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HEPATOPROTECTIVE POTENTIAL OF ETHANOLIC EXTRACT OF *SOLANUM MELONGENA* LEAVES AGAINST ISONIAZID (INH) INDUCED LIVER DAMAGE IN ANIMAL MODELS

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ABSTRACT

Objective: To evaluate the hepatoprotective potential of ethanolic extract of *Solanum Melongena* leaves against Isoniazid (INH) induced liver damage in animal models. **Methods:** Six groups of six rats each were selected for the study. Ethanolic extract of *Solanum melongena* at a dose of 100, 250 and 500 mg/kg as well as Silymarin (100 mg/kg) were administered orally once daily for 21 days in INH treated groups. The serum levels of ALT, AST, ALP (U/L), ASP, ALP, bilirubin, total bilirubin, Albumin (mg/dl) were estimated. Histopathological analysis was carried out to assess injury to the liver. **Result:** The considerably increased serum enzymatic activities of ALT, AST, ALP (U/L), ASP, ALP, bilirubin, total bilirubin, Albumin (mg/dl) and decreased levels of albumin due to INH treatment were restored towards normal in a dose dependent manner after the treatment with ethanolic extract of *Solanum Melongena* leaves. **Conclusions:** The results of this study strongly indicate that ethanolic extract *Solanum Melongena* leaves posses hepatoprotective activity.

KEYWORDS: *Solanum Melongena*, Isoniazid, Silymarin.

1. INTRODUCTION

Liver plays an important role in maintaining the biological equilibrium of vertebrates. The spectrum of its functions include, metabolism and disposition of chemicals (Xenobiotics) to

which the organ is exposed directly or indirectly metabolism of lipids, carbohydrates and proteins, blood coagulation and immunomodulation.[1] It plays an important role in detoxification processes and also an important role in synthesizing useful principles. Therefore, damage to the liver inflicted by hepatotoxic agents is of grave consequences. Liver function tests may be arranged to help diagnose or monitor liver problems. These blood tests may also be called LFTs, liver panel or hepatic function tests. The liver's job is to filter blood as it travels around the body, but it can become damaged or affected by disease. There is an ever increasing need of an agent which could protect it from such damage.[2] Liver diseases pose complications in treating them throughout the world since, conventional or synthetic drugs used in the treatment of liver diseases are few and with the risk of serious side effects. This is one of the reasons for many people all over the world including those in developed countries for turning towards complementary and alternative medicine.[3] The efforts for standardization of herbal preparations can be seen throughout the world as can be ascertained from publications in scientific journals.[4] Several compounds including clinically useful drugs can cause cellular damage through the metabolic activation of the parent compound to highly reactive substances and also provoking the generation of oxygen derived free radicals. E.g. Nimesulide (4-nitro-2-phenoxymethane-sulfoanilide) is such a non-carboxylic acid, nonsteroidal anti-inflammatory drug that has been widely used for the treatment of a variety of inflammatory and pain conditions. If the drug is consumed in overdoses or for a longer period of time, people with weak liver function suffer severely with unpredictable hepatic problems. It has been reported that the drug can cause several types of liver damage, ranging from mild abnormal function such as increase in serum amino transferase' activity to severe organ injuries such as hepatocellular necrosis or intrahepatic Cholestasis.[5]

In view of severe undesirable side effects of synthetic agents, the interest in traditional or herbal medicines with scientific approach is on the rise. About 600 commercial preparations with claimed liver protecting activity are available all over the world. About 100 Indian medicinal plants belonging to 40 families are used for herbal formulation.

Liver damage can be assessed by various biomarkers such as cellular necrosis, increase in tissue lipid peroxidation and depletion in the tissue GSH levels. In addition serum levels of many biochemical markers like Aspartate amino transferase (AST), Alanine amino transferase (ALP), triglycerides, cholesterol, bilirubin, alkaline phosphatase are elevated. Various herbal formulations have been claimed to possess beneficial activity in treating

hepatic disorders.[6] Very few drugs stimulate liver function or offer protection to the liver from damage or help in regeneration of hepatic cells. However there are a number of drugs employed in traditional system of medicine for liver affections. Many formulations containing herbal extracts are sold in the Indian market for liver disorders but management of liver disorders by a simple and precise herbal drug is still an intriguing problem.[7]

Isoniazid (INH) is a widely used medicine as a first line agent in anti- tubercular drug therapy. Studies reveal that, 10% to 20% of Isoniazid recipients manifested biochemical evidence of liver injury and developed clinically overt hepatitis.[8]

INH induced hepatotoxicity is mainly due to its active metabolites like, acetyl Isoniazid (AcINH), acetyl hydrazine (AcHz). Hydrazine and diacetyl hydrazine due to induction of liver cytochrome P-450 activity. The metabolite themselves or by producing free radicals bind to these free radical scavenging enzymes, SH- Protein cell membrane and cell macromolecules.[9] A few compounds produce metabolites that cause liver injury in a uniform, dose dependent fashion. Injury to hepatocytes results in either directly from the disruption of intracellular functions or membrane integrity or indirectly from immune mediated membrane damage.[10]

Chemical constituents

Growing parts of the plant contains carbohydrates, sugars, fat, protein, Vitamin B_6, Vitamin C, Vitamin B_9, calcium, Iron, Magnesium, Potassium, Phosphorus, Zinc, Pantothenic acid, Niacin(Vit.B_3), Riboflavin(Vit.B_2), Thiamine(Vit.B_1).

Traditionally leaves of *Solanum Melongena* are used as antipyretic, analgesic, hypnotic, costive, anti-phlegmatic, hypolipidemic, purgative, constipation, dyspepsia, Leaves are narcotic and seeds are stimulant. It is also used in toothache and hepatoprotective. Since there are no scientific evidence available on *Solanum Melongena* for hepatoprotective activity. Therefore the present study will be designed to evaluate hepatoprotective activity of *Solanum Melongena* leaves extracts.[11] The main objectives of the study are to evaluate the hepatoprotective activity of *Solanum Melongena* leaves extracts in rats.

2. MATERIALS AND METHODS

Collection of plant material

The Solanum Melongena plant leaves was collected from the local market of Belgaum,

Karnataka, India. Identified and authenticated by Dr. Harsha Taxonomist, Regional Medical Research Centre (ICMR), Belgaum, where the herbarium of the specimen is deposited (voucher no. RMRC-580).

Preparation of extract

The leaves were shade dried at room temperature and the alcoholic extract was obtained with 95% V/V alcohol for 18 hour, using soxhlet apparatus. The extract was dried at 50 ^{0}C in a water bath.

3. Experimental design

All animals were divided into six groups with six animals.

Group I was vehicle treated group, administered with distilled water (1 mL/kg, p.o.).

Group II was toxic control group, administered with isoniazid (100 mg/kg each, i.p.) dissolved in water for 21 days.[10] Vehicle was administered one hour prior to isoniazid.

Group III, IV administered with extract of *Solanum Melongena* leaves at 100,250 and 500 mg/kg, p.o. respectively with isoniazid (100 mg/kg each, i.p.) for 21 d. Extract was administered one hour prior to isoniazid administration.

Group VI was standard drug group administered with Silymarin (200 mg/kg, p.o.) suspended in 0.1% carboxymethyl cellulose. Vehicle, extract and Silymarin were administered one hour prior to isoniazid administration each day for 21days. Twenty-four hours after last dosing, blood sample was collected through retro-orbital puncture and animals were sacrificed by cervical dislocation under general anesthesia. Liver was collected for estimation of enzymes involved in histopathological examination.[12,13]

Drugs and Chemicals

- Isoniazid was a generous gift from Get Well pharmaceuticals, India.
- Silymarin was obtained from micro labs (Bangalore)

Ellman's reagent	Sigma-Aldrich (USA)
Thio barbituric acid	HI media Ltd., Mumbai
Trichloroacetic acid	Himedia Ltd., Mumbai

Dose selection

a. Isoniazid single dose of 100mg/kg and dissolved in distilled water and administered i.p for 10 days.

b. Silymarin at 3 different doses 100 mg/kg[53], 150 mg/kg and 200mg/kg were weighed and the residue was dissolved in 1% Tween 80 in normal saline and administered orally for 11 to 21st days after treated with Isoniazid.

4. RESULTS

Screening of alcoholic extract of *Solanum melongena* with Silymarin in Isoniazid induced hepatotoxic Wistar rats and evaluating their effects (Chronic study) on liver weight, liver volume, biomarkers and histology of liver in Isoniazid hepatotoxic rats.

Physical parameters

The effect of extracts on liver weight and liver volume[14]

Determination of wet liver weight

Livers isolated from the animals were washed with alcohol and dried on filter paper strips and weighed on an electronic balance and were expressed with respect to their body weight i.e.; g/100 g.

Determination of wet liver volume

After recording the liver weights, the livers were individually dropped into a measuring cylinder containing a fixed volume of distilled water and the volume displaced was recorded and expressed as ml/100 g body weight.

There was a significant increase in liver weight in 100mg/kg of Isoniazid induced group compared to that of normal control group. Standard drug Silymarin 100mg/kg showed significant reduction ($p<0.001$) in liver weight. Treatment with AESM at a of dose of 100, 250 and 500mg/kg showed more significant reduction ($p<0.001$) in liver weight Compare to that of hepatotoxic control group.

The effect of extracts on biochemical parameters

a) Estimation of Serum SGPT/ALT (UV- Kinetic method)[15]

As mentioned in the above table blank, standard and samples were prepared by considering 500µl of working reagent and 50 µl each of distilled water, standard and sample respectively, later all the samples were incubated at 37^0C, aspirated individually and absorbance was recorded at 340 nm.

b) Estimation of Serum SGOT /AST (UV- kinetic method)[16]

As mentioned in the above table blank, standard and samples were prepared by considering

500 µl of working reagent and 50 µl each of distilled water, standard and sample respectively, later all the samples were incubated at 37^0C, aspirated individually and absorbance was recorded at 340 nm. Animals of toxic control group had significantly elevated (P<0.01) level of SGOT, SGPT, ALP and bilirubin as compared to vehicle treated animals (Table 1). This confirmed the toxic effect of Isoniazid at selected doses on liver. In animals of test group at three different doses (i.e. 100.250 and 500 mg/kg) there was significant protection observed for liver. This was confirmed on the basis of significantly lower P<0.01) level of SGOT, SGPT, ALP and bilirubin as compared to that of animals of toxic control group. While the standard drug Silymarin at a dose of 100mg /kg has also significantly reduced (p<0.001) level of SGOT, SGPT, ALP and bilirubin as compared to animals of toxic control group.Silymarin at a dose of 100mg /kg has also significantly reduced the elevated levels of ASP and ALP level.

C) Estimation of Serum Alkaline phosphatase (ALP)[17]

As mentioned in the above table blank, standard and samples were prepared by considering 500 µl of working reagent &10 µl each of distilled water, standard, sample respectively, later all the samples were incubated at 37^0C, aspirated individually and absorbance was recorded at 405 nm.

D) Estimation of Serum bilirubin[18]

Bilirubin reacts with diazotized sulphanilic acid in acidic medium to form a pink colored azobilirubin with absorbance directly proportional to bilirubin concentration. Direct bilirubin being water soluble directly reacts in acidic medium. However, indirect and unconjugated bilirubin is solubilized using a surfactant and then it reacts similar to direct bilirubin.

E) Estimation of Serum Albumin[18]

Albumin binds with bromo-cresol green (BCG) at pH 4.2 causing a shift in absorbance of the yellow BCG-dye. The blue green colour formed is proportional to the concentration of albumin present, when absorbance is measured spectrophotometrically at 630 nm.

Table no: 1: Effect of AESM on liver weight and Liver volume.

SR. No.	Treatment group	Mean liver weight (g/100g)	Mean liver volume (ml/100g)
1)	Normal control	3.7±0.03	3.30±0.20
2)	Isoniazid(100mg/kg)	6.76±0.06###	6.76±0.06###
3)	Silymarin(100mg/kg)+Isoniazid	3.98±0.06***	4.02±0.04***

4)	AESM(100mg/kg)+Isoniazid	4.74±0.06***	5.18±0.04***
5)	AESM(250mg/kg)+Isoniazid	4.38±0.03***	4.40±0.03***
6)	AESM(500mg/kg)+Isoniazid	4.12±0.03***	4.20±0.03***

*P<0.05, **P<0.01, ***P<0.001 when compare to Isoniazid induced animals.

When compare with normal. Results are expressed as ± S.E.M

N= no. of animals in each group.

Results are compared with one way ANOVA Tukey compare all pairs of columns.

Table no: 2: Effect of AESM on serum biomarker enzymes like SGOT (IU/L), SGPT (IU/L), and ALP (IU/L) Bilirubin (mg/dl).

Treatment group (mg/dl)	SGOT (IU/L)	SGPT (IU/L)	ALP (IU/L) Bilirubin
Vehicle (1 ml/kg/d) 260±0.032	56.21±4.62	43.23±2.82	104.00±5.020.
Isoniazid (100mg/kg) 0.840±0.052a	125.44±9.22a	88.63±6.42a	205.57±8.55a
AESM (100mg/kg)+Isoniazid 0.450±0.021b	78.64±5.82b	62.66±4.67b	132.21±8.75 b
AESM (250mg/kg)+Isoniazid 0.410±0.035b	68.34±4.74b	54.82±3.56b	121.05±10.67b
AESM (500mg/kg)+Isoniazid 0.405±0.029b	65.25±3.28b	51.29±2.29b	116.26±9.29b
Silymarin (100mg/kg)+Isoniazid 0.350±0.022b	61.35±5.21b	49.67±3.98b	118.63±7.83b

All data presented in mean±SD (n=6). A. P<0.01 as compared to vehicle treated group,

B. P<0.01 as compared to toxic control group.

Results are compared with one way ANOVA Tukey compare all pairs of columns.

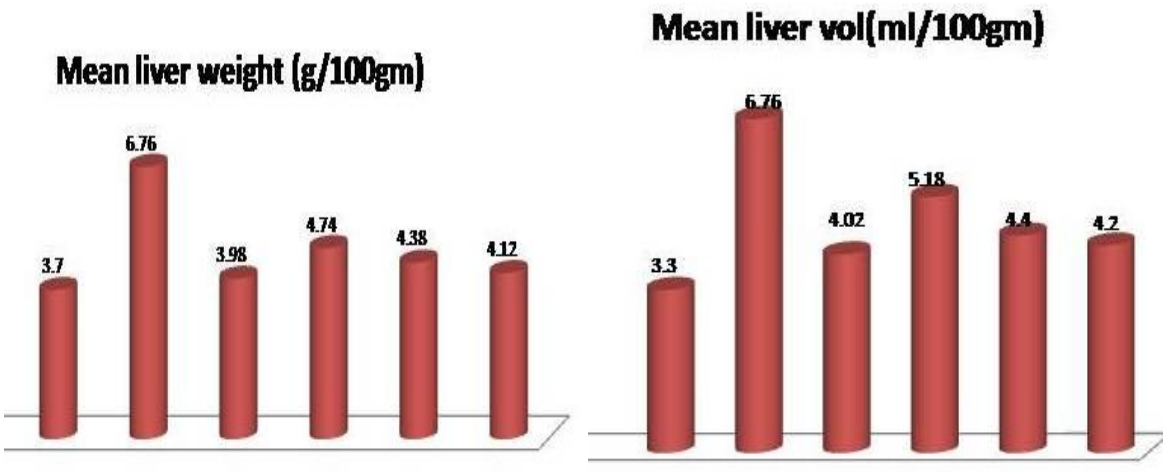


Figure 1: Effect of *Solanum Melongena* Leaves on Liver Weight And Liver Volume.

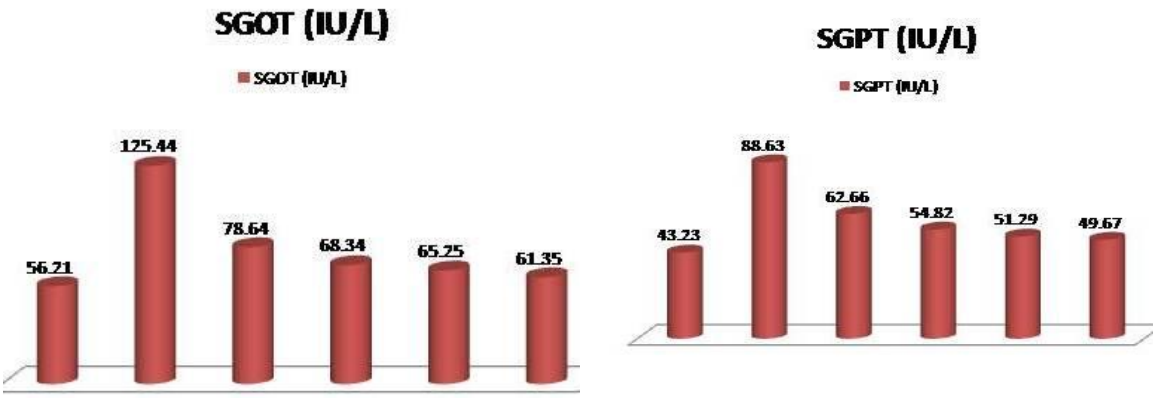


Figure 02: Effect of *Solanum Melongena* Leaves on Ast And Alt.

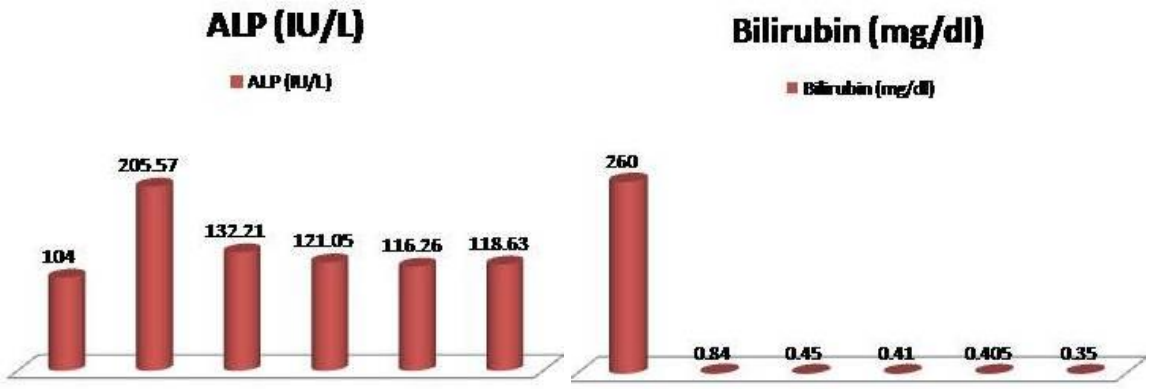
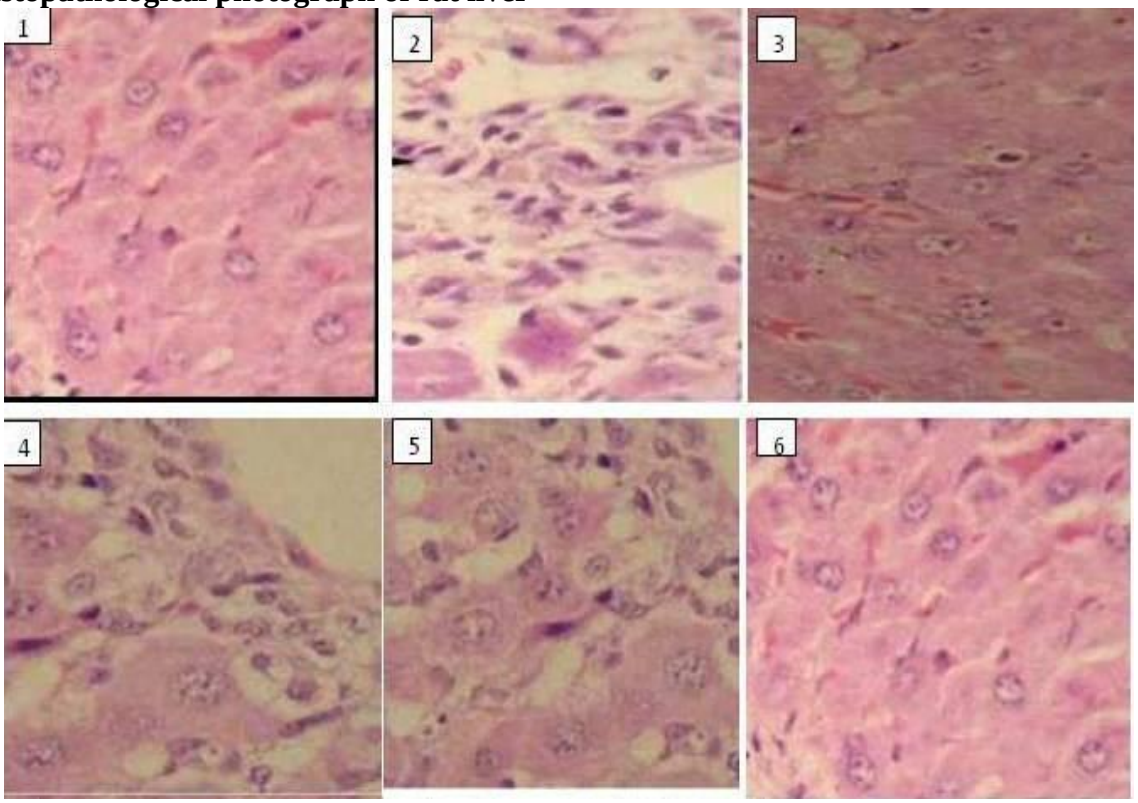


Figure 03: Effect of *Solanum Melongena* Leaves on Alp And Bilirubin.

Histopathological photograph of rat liver



GROUP 1: High power photomicrograph of liver from control group animal showing normal hepatocytes in the periportal area.

GROUP 2: High power photomicrograph of liver from animal treated with Isoniazid only showing loss of hepatocytes around the central vein (CV), inflammatory cell infiltration and haemorrhage.

GROUP 3: High power photomicrograph of liver from animal treated with Isoniazid and Silymarin showing the centrizonal areas with presence of fat vacuoles in scattered hepatocytes.

GROUP 4: High power photomicrograph of liver from animal treated with Isoniazid and 100 mg/ Kg AESM leaf extract showing sinusoidal dilatation and inflammatory cell infiltration.

GROUP 5: High power photomicrograph of liver from animal treated with Isoniazid and 250 mg/kg AESM Leaf Extract showing centrizonal hepatocytes with sinusoidal dilatation and inflammatory cell infiltration.

GROUP 6: High power photomicrograph of liver from animal treated with Isoniazid and AESM leaf extract 500mg/ kg but showing normal hepatocytes with mild fatty change.

DISCUSSION

Human race is largely dependent on the plant kingdom which is not only providing a source of vital nutrients, but also caters to the needs of humans by providing remedies to different types of ailments. This has lead to the evolution of plant science dealing with the usage of plants in treating and controlling many different diseases by trial and error. Herbal medicine is referred to use of plant products to treat or prevent a disease. Herbal medicine is also known as a subset of larger term “Complementary and alternative medicine” (CAM). Long before the advent of modern medicine herbs were the mainstream remedies for nearly all ailments. Now a days due to the adverse effects of modern medicine, people have been turning in increasing numbers to the use of herbal medicine as both an alternative and adjunct to modern drugs.[19]

Medicinal plants have their values due to the presence of chemical constituents, commonly known as secondary metabolites, present in various plant tissues. These substances are alkaloids, glycosides, essential and fatty oils, resins, gums, mucilage, tannins etc. of large use. These active principles may be present in the storage organs of plant, viz. roots, seeds, leaves, wood etc.

Drug like Isoniazid convert to their respective toxic metabolites by cytochrome P-450 dependent mixed function oxidase, which readily bind to glutathione, glutathione-S-transferase etc. This leads to depletion of these antioxidant enzymes and subsequent hepatocellular damage.[20,21,22]

Liver participates in a variety of metabolic activities and contain a lot of enzymes and in this process it could be injured by many toxicants, chemicals and drugs. In our hepatoprotective study, isoniazid is used as a hepatotoxicant to induce liver damage.

Isoniazid mediated hepatic toxicity was taken as an experimental model for liver injury. It has been shown that Isoniazid gets accumulated in the hepatic parenchymal cell and metabolically activated by cytochrome P450 dependent monooxygenases to form a free radical, leading to liver damage. In the present study, Isoniazid treatment significantly elevated the biochemical parameters indicating significant hepatic damage. Methanolic extracts of *Solanum melongena* showed significant reduction in the elevated enzyme level induced by Isoniazid treatment. This subsequent recovery towards normalization of the enzymes suggesting the capability of the above extracts to condition the hepatocytes (seen in histopathological observation) to accelerate parenchymal regeneration, thus protecting against membrane fragility and subsequently decreasing leakage of marker enzymes into the circulation. The histological observation of these selected medicinal plant Methanolic extract treated liver found to have normal architecture with very mild fatty changes when compared with Isoniazid treated liver, which signifies hepatoprotective activity of these selected medicinal plant. The probable mechanism of protective action of these extracts, against Isoniazid induced hepatic metabolic alterations, can be either though an enhanced protein synthesis, or interference with the microsomal activation of Isoniazid or its accelerated detoxification (free radical scavenging activity) or excretion.

Recent study indicates that oxidative stress is involved in the pathogenesis of liver diseases including drug induced hepatic damage, alcohol hepatitis and viral hepatitis or ischemic liver injury.[23]

Isoniazid induced hepatotoxicity was used by several workers as model for screening hepatoprotective activity. The dose used for induction of hepatotoxicity by different workers was found to vary.

Finally the incidence of Isoniazid induced enzyme activity reported was any other value previously reported and might be related to the fact that most of the earlier studies did not consider the elevation in the liver enzymes in their analysis.

The incidence of Isoniazid induced hepatitis reported here was also higher than reported in the literature.[24,25,26,27] As suggested by Huang the real incidence of Isoniazid induced hepatitis could well have been underestimated in previous studies in the absence of systematic assessment.[28,29] In present study the hepatoprotective activity of *Solanum melongena* extract were evaluated in Isoniazid induced liver toxicity by the above mentioned biochemical parameters. Acute administration of Isoniazid produced marked elevation of the serum levels of the parameters in treated rats (Group II) compared to that of the control group (Group I). Treatment with *Solanum melongena* aqueous extract at doses of 500 mg/kg produced dose dependent reduction in Isoniazid induced rise of the parameters.

Conflict of interest statement

The authors declare no conflict of interest.

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