PROTECTIVE EFFECT OF CORIANDRUM SATIVUM L. (CORIANDER) ETHANOLIC LEAF EXTRACT ON ISONIAZID INDUCED HEPATOTOXICITY IN ALBINO MICE

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ABSTRACT
Objective: To study the antioxidant effects of ethanolic extract of coriander leaves on INH induced hepatotoxicity.
Methodology: Total 27 male albino mice were randomly divided through balloting into three groups containing nine animals each. Group A served as control while INH toxicity was produced by oral administration (INH 100mg/kg) to group B. Hepatoprotectivity was investigated by co-administration of single oral dose of ethanolic extract of coriander leaves (200mg/kg) along with INH in groups C for 30 days.
Results: On gross examination, liver of group C animals were found to be normal. Biochemical analysis of liver markers of group B showed that these enzymes were markedly raised while experimental group C showed significant decreased level of liver enzymes. Histological examination of group C revealed normal histology with little evidence of inflammation, vascular congestion, necrosis, pyknosis, apoptosis and vacuolar degeneration as compared to group B.
Conclusion: This study showed the ameliorating effect of ethanolic extract of Coriandrum sativum L. against INH induced hepatotoxicity.

Key words: Coriander, Hepatotoxicity, Isoniazid, Hepatoprotective.

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INTRODUCTION
Tuberculosis (TB) is a disease; caused by Mycobacterium tuberculosis (MTB), its mortality rate is highest among other microbial diseases¹. According to the World Health Organization (WHO) one third of World’s population is infected by Mycobacterium tuberculosis (MTB) among which 9 million people develop active tuberculosis each year². This number increased to 9.6 million in 2014 out of which 1.5 million patients died³. Since 1952, isoniazid (INH) is used to treat active tuberculosis, and also as prophylactic therapy against MTB⁴. Isoniazid, rifampicin, pyrazinamide and ethambutol are first line antituberculous drugs but isoniazid is highly selective choice for prophylactic therapy. All antimicrobial agents cause antituberculous drug-induced hepatitis (ATDH) especially INH as liver is the main organ to be affected by drug toxicity⁵. Despite of its effective response, the drug is also associated with deleterious effects of elevation of liver enzymes which is mild in case of 20% patients and severe in 1-2% of patients receiving this treatment⁶, whereas 10-20% patients on isoniazid therapy show transient harmless increase in liver enzymes; where the rate of hepatotoxicity increases with increasing age⁷ and in also malnourished patients. This condition is 8-20% higher in
This was a randomly controlled experimental study carried out in experimental research laboratory of Anatomy department, University of Health Sciences Lahore. Twenty-seven adult male albino mice used in this study were divided in three groups of nine animals each. Group A served as control and received 0.5 ml distilled water while group B received INH 100mg/kg dissolved in distilled water for 30 days orally. Groups C received 200mg/kg of ethanolic extract of Coriandrum sativum L. leaf extract (EEC) along with 100mg/kg INH for 30 days dissolved in distilled water orally. Herbal extract was prepared at PCSIR laboratories Lahore. Animals were anesthetized 24 hours after the last dose of drugs. Blood samples were drawn for biochemical analysis through cardiac puncture and ALT, AST, ALP and total bilirubin were determined through automated analysis. Animals were dissected and livers were removed and preserved for histological examination. Three to five microns thick sections were cut on a rotary microtome (Leica) and slides were stained with H&E, and were studied under light microscope (Leica DM 1000).

The data was analyzed using SPSS version 20. Mean ± S.E were calculated for quantitative variables while percentages were calculated for qualitative variables. One way ANOVA was applied to compare mean and Fisher’s Exact test was applied to observe associations between qualitative variables. p-Value ≤ 0.05 was considered statistically significant.

RESULTS
Biochemical Analysis: Animals of group A (control) and C (INH 100mg/kg and ethanolic coriander extract 200 mg/kg together) were healthy and active while group B animals which were given INH (100mg/kg) were docile and quite sluggish at the end of experiment. Animals of group C also showed decrease in liver enzymes as compared to group B although this difference was not statistically significant for ALT and AST; however, ALP and total bilirubin decreased significantly (Table 1).

Histological Analysis: Histological study of liver from group A showed normal radiating cords and sheaths of hepatocytes constituting hepatic lobule (Fig.1). In the centre of hepatic lobule was central vein and portal triad located at periphery. Hepatic sinusoids, central vein, hepatic artery and portal vein were normal in appearance. Slides from group B showed loss of general architecture of hepatic lobule with congested vessels and moderate periportal inflammatory infiltrate. There was significant increase in number of necrotic cells and apoptotic bodies. Signet ring cells were also seen around central vein along with inflammatory infiltrate. Inflammatory cells were mainly around portal triad and few focal areas of inflammation were also seen. (Fig. 2). Histological preparations of group C stained with H & E showed preservations of general architecture of hepatic lobules having central vein lined with flattened epithelium at the centre and radiating cords of hepatocytes of one or two cell thickness (Fig.3). Hepatocyte cords enclose sinusoids that were lined with discontinuous flattened epithelium and contain specialized stellate cells called Kupffer cells towards their lumen. Routine H & E staining showed mild periportal inflammation and few dilated vessels in portal triad.

We found that coriander could act as a potential liver protectant and it can be used for the treatment of liver diseases. The results of this study are consistent with previous studies that have demonstrated the protective effects of coriander on liver function. Further studies are needed to investigate the mechanisms by which coriander exerts its protective effects on the liver.

In conclusion, coriander (Coriandrum sativum L.) ethanol leaf extract can be used as a potential natural hepatoprotective agent against Isoniazid induced hepatotoxicity. The results of this study provide evidence for the potential use of coriander in the management of liver diseases.
Fig. 1: Photomicrograph of liver from group A showing central vein (CV) lined with endothelial cell (E). Lumen of central vein contain erythrocytes (Er) and sinusoid opening ( ) into the lumen. Sinusoid (S) lined by polyhedral hepatocytes (H) with round central nucleus (N) and prominent nucleoli (Nu), some of them are binucleated (BN). Cytoplasmic vacuoles (V) are also visible. Kupffer cells (K) with rounded nuclei project into the lumen of sinusoid. H & E. X 400.

Fig. 2: Photomicrograph of liver from group B showing dilated portal vein (PV), hepatic artery (HA) and bile duct (BD) in portal triad infiltrated with lymphocytes (L) and focal inflammatory infiltrate (F). Hepatocytes show vacuolar degeneration (VD). Areas of necrosis (Ne) are also visible. H & E. X 400.

Hepatocytes appear to be of normal size comparable to group A with increased eosinophilia. Many binucleated hepatocytes were also present. Vacuolar degeneration, pyknosis, apoptosis and fatty change was absent. Binucleated hepatocytes with rounded nuclei containing prominent nucleoli and increased eosinophilia represent the signs of regeneration. On staining with PAS, slides showed magenta red granules indicative of glycogen stores within cell with few lymphocytes (Fig. 4).

Fig. 3: Photomicrograph of liver from group C showing general hepatic architecture having central vein (CV), enclosing sinusoids (S) which contain kupffer cells (K). Binucleated (BN) cell are indicative of regeneration. Some of pyknotic nuclei (P) are also present. H & E. X 400.

Fig. 4: Photomicrograph from preparation of liver from group C showing magenta red colour with PAS stain. Portal triad having portal vein (PV), hepatic artery (HA) and bile duct (BD) infiltrated with lymphocytes (L). PAS stain X 400

DISCUSSION
Isoniazid causes hepatotoxicity by its reactive metabolite hydrazine that results in lipid peroxidation (LPO) of plasma membrane including mitochondria. This oxidative stress is evident as increase in liver function markers and various histological changes caused by loss of functional integrity and hepatocellular damage to liver4.
The present study showed that the histological preparations from Isoniazid only group (Fig. 2) showed distorted architecture with congested and dilated vessels and moderate focal and general inflammation. Some animals showed fatty infiltration evident as signet ring cell with peripheral nuclei. Humayun et al\textsuperscript{19}, reported the distorted architecture with subchronic Isoniazid intoxication. Later Jehangir et al\textsuperscript{10}. Also concluded the same results of architectural loss, vascular congestion, dilatation, periportal inflammation with areas of necrosis and apoptosis due to INH toxicity. Our results confirm earlier studies on the hepatic toxicity of Isoniazid. Sarich et al\textsuperscript{2}. reported that areas of necrosis were small less than 10\% and were not uniformly distributed. Isoniazid treatment also elevated, significantly (p<.001) the serum enzymes i.e., serum ALT, AST ALP and total bilirubin when compared with control animals. Our results are comparable to Humayun et al\textsuperscript{20}. WHO studied the effect of propolis on INH induced hepatotoxicity. 

The results of present study are comparable to many earlier studies which provide scientific basis that antioxidant compounds are helpful in hepatoprotection against INH induced hepatotoxicity. Many other studies\textsuperscript{21-22} also showed the presence of phenolic and caffeic acid compounds which are main constituents of plant extract involved in antioxidant activity. Presence of these compounds in Coriandrum sativum could be considered as hepatoprotective against INH induced hepatotoxicity in current study.

It is evident from aforesaid literature that ROS are mainly involved in INH induced hepatotoxicity that can be prevented by antioxidants. EEC contains high levels of phenolic and caffeic acid contents therefore it counteracted the hepatotoxicity of INH and helped in ameliorating the liver enzymes, total bilirubin and restoring the normal histology.

ETHICAL APPROVAL
The study was approved by the University of Health Science, Lahore. Vide No. UHS/Education/126-13/2641 Dated: September 18\textsuperscript{b}, 2013.

REFERENCES

AUTHOR’S CONTRIBUTIONS
MH: Concept, Principal Investigator, Manuscript writing
AR: Manuscript writing
MT: Proof reading
NN: Microscopic Facilitation.