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Protective effect of *Oroxylum indicum* on acetaminophen induced liver injury in rat

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ABSTRACT
Acetaminophen (APAP) is a common antipyretic drug and leads to liver failure at over dose. In this study, the hepatoprotective effect of Aqueous Methanolic Bark Extract of *Oroxylum indicum* (L.)Vent. (*AMBEOI*) has been evaluated in rat model. Rats were treated with 1000 mgkg^{-1} body weight of APAP alone or with *AMBEOI* (10, 50 and 100 mgkg^{-1}). Serum Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Lipid peroxidation (LPO) in liver tissues were estimated 24 hrs after APAP and *AMBEOI* treatment. *AMBEOI* administration effectively reduced serum level of ALT and AST released from liver cells when compared to APAP treated group. *AMBEOI* also inhibited production of LPO in the liver tissues of APAP treated rats. Histopathological examination of liver samples revealed reduced necrotic areas in *AMBEOI* treated APAP group compared to APAP alone treated group. Together, this study confirmed the hepatoprotective activities of *AMBEOI* in APAP induced liver damage in rat.

Key Words: ALT, AST, LPO, hepatotoxicity, AMBEOI, traditional medicine.

INTRODUCTION

Acetaminophen (APAP) is a commonly used analgesic and antipyretic drug and is safe at therapeutic levels, but overdose can leads to potentially fatal hepatic necrosis in humans and experimental model animals (Proudfoot and Wright, 1970; Cobden *et al.*, 1982; Prescott, 1980). APAP overdose is one of the most common/frequent causes of liver failure in western world (Lee, 2004). At overdose APAP is metabolized in the liver by cytochrome P450 (CYP) into reactive metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI) (Dahlin *et al.*, 1984; James *et al.*, 2003b). NAPQI is known to deplete cellular glutathione (GSH), a natural antioxidant level and generate oxidative stress that turn into production of free radicals such as reactive oxygen (ROS) and reactive nitrogen species (NOS) (Mitchell *et al.*, 1973). This results in imbalance of cellular antioxidant defense mechanism in liver hepatocyte cells and thus finally leads to hepatotoxicity (Reid *et al.*, 2005). Due to known mode of its hepatotoxicity APAP is widely used as a model liver toxin for experimental validation of hepatoprotective drugs.

The production of various free radicals and successive oxidative stress leads to adverse effect on cellular level of an organ. Herbal antioxidants are widely used for the treatment and prevention of several diseases (Uttara *et al.*, 2009). Current therapeutic research is directed towards finding naturally occurring antioxidants particularly of plant origin. Many plant species reported to possess potential biomolecules to become a source of hepatoprotective drugs and search is still going on to find the best one. Tangjang *et al.* (2011) has reported the uses of different plant species as hepatoprotective among the traditional medicine practitioners of Arunachal Pradesh, India (Tangjang *et al.*, 2011).

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Oroxylum indicum (L.) Vent. (Bignoniaceae) (Also known *Shyonaka*, *Sonapatha*) is a deciduous tree growing in China, Thailand and Southeast Asia including India characterized by sword shaped seed pods. This plant is also found to occur abundantly in the North-Eastern part of India. *Oroxylum indicum* is widely used in Indian traditional Ayurvedic formulation namely *Dasamula*, *Chyavanprasa*, *Brahma Rasayana*, *Dhanawatara*, *Awalwha and Narayana Taila* (Bhattacharje, 2000). The bark decoction of *Oroxylum indicum* is a traditionally used by the *Adi* tribe of Arunachal Pradesh for curing hepatobiliary diseases and cardiac problems (Tangjang *et al.*, 2011). *Oroxylum indicum* also reported to causes strong antioxidant (Siriwatanametanon *et al.*, 2010; Tenpe *et al.*, 2009; Kumar *et al.*, 2010), anti-inflammatory (Doshi *et al.*, 2012), antiproliferative and antitumor (Mao, 2002; Lambertini *et al.*, 2004; Brahma *et al.*, 2011) activities. The stem bark of *Oroxylum indicum* reported to contain flavonoids like baicalein, chrysin and oroxylin A (Sankara and Nair, 1972a; Sankara and Nair, 1972b). Taking this information into account, the present work was carried out to evaluate the hepatoprotective effect of *Oroxylum indicum* bark extract on APAP induced hepatotoxicity in rat.

MATERIALS AND METHODS

Chemicals

Acetaminophen (APAP) and Thiobarbituric acid (TBA), 1, 1, 3, 3-tetraethoxypropane were purchased from Sigma-Aldrich. Serum ALT and AST enzymes were estimated using commercial kits (Medsource Ozone Biochemicals Pvt. Ltd, India). All other chemicals used during the experiment were analytical grade.

Collection and preparation of Plant extract

The plant material *Oroxylum indicum* was collected from the Rajiv Gandhi University campus, Arunachal Pradesh and was identified with the help of taxonomist from the Department of Botany, Rajiv Gandhi University. The voucher specimen (LBC/RGU/2013/01) was deposited at Centre with Potential for Excellence in Biodiversity (CPEB), Rajiv Gandhi University for future reference. The

Table 1: Serum ALT and AST levels in different experimental groups.

Groups	ALT (U/ml)	AST (U/ml)
Control	65 ± 6.55	71 ± 14.42
OI 100	85.66 ± 10.01	92.74 ± 8.96
APAP 1000	784 ± 107.01a	742.33 ± 56.21 a
APAP 1000 + OI 10	764.66 ± 36.25	717.25 ± 57.49
APAP 1000 + OI 50	580 ± 54.78 b	604.61 ± 38.68 b
APAP 1000 + OI 100	367.86 ± 66.80 b, c	374.2 ± 68.52 b, c

Values are mean ± SD of five animals per group.
[a] *p<0.001*, significantly differ from control,
[b] *p<0.05*, significant differ from APAP group and
[c] *p<0.001*, significantly differ from APAP1000 + OI 50 group.

fresh stem bark of *Oroxylum indicum* was washed 4-5 times with the help of tap water to remove salts, epiphytes, sand etc. and allowed to shade dried and powdered. The powder was dissolved in methanol for overnight and then filtered and evaporated to dryness in an incubator. The residue collected was further dissolved in distilled water, filtered and kept at -20°C for further use.

Animals and experimental design

Adult male Sprague-Dawley rats (*Rattus norvegicus*) (100-120g) rats were procured from the stock animal facility of the Department of Zoology, Rajiv Gandhi University. Animals were housed in polycarbonate cages with rice husk as a bedding material with a 12 h light/dark cycle and were fed standard laboratory diet and water ad *libitum*. All animal experimentation was conducted in accordance with institutional ethical guidelines. After 7 days of acclimatization, rats were divided randomly into six groups of five rats (n=5) in each group. *Group I* received 1 ml distilled water and *Group II* animals received 1 ml of *AMBEOI* (100 $mgkg^{-1}$, s.c.). *Group III* animals received orally 1000 $mgkg^{-1}$ of APAP (dissolved in 1 ml of double distilled water). *Group IV*, *V* and received oral dose of 1000 $mgkg^{-1}$ of APAP with 10, 50 and 100 $mgkg^{-1}$ of *AMBEOI*. After 24 hours APAP administration rats were sacrificed under ether anaesthesia. Blood was collected in EDTA tubes and kept at -20°C for further analysis. A portion of liver from each animal was fixed in 10% neutral buffered formaline for routing histopathological preparation and another part was used for estimation of thiobarbituric acid reactive substances (TBRAS) as a marker of lipid peroxidation.

Estimation of Thiobarbituric acid reactive substances (TBARS) in liver tissues

One part of the liver from each animal was used for the estimation of thiobarbituric acid reactive substances (TBARS) as an index of lipid peroxidation (LPO) as described earlier (Ohkawa *et al.*, 1979) using 1,1,3,3-tetramethoxy propane as the standard. Liver was homogenized in ice cold potassium phosphate buffer. 0.5 ml of the homogenates, 0.5 ml of 8.1% sodium dodecyl sulfate, 0.5 of ml 20% acetic acid (pH 3.3), 0.5 of ml 0.8% thiobarbituric acid and 1 ml of distilled water were added and placed in a boiling water bath for 60 minutes. After cooling, the absorbance of the supernatant was measured spectrophotometrically at 532 nm and expressed as TBRAS (μM) formed per gram of tissue.

Serum ALT and AST estimation

Serum level of ALT and AST, the potential biomarker of hepatic injury was estimated using a commercial kit (Medsource Ozone Biomedicals Pvt. Ltd) (Reitman and Frankel, 1957).

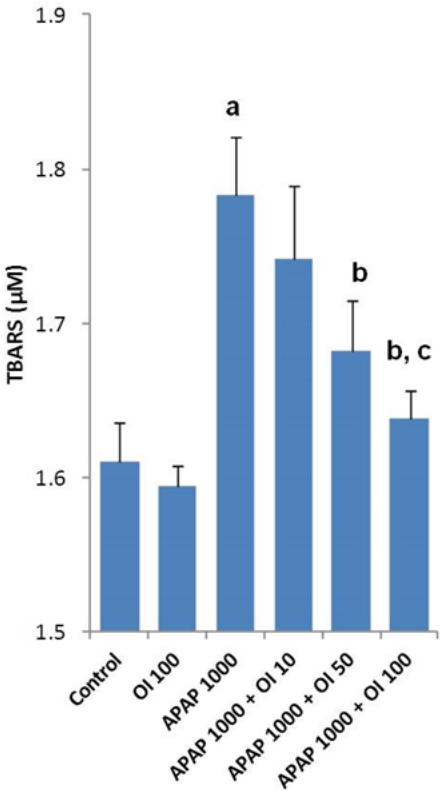

Figure 1: Thiobutaric acid reactive substances (TBRAS) as an index of lipid peroxidation (LPO) was estimated in liver tissue after APAP or APAP + OI treatment. APAP causes an elevation of liver TBARS which was suppressed by OI treatment. Values are mean ± SD of five animals per group. [a] *p<0.001*, significantly differ from control; [b] *p<0.05*, significant differ from APAP group and [c] *p<0.001*, significantly differ from APAP1000 + OI 50 group.

Histopathological analysis

Liver samples were fixed in 10% neutral buffered formalin overnight, washed well in running tap water, dehydrated, cleared in xylene and embedded in paraffin. Liver sections were cut into 5 μm thickness, processed in alcohol grades and stained in haematoxylin and eosin (H&E) (Luna, 1968) for histopathological examinations. Sections were photographed using canon digital image recorder.

Statistical analysis

All data were presented as means ± SEM (n=5). Statistical analysis were performed using one way analysis of variance (ANOVA) followed by Tukey's post hoc test. A level of p-value < 0.05 was considered for determining statistical significance.

RESULTS

Effects of *AMBEOI* on APAP induced ALT & AST in serum

Overdose administration of APAP caused significant elevation of serum ALT and AST in treated groups (table 1, p<0.001). In contrast, AMBEOI co-treatment significantly reduced serum ALT and AST elevation in APAP treated mice compared to only APAP 1000 $mgkg^{-1}$ treated rat group (table 1, P<0.05, 0.001). AMBEOI 100 $mgkg^{-1}$ supplementation caused approximately 50% reduction of serum ALT and AST level compared to control group of rat.

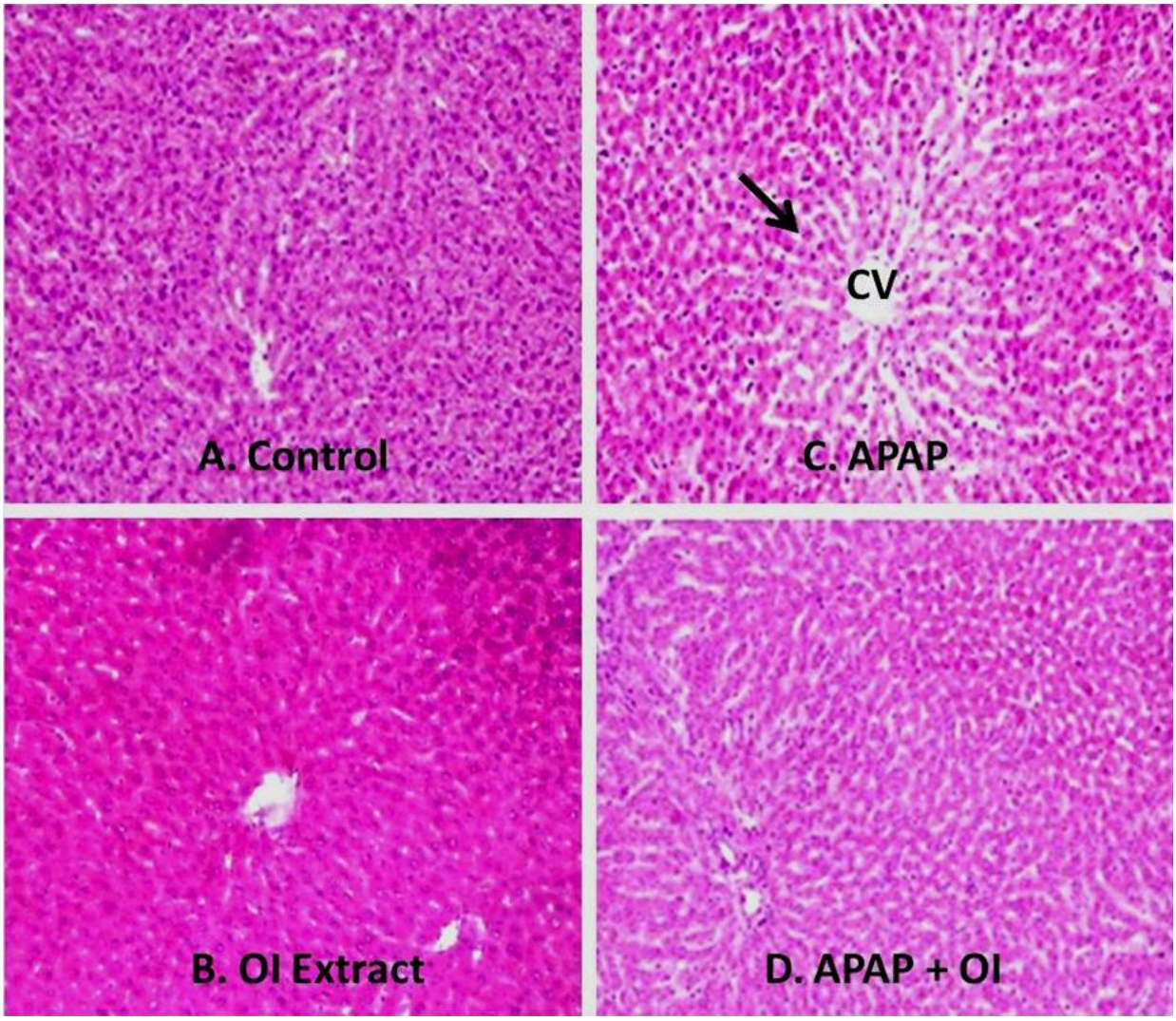

Figure 2: Representative histological microphotographs from (a) Control, (b) OI Extract treated, (c) APAP treated and (d) APAP + OI treated groups. In the control and OI treated groups hepatocytes are well distinguished with clear nuclear morphology and cell membrane structure (A and B). In APAP treated groups hepatocytes membrane are leaky with shrunken nucleus (C). However OI treatment significantly improves liver architecture in APAP treated animals (D). H and E staining, X40 magnifications.

Effect of *AMBEOI* on APAP induced lipid peroxidation (LPO)

APAP treatment caused significant increase in the level of TBRAS, a marker of LPO in the hepatic tissue homogenate compared to control group (figure 1, $p<0.001$). On the other hand co-treatment of rat with *AMBEOI* significantly reduces the tissue level of LPO (Figure 1, $p<0.05$, 0.001).

Effect of *AMBEOI* on APAP induced liver histology

The liver sections in control rat were looking normal with well-defined hepatocytes surrounding the central vein with clear nuclear architecture and cell membrane (figure 2 A). APAP 1000 $mgkg^{-1}$ caused severe centrilobular necrosis in rat 24 hours after treatment. The hepatocytes surrounding central vein shows extensive necrosis with nuclear pycnosis and vacuolar cytoplasmic degeneration (figure 2 C.). *AMBEOI* supplementations reduced the hepatocytes necrosis caused by APAP and restored a near normal morphological feature as was observed in groups receiving 10, 50 and 100 $mgkg^{-1}$ *AMBEOI* (figure 2 D).

DISCUSSION

Oroxylum indicum (L.) Vent. is known to have spacious therapeutic applications in traditional medicinal system, and scientific advancement has provided extensive evidence to support most of its medicinal claims. The present in vivo study has demonstrated the hepatoprotective potential of this plant.

Liver is a major target organ for metabolizing the drugs and xenobiotics (Jaeschkea *et al.*, 2002). APAP when used at high doses could cause acute liver injury via formation of NAPQI, a toxic metabolite, by cytochrome P450. NAPQI are usually inactivated by hepatic GSH, but when produced excessively, it covalently binds to centrilobular hepatic proteins and elicited hepatic toxicity (Jaeschkea *et al.*, 2002; Gardner *et al.*, 1998; Gardner *et al.*, 2002). In this present study hepatocellular damage induced by APAP (1000 $mgkg^{-1}$) intoxication in rat was established based on significant elevations in ALT and AST activities as done by previous workers (Walubo *et al.*, 2004; Kim *et al.*, 2009; Jin *et al.*, 2012).

High concentration of ALT is found mainly in the liver hepatocytes and AST which is localized in the mitochondria, are specific serum biomarkers of hepatic injury caused by drugs or toxic metabolites. But when the damage to hepatocytes occur due to exogenous toxic substances or their metabolites, these enzymes are released into bloodstream and cause an elevation in the serum levels of ALT and AST (Rej, 1978; Schmidt, 1978). Administration of APAP overdose in rat caused significant increases in the serum ALT and AST level compared to the control untreated animals as observed in the present study. *AMBEOI* treatment significantly and dose dependently reduced the release of hepatic ALT and AST as observed from the serum level of these two enzymes in the treated groups. Similar hepatoprotective activities of plant extract such as *Acacia nilotica* and *Moringa oleifera* were noted previously and shown to decreases the level of serum ALT and AST in APAP intoxicated rat (Kannan *et al.*, 2013; Fakurazi *et al.*, 2013).

APAP treatment significantly increased the level of TBARS, a marker of lipid peroxidation (LPO) and an indicator of oxidative stress in the treated rat. The oxidative stress caused by APAP overdose was primarily due to excess formation of NAPQI (Jaeschkea et al., 2003). In normal circumstances, cellular GSH content of the hepatocytes aids in the process of detoxification of NAPQI (Mitchell *et al.*, 1973). But during overdose GSH content deplete earlier than the rate of its synthesis, which create an imbalance in the cellular antioxidant level. In the absence of sufficient GSH, NAPQI binds to the proteins in the centrilobular hepatocytes and caused necrosis (Rej, 1978). The role of GSH depletion in APAP induced liver injury was further confirmed from observation that rats treated with antioxidant such as N-acetylcysteine was immune to APAP overdose (Lauterburg *et al.*, 1983; Smilkstein *et al.*, 1988). This suggested the role of therapeutic supplementation of antioxidants in attenuating oxidative stress induced liver injury in real life scenario.

The plant selected for the present study is reported to possess strong antioxidant properties (Moirangthem *et al.*, 2013). The decrease in the level of TBARS after administration of *AMBEOI* in the liver tissue of APAP intoxicated rat suggested the strong antioxidant property present in the *AMBEOI*. Previously reported studies also confirmed the antioxidant property of the selected plant species under consideration (Moirangthem *et al.*, 2013; Zaveri and Jain, 2007; Shetgiri *et al.*, 2010; Tenpe *et al.*, 2009). The observation that administration of *AMBEOI* reduces formation of TBARS and similar findings from other researchers confirmed that *AMBEOI* act as strong antioxidant and protects the hepatocytes during APAP overdose.

CONCLUSION

The findings of the present study indicated that aqueous methanolic bark extract of *Oroxylum indicum* (L.) Vent. *(AMBEOI)* protect hepatic tissues against APAP induced liver injury in rat. Together this study further confirmed the potential hepatoprotective action of *AMBEOI* in drug induced oxidative damage of the liver in experimental models and can be good candidate to bank upon for further research in experimental drug discovery processes.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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