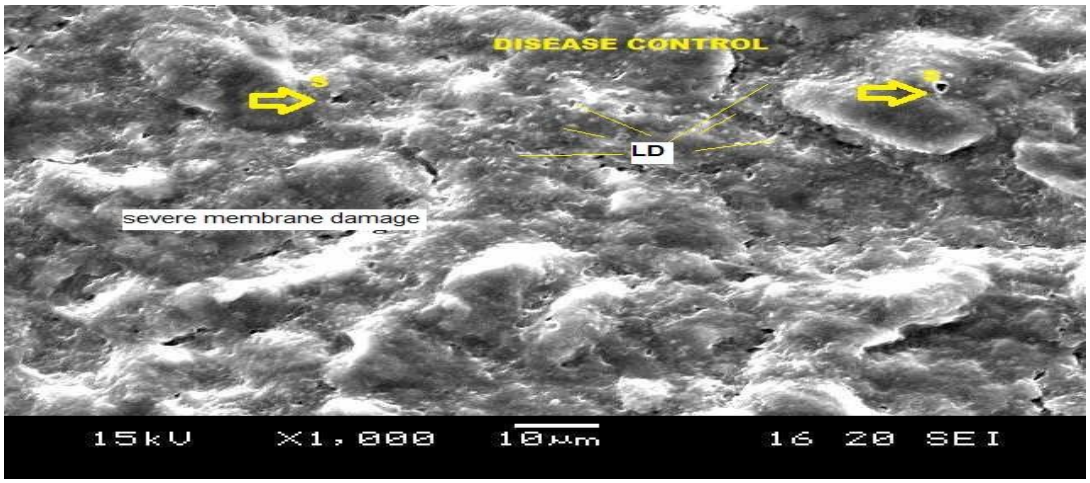


Figure 11: SEM image showing severe membrane damage in disease control group.

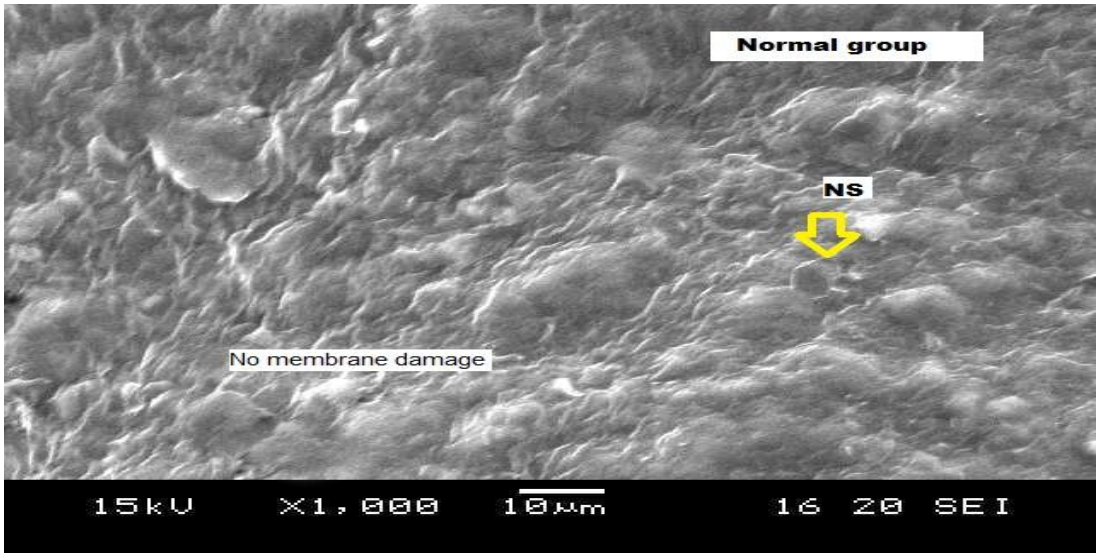


Figure 12: SEM image of normal control group, showed normal extra cellular matrix, normal blood sinusoids with normal hepatocytes in both normal control group.

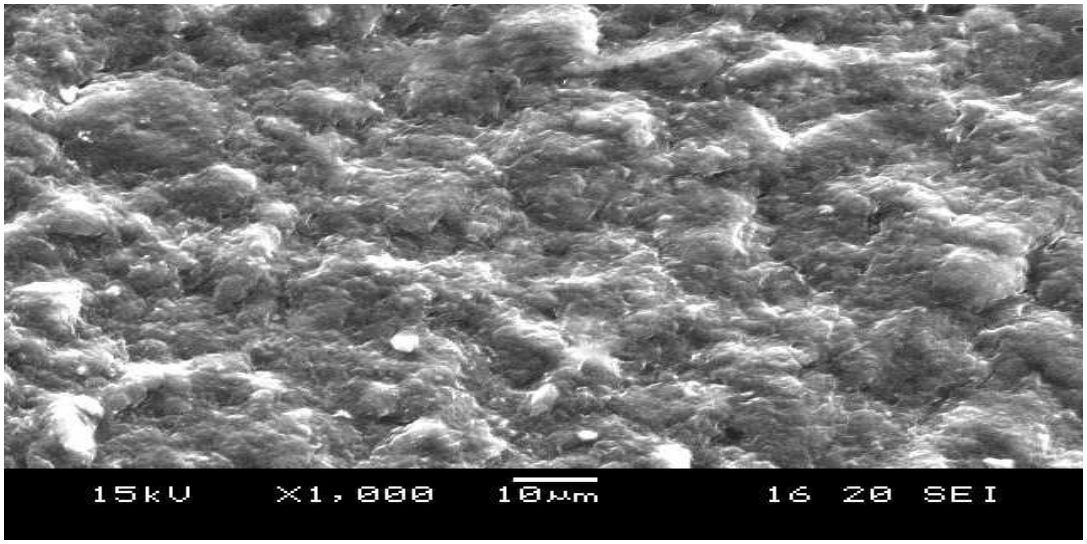


Figure 13: SEM image of standard drug treated group, liver showing normal extra cellular matrix, normal blood sinusoids with normal hepatocytes.

CONCLUSION

Tuberculosis is a familiar ailment in India and worldwide and is chief cause of mortality among all the infectious diseases. The drugs like Isoniazid, Rifampicin, Pyrazinamide and Ethambutol were commonly recommended against TB. These drugs lead to many adverse reactions which are one of the major reasons for non adherence of patients to these drugs that may lead to development of MDR. With the current scenario of MDR cases rising, this problem of adverse drug reactions cannot be taken lightly. Due to lack of successful drugs for treatment of toxicity caused by anti-TB drugs we have to turn towards traditional medicine. From this study, it was clear that the medicinal plants play a significant role against ATT induced hepatoprotective activity. The hepatoprotective activity is probably due to the presence of flavonoids, phenolic compounds, polyphenols etc in KKC polyherbal formula. The results of this study indicate that KKC extract have good potentials for use in hepatic disease. The present study give evidential explore mechanism of action of medicinal plants against experimentally induced hepatotoxicity. The predicted mechanism of action of poly herbs extracts may be attributed to antioxidant properties and the presence of flavonoids, to increase the reduced level of blood glutathione in experimental animal models, to increase total proteins, to inhibit lipid peroxidation and increase in the antioxidant enzymatic activity, to decrease the hepatic marker enzymes (AST, ALT, ALP) and to enhance antioxidative enzymes, including SOD, GPx, CAT and GST, to decrease MDA level, SGOT, SGPT etc. Use of herbal extracts against ATT can be a powerful tool that can fight the problem of adverse reactions caused by TB treatment also this can help in controlling the MDR. Finally, the current evidence from experimental studies demonstrates that supplementation of KKC has potential hepatoprotective and antioxidant activity against anti-tubercular drugs induced

hepatotoxicity on rats. This study report may beneficial to the patients those who are under anti TB drugs treatment regimen.

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