HEPATOPROTECTIVE ACTIVITY OF BOSWELLIA SERRATA EXTRACTS: IN VITRO AND IN VIVO STUDIES.

Running Title: Hepatoprotective activity of Boswellia serrata extracts

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ABSTRACT

AIM: To study the hepatoprotective activity of extracts of Boswellia Serrata in paracetamol treated male rats.

METHODS: - The dried powder of Boswellia Serrata was extracted successively with different solvent systems and concentrated in vacuum. Primary rat hepatocyte monolayer cultures were used for in vitro studies. In vivo, the hepatoprotective capacity of the extracts of the Boswellia Serrata was analyzed in liver injured Paracetamol treated male rats.

RESULTS: In vitro: primary hepatocytes monolayer cultures were treated with paracetamol and extracts of Boswellia Serrata. A protective activity could be demonstrated in the paracetamol damaged primary monolayer culture. In vivo: extracts of Boswellia Serrata were found to have protective properties in rats with paracetamol induced liver damage as compared from serum marker enzyme activities.

CONCLUSION: The extracts of Boswellia Serrata do have a hepatoprotective activity both in vitro on primary hepatocytes cultures and in vivo in a rat model of paracetamol mediated liver injury.

KEY WORDS: - Boswellia Serrata, Hepatoprotective, LIV-52, Paracetamol.

Introduction

Liver is the heaviest gland of the body, weighing about 1.4 kg. In an average adult [1]. It is also one of the largest and most complex internal organs of the body [2]. It plays the vital role in the metabolic activities and important bio-chemical conversion, but at the same time, many factors have been reported which cause hepatitis, such as Prolonged drug therapy, alcoholism, and certain diseased state and toxic industrial chemicals [3]. A slight alteration in hepatic structure and function may result in portal hypertension, ascites, and jaundice and increased bleeding, and cause multiple metabolic changes affecting other organs as well.

Alcoholic liver disease (ALD) is one of the most serious consequences of chronic alcohol abuse. Liver cirrhosis, the culmination of the illness, is one of the leading causes of death in western countries [4,5]. According to Wang [6] chronic and excessive ethanol consumption is associated with cellular proliferation, fibrosis, cirrhosis, and cancer of the liver. An important characteristic
of alcohol–induced liver injury is an impaired vitamin A nutritional status. Studies in human Hep G2 cells have shown that ethanol is cytotoxic to Hep G2 cells, which are transduced to express P-450 2E1 (CYP 2E1) and this toxicity is apoptotic in nature \[^{[7]}\] predominantly in the liver. The main pathways for hepatic oxidation of ethanol to acetaldehyde involve alcohol dehydrogenase \[^{[8]}\] and are associated with the reduction of NAD\(^+\) to NADH\[^{[9]}\].

In view of multiplicity and complexity of the liver functions, it is obvious that no single test can establish the disturbances in liver function. Thus a battery of liver function tests are employed for accurate diagnosis, to assess the severity of damage, to judge prognosis and evaluate therapy \[^{[10, 11]}\]. The magnitude of derangement of liver by disease or hepatotoxin is generally measured by the level of glutamate pyruvate transaminase (ALT), glutamate oxaloacetate transaminase (AST), alkaline phosphatase (ALP), bilirubin, albumin, and whole liver homogenate.

Herbal drugs are playing an important role in health care programs worldwide, and there is a resurgence of interest in herbal medicines for treatment of various ailments including hepatopathy. India, the abode of Ayurvedic systems of medicine, assigns much importance to the pharmacological aspects of many plants. Hepatoprotective effect of some plants like *Spirulina maxima* \[^{[12]}\] , *Eclipta alba* \[^{[13]}\] , *Boehmeria nivea* \[^{[14]}\] , *Cichorium intybus* \[^{[15]}\] , and *Picrorhiza kurroa* \[^{[16]}\] has been well established. Nearly 150 phytoconstituents from 101 plants have been claimed to possess liver protecting activity \[^{[17]}\] . At same time, surprisingly, we do not have satisfactory plant drugs/formulations to treat severe liver diseases. Most of the studies on hepatoprotective plants are carried out using chemical induced liver damage in rodents as models. A few excellent reviews have appeared on this subject in the recent past \[^{[18]}\].

This study is based on the natural products responsible for repairing and healing of adversely affected liver cells. In the present study, we selected the plant *Boswellia serrata* and investigated the hepatoprotective effect of the plant extracts against paracetamol induced liver injury *in vivo*.

Liver being a vital organ, its protection occupies special status in pharmaco therapeutics. The plant *Boswellia serrata* (family Burseraceae) is commonly known as Indian Olibanum \[^{[19]}\] . It is traditionally used as hepatoprotective drug.

In the present study, an effort has been made to establish the scientific validity to the hepatoprotective activity of the leaf extract. For this purpose, male albino rats have been employed as experimental animals, Paracetamol was used as toxicant causing hepatitis \[^{[20]}\] . The Chloroform and aqueous extracts of Gum bark and leaves *Boswellia Serrata* was prepared. The effects of each of these extracts were studied on the experimental animals showing acute hepatitis due to Paracetamol. The hepatoprotective effects were studied by biochemical and histopathological parameters \[^{[21]}\].

**Materials And Methods**

**Plant Materials:** The leaves of *Boswellia serrata* were collected from Narsapur Forest of Medak District and authenticated by Unani Department, Hyderabad. The plant material was dried at room temperature and powdered. Liv-52 \[^{[22]}\] (100mg/kg) was used as standard drug.

**Animals:** Male albino rats weighing 130-160g were obtained from the animal house of Deccan college of medical sciences, Hyderabad and housed in Polycarbonate cages. The rats had free access to standard pellet chow and water and libitum throughout the experiment with the exception of some
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100 gm. of powdered bark, leaves and gum in each case were extracted with chloroform and water by using soxhlet extractor \[23\]. The extracts were concentrated with the help of vacuum evaporator and kept in dessicator. Percentage yield of chloroform and aqueous bark extract of *Boswellia serrata* plant is 29 gm. and 23 gm. respectively. Similarly the percentage yield of chloroform and aqueous leaves extract is 38 gm and 35 gm and percentage yield of chloroform and aqueous gum extract is 19 gm and 22 gm.

**Extraction, separation, and purification of the compounds**

Paracetamol is one of the most powerful hepatotoxin in terms of severity of injury. It causes hepatic injury leading to biochemical changes having clinical features similar to those of acute viral hepatitis \[24\]. Liver injury was produced by administration of paracetamol mixed with rice bran oil. Animals were given an acute dose of 3 gm/kg paracetamol p.o on 9th day of study. Control animals received an equal of rice bran oil.

**Methods for the hepatoprotective evaluation of extracts of Boswellia Serrata In Vitro:**

Fasting Wister male adult rats weighing 280-300 g were used. Liver cells were isolated by using a modified procedure of Kiso *et al*\[25\] & Ibrahim *et al*\[26\]. The animal was cleaned thoroughly using rectified alcohol and anaesthetized with ether. Dissection of the animal was carried out under aseptic conditions using sterilized instruments. A midline incision was made on the abdomen of the anaesthetized animal. The portal vein was canulated with needle no. 25 connected to an infusion set. The needle was tied in place and the inferior vena cava was cut below the renal vein. Perfusion of the liver was started immediately with Ca\(^{2+}\) - Mg\(^{2+}\) free Hanks buffer salt solution (pH 7.4 at 37°C) which was prepared according to the procedure of Ohno (1965). When the liver was thoroughly perfused (i.e has turned white), the flow of HBSS was stopped and the needle was removed. The liver was transferred to a sterile Petri dish containing Ca\(^{2+}\) - Mg\(^{2+}\) free HBSS and minced into small pieces, which were transferred to a conical flask containing 10 mL of 0.075% collagenase in HBSS. This was placed on a magnetic stirrer at 37°C for 10 min. The cell suspension thus obtained was centrifuged at 50 g for 10 min. The supernatant was aspirated and the cells Suspended in the Ca\(^{2+}\) - Mg\(^{2+}\) free HBSS. The cells were washed twice and counted in the presence of trypan blue dye. Viability of the
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Cells in each of the experiment performed was found to be 90%. The isolated hepatocytes were cultured in Eagles MEM, supplemented with 10% inactivated serum at density of 0.5 x 10⁹ cells / L in sterile disposable culture bottles and incubated in a humified incubator at 37°C under 5% CO₂. The viability of hepatocytes was studied after 6, 12, and 24 hrs. The hepatocytes which settled down were observed for their growth. Cytotoxicity of *Boswellia serrata* extracts was tested in primary hepatocytes monolayer cultures. Neither of the extracts caused significant enzymes release or was cytotoxic.

Hepatocytes were prepared from male Wister rats by the collagenase perfusion technique [27]. Cells were purified by several centrifugations and inoculated at density of 0.5 x 10⁸ cells / L on collagen coated plates. One day after the isolated rat hepatocytes were plated, cells were exposed to medium containing 7 mmol / L paracetamol with or without the sample to be tested for the hepatoprotective activity. After the exposure to paracetamol for 1 hr. the culture medium was collected and used for the determination of different parameters. Lipid peroxidation was assessed as TBA – reactive substances using malondialdehyde (MDA) as reference. Rat hepatocytes 1 x 10⁹ cells / L were incubated in a final volume of 1.0 mL HBSS buffer containing test materials in presence of 200 mL FeSo + 100 µmol / L H₂O₂.

The biochemical estimations were carried out by using the usual technique.

**In vivo:** Detailed evaluation of extracts of *Boswellia Serrata* for hepatoprotective activity was carried out against paracetamol. The animals were divided in to nine groups of five animals each. Group 1 rats served as vehicle control and were administered with rice bran oil. Group 2 rats were given paracetamol 3gm/kg, p.o. on 9th day of study checking the biochemical parameters periodically for hepato toxicity. Group 3 rats were given Liv-52 100gm/kg for a period of 9 days, and paracetamol on 9th day of study. Group 4 rats were given CHCl₃ bark extract of *Boswellia Serrata* 250mg/kg for a period of 9 days. Similarly Group 5 rats were given Aqueous bark extract of *Boswellia serrata* 250 mg/kg, p.o. Group 6 rats were given CHCl₃ leaf extract 500mg/kg p.o., Group 7 rats were given Aqueous leaf extract 100mg/kg and Group 9 rats were given Aqueous gum extract 750mg/kg for a period of 9 days. Paracetamol was given at a dose of 3gm/kg to the above groups on 9th day of study.

After 48 hours all the rats were scarified under light ether anesthesia and blood samples were collected by puncturing the retro-orbital plexus [28]. Serum was separated by centrifugation at 2500 rpm for 15 min. and used for investigation of various biochemical parameters. The liver tissue was examined histopathologically.

**STATISTICAL ANALYSIS:** The data obtained was subjected to statistical analysis. All the readings were tabulated and presented in Table 1 and 2 and Mean (±) standard error mean (SEM) of five animals, significant difference among the mean were calculated at the level of pa < 0.001 , b<0.01 , c< 0.05 when compared with those of standard. The statistical significance was calculated with students “t” test [29].

**RESULTS**

**In vitro study**

*Boswellia Serrata* extracts showed significant hepatoprotective activity against Paracetamol induced liver injury in primary hepatocytes cultures (Table 2). The hepatotoxic effects of Paracetamol are attributed to its metabolism by P450 to yield toxic trichloroethylene radicals that can act as free radical initiators. These radicals are believed to induce injury either by interacting with the unsaturated fatty
acids of cell membranes, thereby causing lipid peroxidation, or by binding covalently to important macromolecules such as proteins, lipids, or DNA.[26] The extracts of *Boswellia Serrata* reduced the levels of LDH and GPT released from Paracetamol injured rat hepatocytes into the medium in a concentration dependent manner, thus signifying their hepatoprotective activity.

**In vivo Study:**

In Paracetamol intoxicated rats, serum activities of ALT, AST, ALP and bilirubin were increased significantly when compared to control. (Table 1). The Paracetamol treated group showed a marked increase in serum bilirubin (mg %) (1.83 ± 0.79), ALT (IU/L) (144 ± 1.529), AST (IU/L) (145 ± 1.435), and ALP (IU/L) (1778.94 ± 6.0) activity indicating the injury caused by Paracetamol. It also significantly reduced the total protein level (3.73+0.304). Treatment with the extracts of *Boswellia Serrata* significantly decreased the above elevated parameters, and there was increase in the total protein level the normal architectural liver pattern was restored as given below.

Liver section of control rat showed normal physiological (fig 1). Liver sections from paracetamol treated rats demonstrated severe focal necrosis and intense inflammation (fig.2). Liver sections from LIV-52 treated rats showed minimum necrosis and swelling of hepatocytes (fig.3). Liver sections from aqueous leaf extract of *Boswellia Serrata* treated rats do not show any necrosis and inflammation (fig.4). Liver sections from Aqueous gum extract of *Boswellia Serrata* treated rats showed minimal necrosis and inflammation (fig.5). Liver sections from Aqueous bark extract of *Boswellia Serrata* treated rats showed mild swelling of liver cells with mild inflammation (fig.6). These histopathological findings demonstrate a hepatoprotective effect of the extracts against paracetamol mediated liver damage.

**Discussion:**

The purpose of this study was to explore the hepatoprotective effect of *Boswellia Serrata* extracts in the hepatic damage caused by paracetamol. Administration of paracetamol (in acute dose of 3gm/kg p.o.) as hepatotoxic can produce acute liver injury in rats. Paracetamol gets converted into N-acetyl-p-benzoquinoneimine (NAPQ1) in liver by action of cytochrome p-450 and alters the functional integrity of hepatic mitochondria leading to liver damage.[30] When hepatic cell membrane is damaged, the enzymes ALT, AST and ALP which are normally located in the cytosol, Leak into circulation from hepatocytes.[31] As a result serum levels of ALT, AST and ALP will increase. Similarly paracetamol decreases the membrane bound enzymes viz., Na/k ATPase, Ca ATPase and Mg ATPase. Hyperbilirubinemia, seen in liver injury, can result from impaired hepatic uptake of unconjugated bilirubin.[32,33] Paracetamol induced liver injury results in decreased serum total protein level and an elevated level of SGPT, ALT, AST, ALP and bilirubin and reduced level of membrane bound enzymes and total proteins.[34,35] Treatment with *Boswellia Serrata* Aqueous bark extract 250 mg/kg, Aqueous leaf extract 500mg/kg and Aqueous gum extract 250mg/kg showed reduction in the elevated levels of ALT, AST, ALP and bilirubin and increased membrane bound enzymes and total proteins. *Boswellia Serrata* extracts reduced the damaging effect of paracetamol on hepatocytes membrane. These biochemical restorations may be due to inhibitory effect of *Boswellia Serrata* extracts on the synthesis of 5 LOX (Lipo Oxygenase Enzyme) which is primarily responsible for injury and inflammation of hepatocytes. Histopathological examination of the liver.

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sections of rats treated with paracetamol showed severe focal necrosis, portal – portal bridging necrosis and intense inflammation (fig.2). The group of rats treated with aqueous leaf extract of *Boswellia Serrata* showed minimal injury (fig 4). The group of rats treated with aqueous gum extract of *Boswellia Serrata* showed minimal necrosis and inflammation (fig 5). The group of rats treated with aqueous bark extract of *Boswellia Serrata* showed mild swelling of liver cells with mild inflammation (fig 6). This suggests the reparative quality and maintenance of structural integrity of hepatocytic cell membrane of damaged liver cells by the extracts. The group of rats treated with LIV-52 shows minimum necrosis and swelling of hepatocytes (fig.3).

The ability of *Boswellia Serrata* to reduce the injurious effect or to preserve normal hepatic function disturbed by the hepatotoxin paracetamol is the index of its hepatoprotective effect. These findings show the prophylactic and curative efficacy of *Boswellia Serrata* in maintaining the integrity and functional status of hepatocytes.

In conclusion, the data presented here indicate that the extracts of *Boswellia Serrata* are hepatoprotective. The in vivo studies carried out using the extracts also proved to be highly efficient in terms of dosage, tolerability and restoring the liver.

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Table 1 In vitro cytotoxicity profile of extracts of *Boswellia Serrata* (mean+SE)

<table>
<thead>
<tr>
<th>Sample identity</th>
<th>Test concen (µg/mL)</th>
<th>LDH Sp. activity</th>
<th>LDH % leakage</th>
<th>GPT Sp. activity</th>
<th>GPT % leakage</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>--</td>
<td>4.99±0.01</td>
<td>----</td>
<td>100+0.74</td>
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<tr>
<td>CBE</td>
<td>10</td>
<td>5.01±0.08</td>
<td>NS</td>
<td>121.2±0.37</td>
<td>NS</td>
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<td></td>
<td>50</td>
<td>4.65±0.12</td>
<td>NS</td>
<td>107.4±0.29</td>
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<td>100</td>
<td>5.15±0.01</td>
<td>NS</td>
<td>116.1±0.55</td>
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<td>ABE</td>
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<td>123.6±0.60</td>
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<td>128.4±0.40</td>
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<td>ALE</td>
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<td></td>
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<td>5.07±0.04</td>
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<td>125.1±0.32</td>
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<td>AGE</td>
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<td>114.8±0.37</td>
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<td>5.12±0.05</td>
<td>NS</td>
<td>102.4±0.24</td>
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</table>

NS: Non-significant (t-test)

ALE-Aqueous Leaf Extract
ABE-Aqueous Bark Extract
AGE-Aqueous Gum Extract
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Table 2 In vitro hepatoprotective activity of extracts of Boswellia Serrata (mean+SE)

<table>
<thead>
<tr>
<th>Sample Identity</th>
<th>Test concen (µg/ml)</th>
<th>GSH levels (cells)</th>
<th>Hepatoprotective effect</th>
<th>% restoration of enzyme leakage against toxin challenge (PCM) of enzyme leakage</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>µg/3 x 10^4 cells</td>
<td>% recovery</td>
<td>Sp. activity</td>
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<td>3.20±0.03</td>
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<td>90±1.7</td>
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<td>PCM</td>
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<td>14.8±0.32</td>
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<td>191.8±2.2</td>
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<td>PCM+ABE</td>
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<td>44</td>
<td>138.6±1.0</td>
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<td>65</td>
<td>119.2±1.9</td>
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<td>6.07±0.27</td>
<td>78</td>
<td>104±0.7</td>
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<tr>
<td>PCM+LIV-52</td>
<td>4.22±0.04</td>
<td>5.96±0.02</td>
<td>84</td>
<td>98±2.1</td>
</tr>
</tbody>
</table>

PCM-Paracetamol
ALE-Aqueous Leaf Extract
ABE-Aqueous Bark Extract
AGE-Aqueous Gum Extract

Table 3 Effect of Boswellia Serrata extracts on serum biochemical parameters against PCM induced hepatic injury in rats (Curative study, mean±SE)
P<0.001Vs Control, *<0.01, †<0.05 Vs Control

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose(mg/kg,p.o)</th>
<th>Serum Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ALT(IU/L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(mg)</td>
</tr>
<tr>
<td>Vehicle control</td>
<td>3gm/kg</td>
<td>144±1.529</td>
</tr>
<tr>
<td>Vehicle+PCM</td>
<td>250mg/kg</td>
<td>61±2.517</td>
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<tr>
<td>PCM+ABE</td>
<td>500mg/kg</td>
<td>58.82±0.722</td>
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<td>250mg/kg</td>
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<td>100mg/kg</td>
<td>39.67±0.48</td>
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PCM-Paracetamol
ALE-Aqueous Leaf Extract
ABE-Aqueous Bark Extract
AGE-Aqueous Gum Extract

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