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Assessment of Hepatoprotective Potential of *Solanum xanthocarpum* (whole plant) Linn. against Isoniazid & Rifampicin induced hepatic toxicity in wistar rats

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ABSTRACT

The scientific assessment of medicinal plants used in the preparation of folk remedies has contributed modern medicine with effective pharmaceuticals for the treatment of diseases. Objective. The 50% ethonolic extract of *solanum xanthocarpum* (Solanaceae) whole plant was explored for its hepatoprotective and antioxidant effects on RIF+INH (50 mg/kg) induced acute liver damage in Wistar rats. The Whole plant (*SX*) were further subjected to various phytochemical study and the studies conclude the presence of alkaloids, flavanoids, glycosides, protein & amino acid etc. Hepatoprotection activity was measured by using enzymatic (serum glutamate oxalate transaminase and serum Glutamate Pyruvate Transaminase (SGOT and SGPT), alkaline phosphatase (ALP), total bilirubin and non enzymatic parameters (GSH, LPO, SOD, CAT) produced significantly increased and decreases serum level in a dose dependant manner. The Whole plant extract *SX at* the doses of (125 mg/kg &250 mg/Kg) significant liver protective effect by decreasing the serum enzymatic and non enzymatic parameters, although Histopathological profile of liver at dose level 125 mg/kg showing hepatic cells with well preserved cytoplasm prominent nucleus, some of central vein and sinusoids exhibited congestion. At the same time fourth group test dose at 250 mg/kg showing well brought out central vein, hepatic cell with well preserved cytoplasm prominent nucleus. These all result recommended that 50% ethonolic extract of whole plant of *Solanum xanthocarpum* posses significant hepatoprotective activity.

Introduction

The liver is that the largest organ of the body and its management many very important performs in regulation of physiological state, secretion, storage and metabolism by eating substances like lipids, carbohydrates, proteins, coagulation (Rajesh et.al 2004). Liver diseases are the most serious problem and mainly caused by toxic chemicals like, excess consumption of alcohol, high doses of paracetamol etc. within 24 h of ingestion (Maheswari et.al 2008). In the absence of a reliable liver protective drug in the modern system of medicine, a number of medicinal preparations in Ayurveda, the Indian system of medicine, are recommended for the treatment of liver disorders **(**Chatterjee, 2000**).**

Solanum xanthocarpum (Family Solanaceae) generally known as Yellow Berried Nightshade (syn: Kantakari), is a prickly diffuse bright green perennial herb, woody at the base, 2-3 m height constitutes all over India in Nov-Jan, mostly in dry places as a weed on roadsides and waste lands (Singh et.al., 2010). This plant is also known as Choti Katheri, Bhutkatya or Bhumiringani (Bhatt et.al., 2011).The whole plant part (leave, fruit, root, flower, stem) reported several type of activity and the part of plant have many chemical constituent life fruits are contain several steroidal alkaloids like solanacarpine (Gupta et.al., 1938) solanacarpidine, solancarpine, solasonine (Saived 1963) and solamargine (Siddiqui et.al., 1983) and the other constituents caffeic acid, coumarins like aesculetin and aesculin, steroids carpesterol, diosgenin, campesterol, daucosterol and triterpenes like cycloartanol and cycloartenol (Paul et.al., 2008). *Solanum xanthocarpum* has been reported as an effective medicine in the treatment larvicidal (Bansal,2009) anthelmintic (Gunaselvi et.al., 2010) asthma (Savithramma,2007) immunomodulatory (Sultana,2011) antinociceptive (Rahman,2003) antifungal (Saini,2006) larvicidal defect (Mohan et.al.,2007) hypoglycemic (Kar et.al., 2006) anti-inflammatory, analgesic (Thabrew et.al.,2003) antibacterial **(**Usman et.al., 2010) antimicrobial (Salar et.al.,2009) and wound healing activities (Kumar et.al., 2010). Leaf paste prepared with water is applied topically on forehead to getting relief from had to get relief from headache it has also used in astringent, aphrodisiacs, laxative, diuretic, stomachic, cardiotonic and refrigerant activities (Duraipandiyan et.al.,2006). The stem, flowers and fruits are prescribed for relief in burning sensation in the feet accompanied by vesicular eruptions (Chopra 1956).

Choice of scientific and standardized approach to the biological analysis of plant product supported their use within the ancient systems of medication forms the idea for a perfect approach within the development of latest drugs from plants.

The current study mainly focused on the liable benefit of hepatoprotective activity of 50% ethonolic whole plant extract *SX* and also specifies a viable mechanism for its hepatoprotection by analysis with biochemical and histopathological parameter against drug induced hepatotoxicity in rats.

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Material and method

Collection of plant materia

The 50% ethonolic whole plant extract *SX* (family Solanaceae) was collected from the Botanical Garden of N.B.R.I (National Botanical Research Institute) Lucknow, India in the month of December - January and specimen were prepared and matched to the existing live reference.

Extraction of plant material

After collection and authentication whole plant, including leaves, stems, flowers, fruit and root were collected and then shade dried and glided, the powdered plant material (900 g) was macerated with petroleum ether, the marc was exhaustively extracted with of 50% ethanol for three days. The extract was separated by filtration and concentrated on rotavapour (Buchi R-200 USA) and then dried in lyophilizer (Labconco, USA) under reduced pressure.

Animals

Sprague-Dawley rats (160-200g) of either sex were procured and were kept under controlled conditions of temperature 27±2^{0}C and relative humidity 44-56%, light/dark cycles of 12 hours respectively for one week before and during the experiments. Animals were provided with a standard rodent pellet diet (Amrut, India) and the food was withdrawn 18-24 h before the experiment though water was allowed *ad libitum*. The composition of diet is 10% protein, 4% arachis oil, 1% fiber, 1% calcium, 1000 IU/gm vitamin A and 500 IU/gm vitamin D. All experiments were performed in the morning accordance with the current guidelines for the care of laboratory animals and the ethical guidelines for investigations of experimental pain in conscious animals (Zimmerman,1983) . The protocol for this study has been approved by the Institutional Animal Ethics Committee as per the guidance of Committee for the Purpose of Control and Supervision of Experiments on Animals CPCSEA, New Delhi, with number (IAEC CPCSEA/07/2014).

Preliminary Phytochemical analysis

The 50% ethonolic whole plant extract *SX* was screened for the latency of various phytochemical constituents such as alkaloids (wager's reagent), Flavanoids (Shinoda test), Glycoside (Anthroquinone test), saponins (hemolysis test), tannins (ferric chloride test) and steroids (acetic anhydride test) as described by (Trease et al.,1989) and Harborne (Harborne1,993) according to a previously described method for extraction.

Biochemical assessment

The biochemical parameters like serum enzymes, which include Aspartate aminotransaminase (AST) Alanine aminotransaminase (ALT) [Reitman1957] Alkaline phosphatase (ALP) (Horn1972) and Total bilirubin (Jendrassik.,1938) Total proteins (Lowry,1951). Liver homogenates (5% w/v) were prepared in cold 50mM potassium phosphate buffer (pH 7.4) using a Remi Homogenizer. The unbroken cells and cell debris were removed by centrifugation at 1000 RPM for 10 using a Remi refrigerated centrifuge. The supernatant was used for the estimation of reduced glutathione (Moron et.al., 1979) malondialdehyde (MDA) (Slater, 1971) superoxide dismutase (SOD) (Misra, 1972) and catalase (Aebi, 1974) levels.

Liver Histopathological Assessment

10% formalin was freshly planned and the right liver lobe of treated and control were fixed in 10% formalin for 48 hours and subsequently dehydrated in alcohol, cleared with xylem and embedded in paraffin wax. Sections of lobe at about 5µm were mounted on glass slides and stained with haematoxylin and eosin (Lillie1965).

Induction of experimental hepatotoxicity

INH + RIF solution was prepared in sterile distilled water. Rats were treated with INH+RIF at the dose of 50 mg/kg B.w. Orally each of the experimental animals for 10 and 28 days **(**Pal, 2006). In order to study the whole plant extract *SX* in rat 125, 250 mg/kg b.w. was administered by oral route. Silymarin (100mg/kg) was used as a standard drug in this study. Rats were divided into five groups. Each group contains 6 animals and treatments were followed as per treatment protocol given below.

Group1 – Rats were treated with normal saline

Group2 – Rats were treated with INH + RIF (50mg/kg)

Group3 – Rats were treated with INH + RIF + *(SXE)* (125 mg/kg)

Group4 – Rats were treated with INH + RIF + *(SXE)* (250 mg/kg)

Group5 – Rats were treated with INH + RIF + Silymarin (100 mg/kg)

Animals were killed, 24 h after the last dose. Blood was collected by cardiac puncture under ether anesthesia and allowed to clot for 30 min at r.t. The serum was separated by centrifugation at 2500 RPM at 30 °C for 15 min and used for the estimation of marker enzymes, namely SGOT, SGPT, ALP, TB and TP. The livers were dissected out immediately, washed with ice cold saline and 10% homogenates in 1.15% (w/v) KCl were prepared. The homogenates were centrifuged at 7000 ×g for 10 min at 4 °C and the supernatants were used for the assays of LPO, GSH, SOD, CAT and MDA.

Statistical analysis

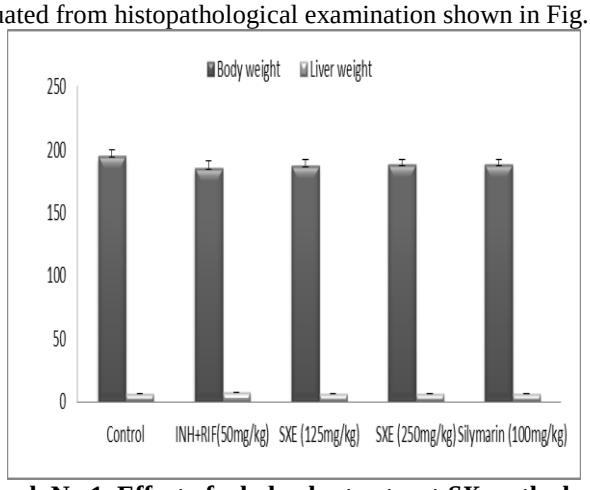
Data were analyzed by analysis of variance (ANOVA) followed by multiple Comparisons using Dunnett's procedure, to compare all groups against control and Student–Newman–Keul's procedure to compare all the groups pair wise.

Result

Exploratory phytochemical analysis

The 50% ethonolic whole plant extract *SX* was screened for the existence of various phytochemical constituents such as of flavanoids, glycoside, proteins and amino acids, alkaloids, tannins and phenol.

Oral administration of RIF+INH at a dose of 50mg/kg caused a significant increase different biochemical parameters like SGOT, SGPT, ALP and total billirubin were found to be increased above normal levels. Two different doses of whole plant extract *SX* are administered and compare with the standard drug silymarin shows a dose dependent activity which is further evaluated from histopathological examination shown in Fig.1.



Graph No 1. Effect of whole plant extract *SX* on the body and liver weight of RIF+ INH induced hepatotoxicity in rats

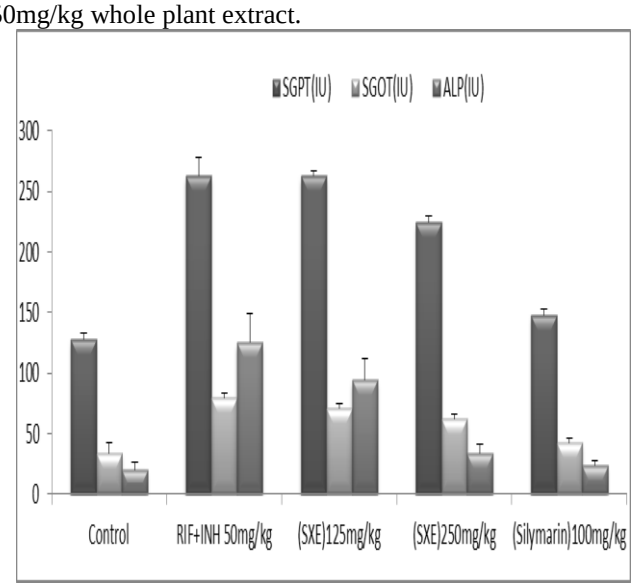
Values are expressed as Mean ± SEM of 6 rats in each group.

Table 1. The phytochemical results were presented as below

S.No.	Inference	Test	Observation	Result
1.	Tannins & phenol	Ferric Chloride Test	green or blue colour	+ve
2.	Saponins	Froth Formation Test	No froth (foam)	-ve
3.	Flavanoids	Ferric Chloride Test	blackish red colour	+ve
4.	Terpenoids	Libermann-Burchard Test	deep red colour	+ve
5.	Cardiac glycosides	Baljet's Test	Orange colour	+ve
6.	Carbohydrates	Molisch Test	No colour	–ve
7.	Triterpenoids & steroid	Salkowski's Test	No colour	–ve
8.	Protein + Amino acid	Million's Test	brick red colour	+ve
9.	Alkaloid	Hager's Reagent	yellow precipitates	+ ve

Values are expressed as Mean ± SEM of 6 rats in each group. *p<0.01, **p<0.001, when compared with respective RIF+INH treated group.

50% ethonolic whole plant extract of *SX* at a dose of 125 & 250 mg/kg and standard drug Silymarin at a dose of 100mg/kg once daily for twenty eight days was subjected to perceptive body and liver weight in toxic rats. The study showed that the body weights were considerably belittled from in RIF+INH teams. However, 50% ethonolic whole plant extracts showed normalized the weight in an exceedingly dose dependent manner. In a correlate plant extract with Silymarin (100mg/kg). it shows that *SX* at 125mg/kg is a smaller amount effective than 250mg/kg whole plant extract.

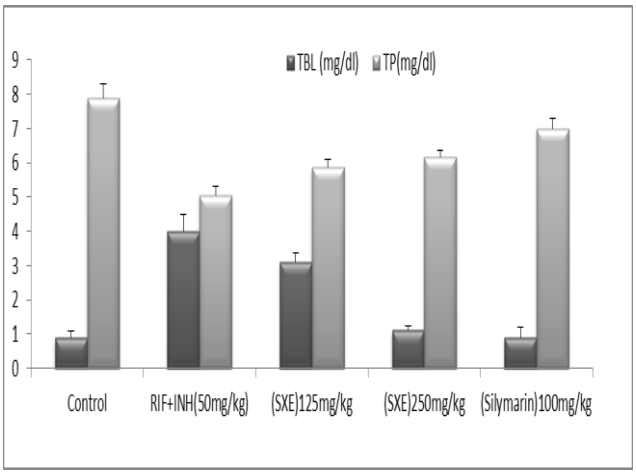


Graph No 2. Effect of whole plant extract *SX* on biochemical parameter of RIF+INH induced hepatotoxicity in rats

Values are mean ± SEM of 6 animals in each group.

Values are expressed as Mean ± SEM of 6 rats in each group. *p<0.01, **p<0.001, when compared with respective RIF+INH treated group.

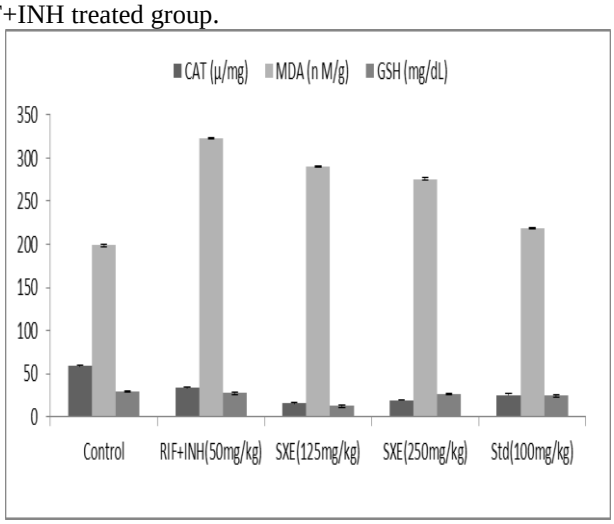
Administration of RIF+INH 50mg/kg for the period of 28 days caused considerably (p<0.001) raise the amount of SGOT, SGPT, ALP in serum once compare with normal control. The result of the *SX* whole plant extract on serum SGOT, SGPT, ALP in RIF+1NH 50mg/kg treated rats showed vital dose dependent (p<0.001, p<0.01, p<0.05 respectively). Decline as compare to 50mg/kg RIF+1NH treated cluster. The degree of protection by *SX* whole plant extract (125,250 mg/kg) was ascertained statically similar to the quality drug.



Graph No 3. Effect of whole plant extract *SX* on biochemical parameter of RIF+ INH induced hepatotoxicity in rats

Values are expressed as Mean ± SEM of 6 rats in each group.

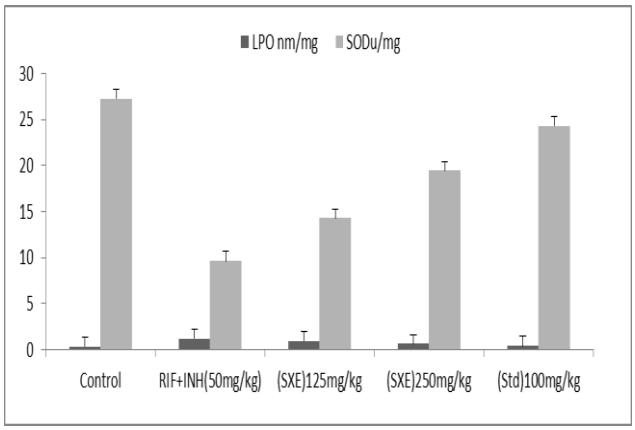
Values are expressed as Mean ± SEM of 6 rats in each group. *p<0.01, **p<0.001, when compared with respective RIF+INH treated group.



Graph No 4. Effect of whole plant extract *SX* on antioxidant and lipid peroxidation in liver homogenate of RIF+INH induced Hepatotoxicity in rats

Values are expressed as Mean ± SEM of 6 rats in each group.

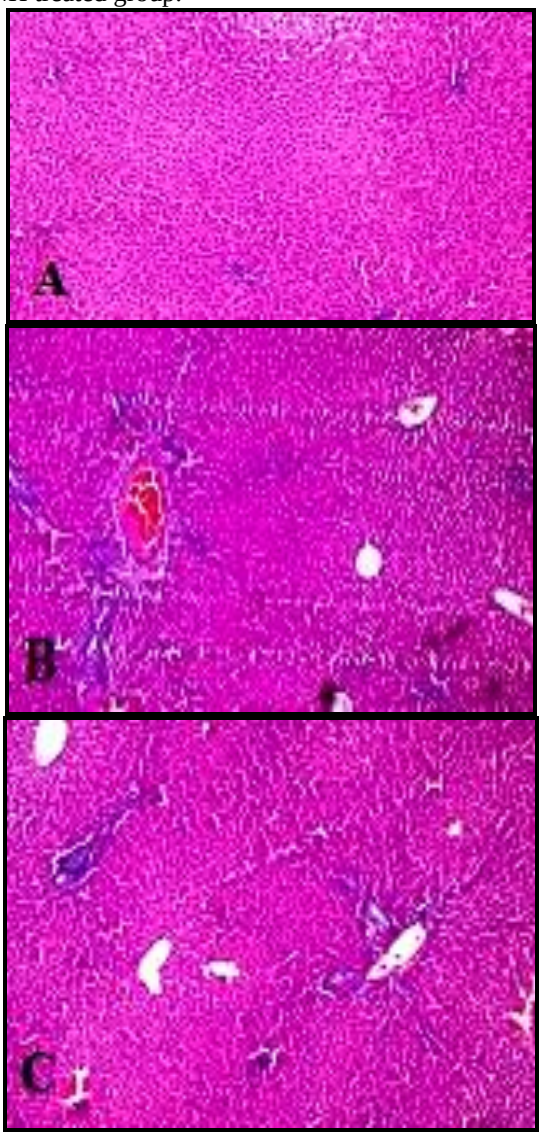
Values are expressed as Mean ± SEM of 6 rats in each group. *p<0.01, **p<0.001, when compared with respective RIF+INH treated group.



Graph No 5. Effect of whole plant extract *SX* on antioxidant and lipid peroxidation in liver homogenate of RIF+INH induced Hepatotoxicity in rats

Values are expressed as Mean ± SEM of 6 rats in each group.

Values are expressed as Mean ± SEM of 6 rats in each group. *p<0.01, **p<0.001, when compared with respective RIF+INH treated group.



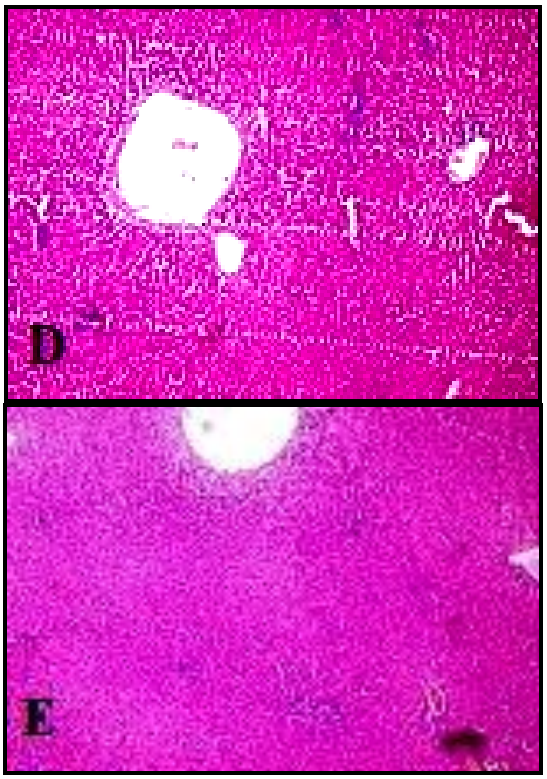


Figure 1. Liver Histopathological effect of whole plant (*SXE*)

(Fig.1) Control group normal liver tissue of rats showing normal internal organ cells with central vein and curved dilation. Liver section from RIF+INH treated rat showing intense centrilobular mortification, cloudy Swelling, congestion of sinusoids with tiny lipid globules and gross hydropic vocalization, treatment as a RIF+INH + whole plant (SXE) 125mg/kg for 28 days, showing internal organ cells with well preserved living substance distinguished nucleus, a number of central vein and sinusoids exhibited congestion. Rats treated with RIF+INH + whole plant extract *SX* 250mg/kg for 28 days showing well brought out central vein, hepatic cell with well secure living substance simply seen nucleus, rats treated with RIF+INH + Silymarin (100mg/kg) for 28 days showing traditional hepatocytes, hepatic portal vein (V) and portal artery.

Effect of *SX* (whole plant) Extract on Histopathology

After assessing the liver histology, the control group showed normal hepatic cells with the well preserved cytoplasm; well brought out Central veins; prominent nucleus in all animals. In RIF+ INH treated group, Section shows macro vesicular fatty change around central vein and large areas of necrosis with inflammation. Animals treated with RIF+INH (50 mg/ kg) + *SX* (whole plant) (125mg/kg & 250mg/kg) x 28 days, showing hepatic cells with well conserve cytoplasm, prominent nucleus, some of central veins and sinusoids exhibited congestion, hepatic cells with well preserved cytoplasm & prominent nucleus. Treatment with Silymarin showed improvement from toxicity.

Discussion

Drug-induced liver injury is a major health problem that challenges not only health care professionals, but also the pharmaceutical industry and drug regulatory agencies (Michael et.al., 2006). Isoniazid (INH) and rifampicin (RIF) are the most important first line drugs, used for the treatment of tuberculosis. Isoniazid (INH) can cause hepatotoxicity in 20% of patients and is usually associated with an inflammatory response (Tafazoli., 2008). These anti-tubular drugs are reported to induce hepatotoxicity judged by elevated serum ALT, AST, ALP and total bilirubin levels, presence of focal hepatocytic necrosis and

portal triaditis (Pal et.al.,2006), it convinced hepatitis is expected to their biotransformation to reactive metabolites that are capable of binding to cellular macromolecules (Georgieva et.al., 2004).The administration of INH and RIF, the most common medication arbitrary across tuberculosis, produces many metabolic and morphological aberrations in liver due to the fact that liver is the main detoxifying location for these antitubercular drugs. These antitubercular drugs activated hepatotoxicity by a multiple step tool, but the exact mechanism answer for liver injury lead by these drugs is not clear. Isoniazid is acetylated and then hydrolyzed, resulting in isonicotinic acid and monoacetylhydrazine; the later compound can be activated to a toxic species by *cytochrome* P-450 (Thomas et.al., 1981). Rifampicin also increases the metabolism of INH to isonicotinic acid and hydrazine, both of which are hepatotoxic (Padma et.al.,1998).

In the gift study, the hepatotoxicity model in Wistar rats was with success made by administering bactericide and RIF (50 mg/kg per day each). All humor markers were markedly will increase from higher than the conventional limits of twenty eight days of the experiment that indicate liver injury. At the premiere screening of chemical science qualitative analysis of the whole plant (*SX*) discovered the presence of alkaloids, flavonoids, Glycoside, saponins, tannins and steroids are the most important chemical constituents. The Phytochemical screening of whole plant extract *SX* shows the presence of anti aerophilic elements. These are useful within the hepatoprotection against RIF+INH induced liver injury in rats.

Conclusion

In this study the results suggest that the statistically significant differences in biochemical parameters in toxic group indicate that hepatic damage has been induced by INH+RIF. Following treatment with whole plant *(SXE)* (125 & 250 mg/kg b.w.) and Silymarin (100 mg/kg), all the parameters were reduced and total bilirubin and ALP restored to the normal values. However, further investigations suggest that 50% ethonolic whole plant extract *SX* constituents responsible for hepatoprotection.

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