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HEPATIC PROTECTIVE ACTIVITY OSBECKIA CHINENSIS

Md. Khaja Moinuddin[1] , Musarrath Mubeen*, Koteswari Poluri

[1]Department of Pharmacology, Smt. Sarojini Ramulamma College Of Pharmacy, Palamuru University, Seshadrinagar, Mahabubnagar, Telangana-509001

Abstract:

Osbeckia chinensis leaves (Family Melastomataceae) commonly known as Melastoma a vigorously growing in India. In the present study a pharmacognostic evaluation of the leaves was undertaken. In addition to the evaluation of physicochemical characteristics; preliminary phytochemical parameters and pharmacological activities of Ethanolic extracts has been carried out. The aim of the present study was carried out with the objective of phytochemical screening and to evaluate the hepatoprotective activity of Ethanolic extract of Osbeckia chinensis.

Liver is the largest organ in the body which serves as a gland also. It plays an important role in the maintenance of internal environment through its multiple and diverse functions. Any damage to the liver or impairment of its functions leads to injurious effects. Liver diseases (like jaundice) are the common ailments affecting mankind, though no remedy is available in allopathic at present. In the recent past years many medicinal plants are screened for their hepatoprotective activity and quite a few of they are already successful in entering the market, Hence the present study is planned to find out the hepatoprotective activity of Osbeckia chinensis drug induced hepatotoxicity methods. The rats were divided into five groups with three rats in each for three models. Group I (Control) served as normal and received the vehicle alone (Sterile distilled water, 10 ml/kg, p.o.) for 21 days. Group II (control and 40% ethanol) animals on the 21 day. Group III Received 40% ethanol v/v (2.0ml/l00g body wt, p.o.) for 21 days and standard drug silymarin (25 mg/kg. p.o.) for 21 days once daily and IV were treated with 40% ethanol and Ethanolic extract of Osbeckia chinensis (400 mg/kg) 21 days once daily. Group V was treated with Received 40% ethanol and Ethanolic extract of Osbeckia chinensis (200 mg/kg) 21 days once daily the animals were sacrificed 48 h after the last injection of hepatotoxic drugs under mild ether anesthesia. The blood was collected and allowed to stand for 30 min at 37°C and then centrifuged to separate the serum to estimate various biochemical parameters.

In hepatoprotective studies, the toxicity elevated levels of serum marker enzymes Total Bilirubin ALT, AST, ALP, SGOP and SGPT levels. Ethanol induced hepatotoxicity was significantly prevented by pretreatment ethanolic extract of leaves. Decrease in wet liver weight, reduction in elevated biochemical parameter levels like serum SGPT, SGOT, and total bilirubin, after treatment with Ethanolic extract of Osbeckia chinensis leaves confirmed the hepatoprotective effect of extract under study. In liver injury models in rats restoration of hepatic cells with minor fatty changes and absence of necrosis after treatment with extract was observed, indicating satisfactory hepatoprotection.

The data obtained from animal experiments are expressed as mean ± SEM (standard error of mean). For statistical analysis data were subjected to analysis of variance (ANOVA) followed by Student's t-test. Values are considered statistically significant at $p < 0.01$ for ANOVA and $P < 0.05$ for t-test.

Keywords: *Osbeckia chinensis, Hepatoprotective activity, Alkaline Phosphate, Aspartate amino trasferase, Alanine amino transferase.*

Corresponding author:

Mrs. Musarrath Mubeen *

Department of Pharmacology,
Smt. Sarojini Ramulamma College Of Pharmacy ,
Seshadrinagar, Mahabubnagar, Telangana 509001.
Email Id- musarrath.mubeen@gmail.com,Ph: +91-9494466340

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INTRODUCTION:

LIVER

Liver is the most important organ, which plays a pivotal role in regulating various physiological processes in the body. It is involved in several vital functions, such as metabolism, secretion and storage. It has great capacity to detoxicate toxic substances and synthesize useful principles [1].

Anatomical Position

The liver is predominantly located in the **right hypochondrium** and epigastric areas, and extends into the left hypochondrium.

When discussing the anatomical position of the liver, it is useful to consider its external surfaces, associated ligaments, and the anatomical spaces (recesses) that surround it.

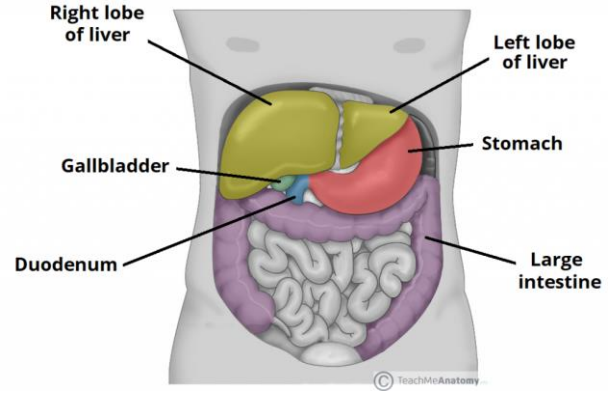


Figure : 1: Anatomical position of liver

Liver Surfaces

The **external surfaces** of the liver are described by their location and adjacent structures. There are two liver surfaces – the diaphragmatic and visceral:

- **Diaphragmatic surface** – the anterosuperior surface of the liver.
  - It is smooth and convex, fitting snugly beneath the curvature of the diaphragm.
  - The posterior aspect of the diaphragmatic surface is not covered by visceral peritoneum, and is in direct contact with the diaphragm itself (known as the 'bare area' of the liver).
- **Visceral surface** – the posteroinferior surface of the liver.
  - With the exception of the fossa of the gallbladder and porta hepatis, it is covered with peritoneum.
  - It is moulded by the shape of the surrounding organs, making it irregular and flat.
  - It lies in contact with the right kidney, right adrenal gland, right colic flexure, transverse colon, first part of the duodenum, gallbladder, oesophagus and the stomach.

Ligaments of the Liver

There are various ligaments that attach the liver to the surrounding structures. These are formed by a double layer of peritoneum.

- **Falciform ligament** – this sickle-shaped ligament attaches the anterior surface of the liver to the anterior abdominal wall and forms a natural anatomical division between the left and right lobes of the liver. The free edge of this ligament contains the ligamentum teres, a remnant of the umbilical vein.
- **Coronary ligament (anterior and posterior folds)** – attaches the superior surface of the liver to the inferior surface of the diaphragm and demarcates the bare area of the liver The anterior and posterior folds unite to form the triangular ligaments on the right and left lobes of the liver.

- **Triangular ligaments (left and right):**
  - The left triangular ligament is formed by the union of the anterior and posterior layers of the coronary ligament at the apex of the liver and attaches the left lobe of the liver to the diaphragm.
  - The right triangular ligament is formed in a similar fashion adjacent to the bare area and attaches the right lobe of the liver to the diaphragm.

- **Lesser omentum** – Attaches the liver to the lesser curvature of the stomach and first part of the duodenum. It consists of the hepatoduodenal ligament (extends from the duodenum to the liver) and the hepatogastric ligament (extends from the stomach to the liver). The hepatoduodenal ligament surrounds the portal triad.

In addition to these supporting ligaments, the posterior surface of the liver is secured to the **inferior vena cava** by hepatic veins and fibrous tissue.

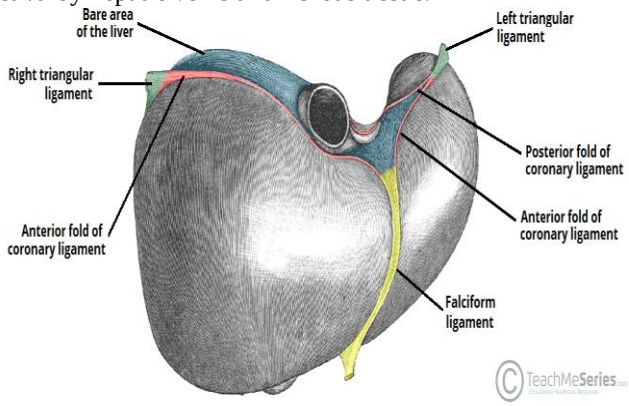


Fig 2 – Diaphragmatic surface of the liver, demonstrating the three main ligaments. The bare area

of the liver lies between the anterior and posterior folds of the coronary ligament.

Hepatic Recesses

The **hepatic recesses** are anatomical spaces between the liver and surrounding structures. They are of clinical importance as infection may collect in these areas, forming an abscess.

- **Subphrenic spaces** – located between the diaphragm and the anterior and superior aspects of the liver. They are divided into a right and left by the falciform ligament.
- **Subhepatic space** – a subdivision of the supracolic compartment (above the transverse mesocolon), this peritoneal space is located between the inferior surface of the liver and the transverse colon.
- **Morison's pouch** – a potential space between the visceral surface of the liver and the right kidney. This is the deepest part of the peritoneal cavity when supine (lying flat), therefore pathological abdominal fluid such as blood or ascites is most likely to collect in this region in a bedridden patient.

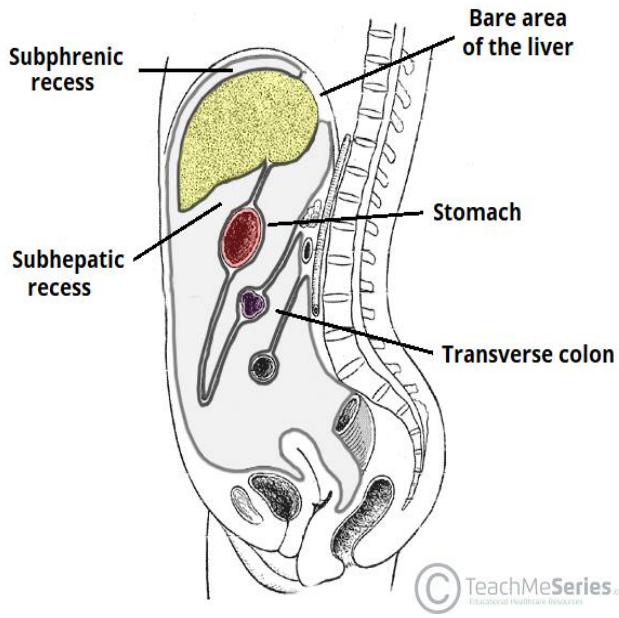


Fig 3 – The subphrenic and subhepatic recesses.

Anatomical Structure

The structure of the liver can be considered both macroscopically and microscopically.

Macroscopic

The liver is covered by a fibrous layer, known as **Glisson's capsule**.

It is divided into a right lobe and left lobe by the attachment of the **falciform ligament.** There are two further 'accessory' lobes that arise from the right lobe, and are located on the visceral surface of liver:

- **Caudate lobe** – located on the upper aspect of the visceral surface. It lies between the inferior vena cava and a fossa produced by the ligamentum venosum (a remnant of the fetal ductus venosus).
- **Quadrate lobe** – located on the lower aspect of the visceral surface. It lies between the gallbladder and a fossa produced by the ligamentum teres (a remnant of the fetal umbilical vein).

Separating the caudate and quadrate lobes is a deep, transverse fissure – known as the **porta hepatis**. It transmits all the vessels, nerves and ducts entering or leaving the liver with the exception of the hepatic veins.

Microscopically, the cells of the liver (known as hepatocytes) are arranged into **lobules**. These are the structural units of the liver.

Each anatomical lobule is hexagonal-shaped and is drained by a **central vein**. At the periphery of the hexagon are three structures collectively known as the portal triad:

- **Arteriole** – a branch of the hepatic artery entering the liver.
- **Venule** – a branch of the hepatic portal vein entering the liver.
- **Bile duct** – branch of the bile duct leaving the liver.

The portal triad also contains **lymphatic vessels** and **vagus nerve** (parasympathetic) fibres.

Arterial Supply and Venous Drainage

The liver has a unique dual blood supply:

- **Hepatic artery proper (25%)** – supplies the non-parenchymal structures of the liver with arterial blood. It is derived from the coeliac trunk.
- **Hepatic portal vein (75%)** – supplies the liver with partially deoxygenated blood, carrying nutrients absorbed from the small intestine. This is the dominant blood supply to the liver parenchyma, and allows the liver to perform its gut-related functions, such as detoxification.

Venous drainage of the liver is achieved through hepatic veins. The central veins of the hepatic lobule form collecting veins which then combine to form

multiple hepatic veins. These hepatic veins then open into the **inferior vena cava**.

MATERIALS AND METHODS:

Chemicals

Ethanol Absolute
Petroleum ether
Silymarin
SGOT enzyme Kit (Giri diagnostic kit pvt ltd)
SGPT enzyme kit (Giri diagnostic kit pvt ltd)
Chloroform (Central drug house pvt ltd) New Delhi

Animals

Wistar albino rats of both sexes (180-220 g) were used for the study. All the rats were kept in standard plastic rat cages with stainless steel coverlids and wheat straw was used as bedding material. The animals were kept at the animal house of Department of Pharmacology. The animals were facilitated with standard environmental condition of photoperiod (12:12 h dark: light cycle) and temperature (25 ± 2°C). They were provided with commercial rat and mice feed (Pranav Agro Industries Ltd., Baroda. Amruth Brand rat & mice pellet feed) and water given ad libitum. The use of these animals and the study protocols were approved by CPCSEA recognized local ethical committee.

Acute toxicity studies:

Healthy Wistar albino female rats of sex weighing 100-170 g maintained under standard laboratory conditions were used for acute oral toxicity test according to Organization for Economic Co-operation and Development guidelines 423. Animals were observed individually at least once during first 30 min after dosing, periodically during first 24 h. Observations were done daily for changes in skin and fur, eyes, mucus membrane (nasal), respiratory rate, circulatory signs (heart rate), autonomic effect (salivation, lacrimation, perspiration, urinary incontinence and defecation) and central nervous system (drowsiness, gait, tremors and convulsion) changes (Sharma A et al; 2012)

Determination of acute toxicity (LD50):

14 days single dose oral acute toxicity and gross behavioral study Number of animals required: 6 rats (male) Number of groups: 2 groups (3 animals each group)
Dose levels: 4000 mg/kg body weight of the animals.
Study duration: 14 days

Preparation of dose:

Ethanolic extract of *Osbeckia Chinensis* leaves was suspended in 3% CMC, to prepare a dose of 4000 mg/kg body weight of animal, and administered 1ml/100gm body weight of the animal.

Procedure:

The procedure was divided into two phases, Phase I (observation made on day one), and Phase II (observed the animals since next 14 days). Two set of healthy female animal (each set of 3 rats) were used for the experiment. First set animals were divided and fasted for 18 hours deprived from food, water withdrawn before 4 hours of the dosing, body weights were noted before and after dosing with Ethanolic extract of *Osbeckia chinensis* (4000 mg/kg) orally. Individually animals were observed for 4 hours to see any clinical symptoms, any change in behaviour or mortality. 6 hours post dosing again body weights recorded. Form the next day onwards, each day for 1 hour the behavioral change, clinical symptoms or mortality was observed in the same animals for next 14 days and animal body weights were recorded on 8th and 14th day. The same procedure was repeated with another set of animals to nullify the errors.

Experimental procedure:

The rats were weighed after the adaptation period and marked with serial numbers and divided randomly into 5 groups, 5 rats each, and then the doses were calculated according to individual body weights.

Blood samples:

Blood was obtained by puncturing retro orbital plexus (Poole, 1989), under anesthesia using Halothane and heparinized capillary tubes. Blood drops were collected, gently, serum was separated by centrifugation (2500 rpm for 15 min), and EDTA was used as an anticoagulant for hematological parameters. Samples were collected before and after dosing with the tested plants extracts at day 0, 5 and at day 10.

Assessment of liver function:

Blood sample were collected into dry clean bottles and allowed to clot for 30 min at room temperature. Serum separated by centrifugation at 2500 rpm for 15 min and stored at -20c° until analyzed. Biochemical parameters, i.e. alanine amino transeferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALP), total bilirubin (TBIL) were analyzed according to the reported methods.

Total Bilirubin:

Total Bilirubin in serum is determined using the method of Jendrassik and Grof, (1938).

Calculation:

Total Bilirubin is calculated as follow:
Absorbance tube Total × 17.5 = Total Bilirubin (mg/dl).

Alkaline phosphatese:
It is an optimized method according to recommendation of Chemie (1972).

Reaction:
P-nitrophenylphosphate + H2o ALP phosphate + p-nitro phenol

Calculation:
ALP is calculated as follows:
U/1 = 2760 × A 405nm/min
(A = the mean of sample absorbance reading)

Alanine amino transeferase (ALT):
It is an enzymatic method, which measure gultamic pyruive transamine in serum according to Reitman and Frankel (1957), and Schmidt and Schmidt, (1963).

Reaction:
α - oxoglutarate + L-alanine ALT L-glutrate + pyruivate
The absorbance of samples was read against the reagent blank after 5min at wavelength 546 nm in spectrophotometer.

Aspartate amino transferase (AST):
It is an enzymatic method that measure gultamic oxaloacetic transaminase in serum according to Reitman and Frankel (1957), and Schmidt and Schmidt,(1963).

Reaction:
α- oxoglutarate +L-aspartate AST L-glutarate + oxaloacetate The absorbance of samples was read against the reagent blank after 5min at wavelength 546 nm in spectrophotometer and cuvette of 1cm light path.

Haematological studies:
Haemoglobin concentration (Hb), packed cell volume (PCV), red blood cells count (RBC), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC), were measured. Blood samples were collected into dry clean bottles; the anticoagulant was ethylene diamine tetra acetic acid (EDTA).

Red blood cell count (RBCs):
Total erthrocytes were counted by using Neubauer haemocytometer and Hayem's solution. (Kelly, 1984).

Calculation:
200 × 50 × R cells = 10.000 × R µl.

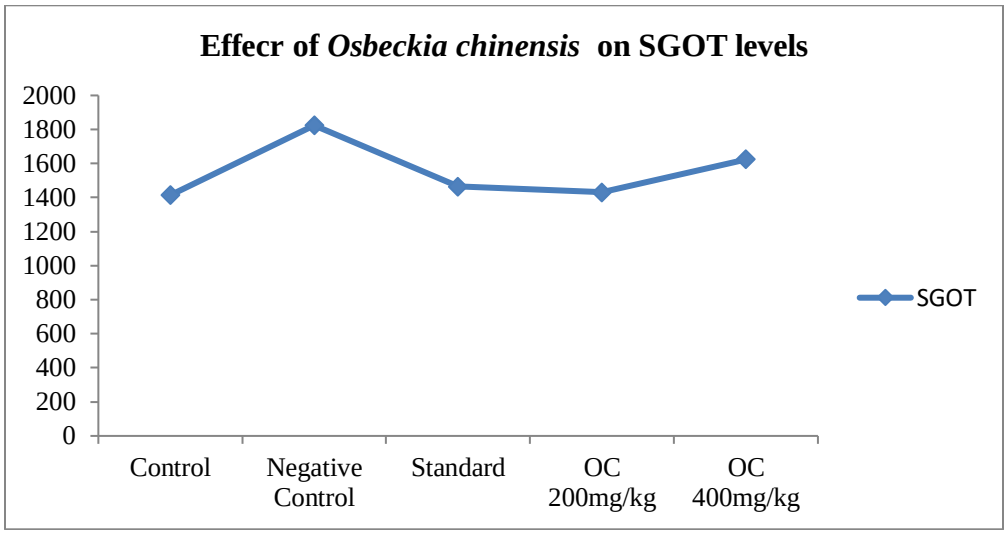
Haemoglobin concentration (Hb):
The concentration of Hb was measured by the cyanmethaemoglobin method (Kelly, 1984). The procedure consists of adding 20 µl of blood to 5 ml of a modified Drabkin's solution. After 10 min the solution of cyanmethaemoglobin is compared against a standard in either spectrophotometer (wavelength 540 nm).

Assessment of hepatoprotective activity
After 24 h of ethanol administration, on 22nd day, blood was obtained from animals by puncturing retro orbital plexus. Blood samples were allowed to clot for 45 min at room temperature. Serum was separated by centrifugation at 2500 rpm at 30°C for 15 min and utilized for the estimation of various biochemical parameters including SGOT & SGPT (Reitman et al., 1957), ALP (Kind et al., 1954), serum bilirubin (Amour et al., 1965) and serum protein (Lowry et al., 1951) After collection of blood samples, the animals were sacri-ficed under deep ether anesthesia. Morphological parameters like weight of animals, weight of liver have also been used to evaluate the protective effect of the drug. Hepatoprotective chemical causes loss in liver weight/100 gm body weight of rats (Avadhoot et al., 1991; Bhanwra et al., 200

RESULTS:

Effect of extracts of Ethanolic extracts *Osbeckia chinensis* leaves on SGOT

GROUP	SGOT level mean ± SEM
Control	1414±1.06
Negative Control	1824.01± 2.241**a
Standard	1464.24±1.10**b
CSV 200mg/kg	1431.61±1.25 *b
CSV 400mg/kg	1624.14±2.05 ***b



Graphical representation of Effect of *Osbeckia chinensis* on SGOT

EFFECT OF OSBECKIA CHINENSIS ON SGOT

There was significant (p<0.001) increase in serum SGOT in Ethanol induced group when compared to control group. There was significant (p<0.001) decrease in serum SGOT in Silymarin treated group when compared to control group. There was significant (p<0.001) decrease in serum SGOT in *Osbeckia chinensis* treated group at a dose of 200mg/kg/p.0 when compared to control group. There was significant (p<0.001) decrease in serum SGOT in *Osbeckia chinensis* treated group at a dose of 400mg/kg/p.o when compared to control group.

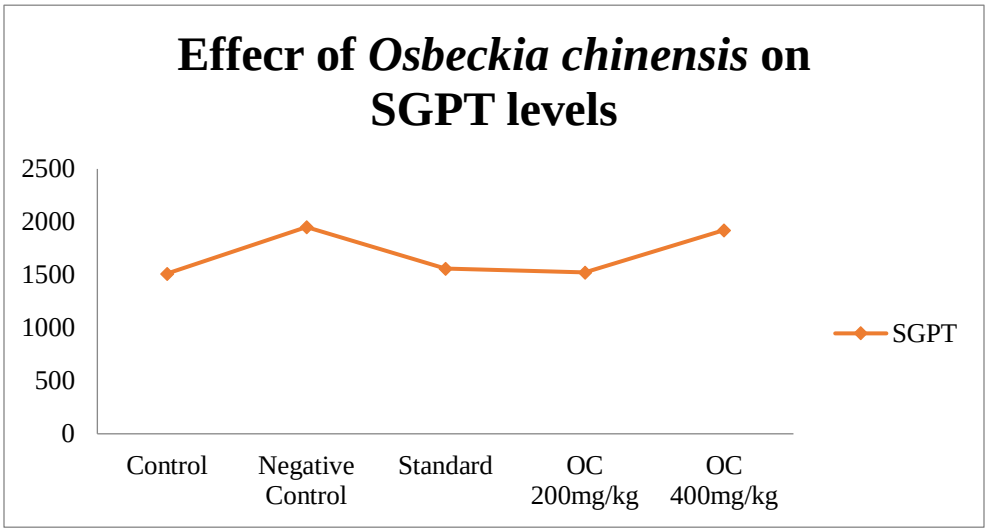
There was a significant (p<0.01) decrease in serum SGOT level in Silymarin treated rats when compared to ethanol induced. The *Osbeckia chinensis* at a dose of 200mg/kg/p.o showed a significant (p<0.010) decrease in serum SGOT level when compared to ethanol induced group. The *Osbeckia chinensis* at a dose of 400 mg/kg/p.o showed a significant (p<0.001) decrease in serum SGOT level when compared to Ethanol induced group.

The results were shown in the Table no.1 and Graph no.2.

Table 2: Effect of extracts of Ethanolic extracts *Osbeckia chinensis* leaves on SGPT

GROUP	SGOT level mean ± SEM
Control	1512±1.14
Negative Control	1951.36± 2.204**a
Standard	1559.42±2.60**b
Osbeckia chinensis 200mg/kg	1524.21±1.60 *b

Osbeckia chinensis 400mg/kg	1924.56±2.45 ***b



Graphical representation of Effect of *Osbeckia chinensis* on SGPT

EFFECT OF *OSBECKIA CHINENSIS* ON ALP

There was significant ($p<0.01$) increase in ALP in ethanol induced group when compared to control group. There was significant ($p<0.01$) decrease in ALP in Silymarin treated group when compared to control group. There was significant ($p<0.05$) decrease in ALP in *Osbeckia chinensis* treated group at a dose of 200mg/kg/p.0 when compared to control group. There was significant ($p<0.001$) decrease in Alp in *Osbeckia chinensis* treated group at a dose of 400mg/kg/p.o when compared to control group.

There was a significant ($p<0.05$) decrease in ALP in Silymarin treated rats when compared ethanol treated. The *Osbeckia chinensis* at a dose of 200mg/kg/p.o showed a significant ($p<0.001$)
decrease in ALP when compared to Ethanol induced group. The *Osbeckia chinensis* at a dose of 400 mg/kg/p.o showed a significant ($p<0.05$) decrease in ALP when compared to Ethanol induced group.

Histopathological studies of the liver in paracetamol induced hepatotoxicity

The histopathological evaluation of paracetamol toxicity in all the groups was examined and shown in figure. The description is as follows, Section of rat liver treated with vehicle control group shows liver parenchyma with intact architecture which is the normal appearance. Section of liver in toxicant control group shows partially effaced architecture. Some of the hepatocytes show apoptotic changes, perivenular mononuclear inflammatory infiltration, scattered inflammatory infiltration within the parenchyma which is due to toxicity. Section of liver in silymarin treated group shows liver parenchyma with intact architecture. Some of the central veins show congestion with diffuse congestion of sinusoids.

Section of liver in test drug ethanolqueous treated groups shows intact architecture, few regenerative hepatocytes, sinusoidal congestion and scattered mononuclear inflammatory cells which is similar to silymarin treated group.

DISCUSSION:

There are many factors which are responsible for the liver damage or injuries such as chemicals and drugs. In the present study ethanol was used to induce Hepatotoxicity, since it is clinically relevant. Ethanol produces a constellation of dose related deleterious effects in the liver (Leo et al., 1982). The majority of ethanol is metabolized in the liver and individuals who abuse alcohol by routinely drinking 50-60 g (about 4 to 5 drinks) of ethanol per day are at risk for developing alcoholic liver disease (Zakhari et al., 2007). In addition, both acute and `chronic ethanol administration cause enhanced formation of cytokines, especially TNF-alpha by hepatic Kupffer cells, which have a significant role in liver injury (Zhou et al., 2003; Thurman et al., 1998; Tsukamoto et al., 2001). Besides the development of fatty liver (steatosis), another early sign of excessive ethanol consumption is liver enlargement and protein accumulation, both of which are common findings in alcoholics and heavy drinkers (Baraona et al., 1975; Baraona et al., 1977).

Osbeckia chinensis are commonly used in the native system of medicine. Various parts of the plant like leaves and roots are medicinally important.

In order to investigate the medicinal use of *Osbeckia chinensis* in hepatoprotective, we evaluated crude extract for its Hepatoprotective activity using different *in vitro* assays and *in vivo* rat model of Hepatoprotective activity.

Elevated levels of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) are indications of hepatocellular injury (Yue et al., 2006). In the present study AEOC and AQEOC at a dose of 500 mg/kg, p.o caused a significant inhibition in the levels of SGOT and SGPT towards the respective normal range and this is an indication of stabilization of plasma membrane as well as repair of hepatic tissue damage caused by ethanol.

On the other hand suppression of elevated ALP activities with concur-rent depletion of raised bilirubin level and an increase in the total plasma protein content suggests the stability of biliary dysfunction in rat liver during hepatic injuries with toxicants (Mukherjee et al., 2002). These results indicate that AEOC and AQEOC preserved the structural integrity of the hepatocelluar membrane and liver cell architecture damaged by ethanol which was confirmed by histopathological examination.

On examining the liver function tests of ethanol induced animals, the SGOT, SGPT, ALP, Total bilirubin has significantly increased After treatment with the ethanolic extract of *Osbeckia chinensis* (200 mg/kg and 400 mg/kg) the excretion of has SGOT, SGPT, ALP, Total bilirubin significantly decreased Although the low dose was more potent than the high dose when compared with silymarin treated group, which is a standard.
Ethanolic extract *Osbeckia chinensis* of has shown promising *invitro* efficacy on Hepatoprotective activity, we have observed increase in the absorbance indicating the inhibition of Nucleation and Aggregation of calcium oxalate in *invitro* studies.

For the in vivo Hepatoprotective activity, of *Osbeckia chinensis*, Ethanol-induced hepatotoxicity rat model of was used. Since the liver damage inducing treatment, Ethanol, was given orally, therefore, the extract was given p.o. in order to prevent any potential interaction of Ethanol with plant constituents inside gut, interfering with absorption of either of the two. Administration of Ethanol resulted in the increased toxicity, which might be due to the Hepatotoxicity, as evident by increase in SGOT, SGPT, and ALP as compared to normal.

CONCLUSION:

The hepatoprotective effect of Ethanolic extract of *Osbeckia chinensis* leaves was confirmed by the following measures: The isolated livers from the toxicant (ethanol) treated animals exhibited increase in wet liver weight. Indeed, extract treated animals exhibited decrease in the values of above physical parameters as an indication of hepatoprotection. Serum marker enzymes such as SGPT, SGOT and total bilirubin, showed marked increase. The same is observed in liver diseases in clinical practice and hence are having diagnostic importance in the assessment of liver function. In the present study, the methanolic and aqueous extract of *Osbeckia chinensis* leaves significantly reduced the elevated levels of above mentioned serum marker enzymes. Hence, at this point it is concluded that the methanolic and aqueous extract of *Osbeckia chinensis* leaves possesss hepatoprotective activity.

Finally based on improvement in serum marker enzyme levels, physical parameters, functional parameters and histopathological studies, it is concluded that the Ethanolic extract of *Osbeckia chinensis* leaves possesses hepatoprotective activity and thus supports the traditional application of the same under the light of modern science.

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