Original Article

Safety Evaluation of Alcoholic Extract of *Boswellia ovalifoliolata* Stem-bark in Rats

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ABSTRACT

The safety profile of alcoholic extract of stem-bark of *B. ovalifoliolata* was investigated in male Wistar albino rats as per OECD guidelines 407. A total of 24 male Wistar rats were divided into four groups of six rats each. Group 1 served as control and was given 0.3% carboxymethylcellulose, groups 2, 3 and 4 were given alcoholic extract of *B. ovalifoliolata* @ 100, 500 and 1000 mg/kg respectively in 0.3% carboxymethylcellulose orally for 28 days. The animals were observed daily for clinical signs, mortality, physiological and behavioral changes. Body weights were measured at weekly intervals and various hematological parameters like Hb, PCV, TEC, TLC and serum biochemical profile which included AST, ALT, creatine phosphokinase, creatinine, total protein and antioxidant parameters like TBARS and GSH in liver were estimated at the end of experimental period. There were no clinical signs of abnormality. The weekly body weights, organ weights and hematological parameters did not vary significantly amongst the groups. The mean activity of AST, ALT and CPK, and the concentration of serum creatinine, total protein, TBARS and GSH did not differ significantly among the groups. Histological abnormalities of toxicological significance were not detected in groups 2 and 3. However, mild histopathological alterations were observed in higher dose group 4. In conclusion, the present study revealed that the alcoholic extract of stem-bark of *B. ovalifoliolata* is safe at lower doses of 100 and 500 mg/kg. Hence, alcoholic extract of stem bark of *B. ovalifoliolata* is safe and no observed adverse effect level (NOAEL) is found to be 500 mg/kg following repeated oral administration for 28 days in rats.

Key words: *B. ovalifoliolata*, hematology, oxidative stress, safety evaluation, serum biochemistry

INTRODUCTION

Herbal remedies have been used in the management of various diseases from ages and herbs are considered to be safe (Oduola *et al*.).[1] These remedies are commonly self-medicated, more often with no proper dose regimen. Such indiscriminate use without recourse to safety and adverse effects on biological system is considered as dangerous (Aboyade *et al*.).[2] Although, the literature has documented several toxicities resulting from the use of herbs on many occasions, still the potential toxicity of herbs has not been recognized by the general public or by professional groups of traditional medicine (Jou-fang).[3] The use of medicinal plants as raw materials in the production of drugs is gaining popularity (Olaleye)[4] and hence, it has become imperative to assess the safety or toxicity of plants used in folklore medicine.

Boswellia ovalifoliolata (Family: Burseraceae), an endangered plant vernacularly known as Konda guggilam, is a deciduous

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tree endemic to Seshachalam hills of Chittoor and Kadapa districts of A.P. In folklore, the stem and bark are used to cure hydrocoel, inflammation and swellings and stomach ulcers (Pullaiah).[5] Two macrocyclic diaryl ether heptanoids were identified from the stems of *B. ovalifoliolata* viz., ovalifoliolatin A and B together with three compounds acerogenin c, 3 α-hydroxyurs-12-ene and sitost-4-ene-3-one. This class of diaryl heptanoids exhibit a broad range of potent biological activities that include anti-inflammatory, anti-hepatotoxic, antifungal, antibacterial and related effects (Niranjan Reddy *et al*.).[6] The alcoholic extract of *B.ovalifoliolata* stem bark extract is reported to exhibit anti-inflammatory activity in rats (Sakunthala Devi *et al*.).[7] The present effort is, therefore, aimed to investigate the safety profile of the stem bark alcoholic extract of the plant following oral administration for 28 days in adult male Wistar rats as per OECD guidelines 407(OECD).[8]

MATERIALS AND METHODS

Plant extract

The stem-bark of *B.ovalifoliolata* was collected, cleaned, shade dried and ground into a coarse powder. About 100 g of stem-bark powder was macerated in 500 ml of 95% ethanol v/v with intermittent mixing using a glass rod for 72 h and filtered. The filtrate was evaporated at 55°C on a hot plate to one fourth of the volume. The yield obtained was 10% w/w.

Animals

Male Wistar albino rats weighing 270-320 g were used in the present study. The animals were housed in a well cross ventilated room at 27±2°C, relative humidity 44-56%, light and dark cycles of 12 h and 12 h, respectively throughout the experiment. The animals were provided with standard pellet diet supplied by Hindustan Lever Ltd., Bangalore and water ad libitum. The study was conducted with prior permission of Institutional animal ethics committee and in accordance to OECD guidelines 407 (OECD).[8]

Experimental design

A total of 24 rats were randomly allotted to control and three treatment groups consisting of six rats each. The control group received 0.3% carboxymethylcellulose. The extract was made into suspension with 0.3% carboxymethylcellulose and administered orally in three doses of 100, 500, 1000 mg/kg to groups 2, 3 and 4 respectively on a daily basis for a period of 28 days.

Clinical signs

During the period of administration of the extract, the rats were observed daily for signs of toxicity, physiological and behavioral changes, if any.

Body weight changes

The body weights of all the animals were monitored at the onset of the study and at weekly intervals till the end of the experimental period.

Blood collection

On day 29, rats were anesthetized with ether and blood was collected by orbital puncture. Whole blood collected in EDTA was utilized for hematological studies and serum obtained after clotting and centrifugation of blood was utilized for biochemical analysis.

Serum biochemical parameters

Serum was separated from clotted blood samples by centrifugation at 3000 rpm for 10 min and was utilized for biochemical analysis. The activities of aspartate transaminase (AST), alanine transaminase (ALT), creatinine phosphokinase (CPK), creatinine, and total protein were estimated using standard kits supplied by Qualigens, Pvt. Ltd, Mumbai.

Hematology

Hematological parameters viz., hemoglobin, packed cell volume (PCV), total erythrocyte count (TEC), total leukocyte count (TLC) were estimated using standard laboratory procedures.

Antioxidant profile

Liver samples were collected and homogenized in ice-cold phosphate buffer (pH 7.4) for the estimation of lipid peroxidation (TBARS) (Subramanian *et al*.)[9] and reduced glutathione (GSH) content (Moron *et al*.).[10]

Gross and histopathology

A detailed post-mortem examination was conducted on the rats sacrificed from each group. Vital organs such as liver, heart, kidney, spleen and testes were weighed immediately after dissection to avoid drying and examined macroscopically for gross lesions, if any. Tissue portions were then fixed in 10% neutral buffered formalin and were processed for routine histopathological processing. Sections of 5-6 μm thickness were prepared and stained by hematoxylin and eosin (Singh and Sulochana).[11] The stomachs were cut open along the greater curvature and gently washed with normal saline and gastric mucosa was examined for the presence of erosions, hemorrhagic spots, ulcers and perforations, if any, with the help of magnifying lens.

Statistical analysis

The data was expressed as mean±S.E. Statistical differences between groups were tested using one way ANOVA followed by Duncan's multiple comparison test using SPSS 15.0 V software and the level of significance was set at $P<0.05$.

RESULTS

The results of weekly body weights, organ weights, hematology, sero-biochemical profile, and oxidative profile are presented in Tables 1-5 respectively.

Clinical signs

The clinical signs in the treatment groups showed no abnormalities in terms of changes in skin, fur, eyes, mucous membranes, occurrence of secretions and excretions and autonomic activity (e.g. lacrimation, piloerection, pupil size, unusual respiratory pattern) gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypes (e.g. excessive grooming, repetitive circling) or bizarre behavior (e.g. selfmutilation, walking backwards). Further, there were no signs of toxicity in all the groups.

Body weights and organ weights

The body weights [Table 1] and organ weights [Table 2] of liver, kidney, heart, spleen, lungs and testes showed no significant difference between the treated groups and control group and further, at the doses studied, there was no swelling, atrophy or hypertrophy of various organs.

Biochemical parameters

The biochemical parameters like AST, ALT, CPK, creatinine, total protein showed no significant difference between treatment groups and control group indicating that the extract is not toxic to vital organs like liver, kidney and heart [Table 3].

Hematological parameters

The hematological parameters like PCV, Hb, TEC and TLC showed no significant difference between treatment groups and control group, which shows that the extract is not toxic to the hematopoietic system [Table 4].

Antioxidant parameters

The antioxidant status of liver assessed in terms of TBARS and GSH levels was not altered indicating that there are no potential toxic compounds in the extract that can cause oxidative damage [Table 5].

Table 1: Effect of alcoholic extract of *B. ovalifoliolata* on weekly body weights (g)

Group	Day 0	Day 7	Day 14	Day 21	Day 28
CMC (0.3%) *p.o*	318.66 ± 0.02	320.23 ± 0.02	320.11 ± 0.02	312.23 ± 0.03	318.44 ± 0.02
B. ovalifoliolata alcoholic extract, 100 mg/kg *p.o*	283.13 ± 0.01	282.56 ± 0.02	289.45 ± 0.01	281.11 ± 0.01	282.16 ± 0.01
B. ovalifoliolata alcoholic extract, 500 mg/kg *p.o*	293.11 ± 0.01	286.22 ± 0.01	285.34 ± 0.01	283.13 ± 0.01	279.22 ± 0.01
B. ovalifoliolata alcoholic extract, 1000 mg/kg *p.o*	295.67 ± 0.02	291.24 ± 0.02	301.55 ± 0.01	283.24 ± 0.01	305.11 ± 0.01
Sig	NS	NS	NS	NS	NS

Values are (mean±S.E); *n*=6; One-way ANOVA followed by Duncans multiple comparison test using SPSS software 15.0 V ($P<0.05$)

Table 2: Effect of alcoholic extract of *B. ovalifoliolata* on organ weights (g)

Group	Heart	Lungs	Liver	Spleen	Kidneys	Testes
Normal saline *p.o*	0.93 ± 0.02	1.65 ± 0.07	7.41 ± 0.89	0.78 ± 0.08	1.96 ± 0.06	5.08 ± 0.30
B. ovalifoliolata alcoholic extract, 100 mg/kg *p.o*	1.04 ± 0.09	1.44 ± 0.13	7.99 ± 0.33	0.86 ± 0.05	1.91 ± 0.06	4.96 ± 0.28
B. ovalifoliolata alcoholic extract, 500 mg/kg *p.o*	1.09 ± 0.07	1.66 ± 0.08	8.27 ± 0.24	0.91 ± 0.08	1.71 ± 0.17	5.24 ± 0.12
B. ovalifoliolata alcoholic extract, 1000 mg/kg *p.o*	1.03 ± 0.05	1.68 ± 0.07	8.69 ± 0.22	0.85 ± 0.05	1.85 ± 0.08	5.56 ± 0.18
Sig	NS	NS	NS	NS	NS	NS

Values are (mean±S.E); *n*=6; One-way ANOVA followed by Duncans multiple comparison test using SPSS software 15.0 V ($P<0.05$)

Table 3: Effect of alcoholic extract of *B. ovalifoliolata* on serum biochemical parameters

Group	AST (IU/L)	ALT (IU/L)	Creatinine (mg/dl)	CPK (IU/L)	Total protein (g/dl)
Normal saline *p.o*	90.36 ± 10.48	22.13 ± 3.21	1.50 ± 0.11	573.93 ± 29.90	7.29 ± 0.47
B. ovalifoliolata alcoholic extract, 100 mg/kg *p.o*	72.12 ± 18.19	25.11 ± 0.92	1.62 ± 0.18	589.26 ± 40.80	6.84 ± 1.28
B. ovalifoliolata alcoholic extract, 500 mg/kg *p.o*	98.22 ± 9.82	27.55 ± 1.90	1.70 ± 0.04	589.58 ± 38.40	6.83 ± 0.76
B. ovalifoliolata alcoholic extract, 1000 mg/kg *p.o*	83.49 ± 5.83	24.46 ± 0.62	1.84 ± 0.04	595.65 ± 38.55	6.84 ± 0.56
Sig	NS	NS	NS	NS	NS

Values are (mean ± S.E); *n*=6; One-way ANOVA followed by Duncans multiple comparison test using SPSS software 15.0 V ($P<0.05$)

Table 4: Effect of alcoholic extract of *B. ovalifoliolata* on hematological profile

Group	PCV (%)	Hb (g%)	TEC (millions/μl)	TLC (thousands/μl)
Normal saline *p.o*	37.41 ± 1.11	12.53 ± 0.39	6.25 ± 0.18	6.48 ± 0.66
B. ovalifoliolata alcoholic extract, 100 mg/kg *p.o*	37.57 ± 1.59	12.53 ± 0.53	6.26 ± 0.26	6.52 ± 0.72
B. ovalifoliolata alcoholic extract, 500 mg/kg *p.o*	40.50 ± 1.52	13.52 ± 0.50	6.75 ± 0.25	6.58 ± 0.67
B. ovalifoliolata alcoholic extract, 1000 mg/kg *p.o*	40.51 ± 1.45	13.61 ± 0.44	6.83 ± 0.23	6.62 ± 0.72
Sig	NS	NS	NS	NS

Values are (mean±S.E); *n* =6; One-way ANOVA followed by Duncans multiple comparison test using SPSS software 15.0 V (*P*<0.05)

Table 5: Effect of alcoholic extract of *B.ovalifoliolata* on oxidative stress in liver

Group	MDA (TBARS) (nM MDA/g of tissue)	GSH (mg/g of tissue)
Normal saline *p.o*	225.33 ± 52.30	1.34 ± 0.16
B. ovalifoliolata alcoholic extract, 100 mg/kg *p.o*	242.71 ± 33.34	1.33 ± 0.06
B. ovalifoliolata alcoholic extract, 500 mg/kg *p.o*	268.70 ± 32.66	1.32 ± 0.07
B. ovalifoliolata alcoholic extract, 1000 mg/kg *p.o*	273.66 ± 26.32	1.32 ± 0.07
Sig	NS	NS

Values are (mean±S.E); *n*=6; One-way ANOVA followed by Duncans multiple comparison test using SPSS software 15.0 V (*P*<0.05)

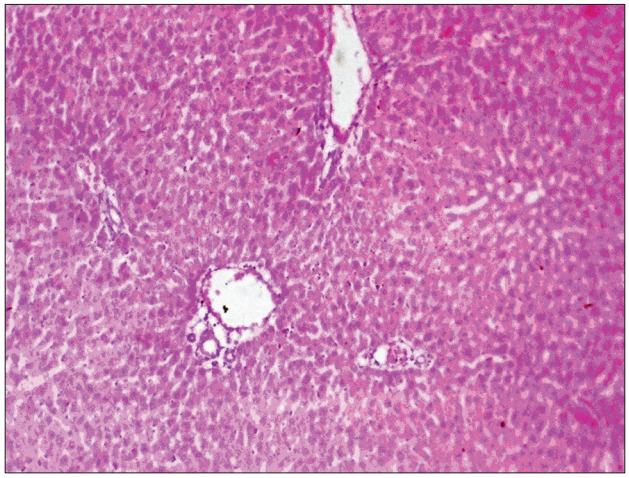

Figure 1: Group 4 liver showing mild proliferation of bile duct (H and E, ×70)

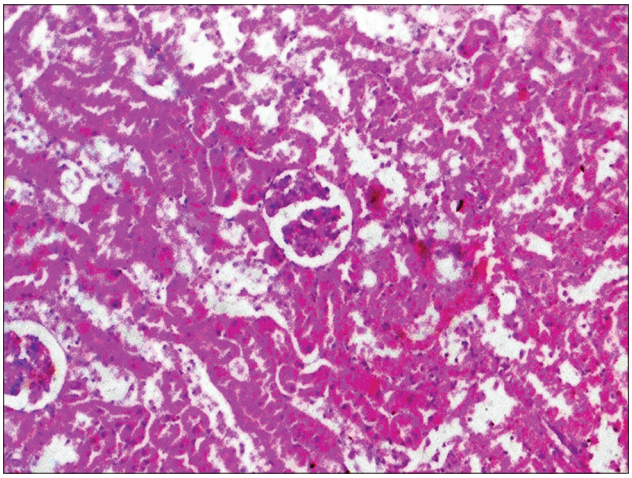

Figure 2: Group 4 kidney section showing mild necrotic changes in tubular epithelial cells (H and E, ×70)

Gross and histopathology

Histopathological examination of liver, kidney, heart and testes did not reveal any lesions of toxicological significance in lower dose groups 2 and 3; however, in higher dose group 4 (1000 mg/kg) mild proliferation of bile ducts in liver [Figure 1], mild necrotic changes in tubular epithelial cells of kidney [Figure 2], mild congestion in heart [Figure 3] and inter tubular edema and severe necrotic degeneration of seminiferous tubules in testes were observed [Figure 4]. Further, at higher doses (1000 mg/kg), rats showed desquamation of epithelium lining of gastric mucosa [Figure 5].

DISCUSSION

The use of herbal remedies is wide spread with about 80% of the population in developing countries depending on them. Despite this widespread use, few scientific studies are available that ascertained the safety of traditional remedies (Saggu *et al*.).[12] Therefore, the need to provide information on the toxic implications of these remedies cannot be over emphasized. In this scenario, in the present study, the repeated 28 day oral toxicity of alcoholic extract of stem bark of *B.ovalifoliolata* was investigated for its safety in male rats by assessing clinical signs, hematological parameters, biochemical parameters, antioxidant parameters and histopathological studies of liver, kidney, heart, testes and gastric mucosa.

The clinical signs were normal in all the treatment groups and there was no significant difference in terms of body weight and organ weights in the treatment groups indicating the absence of potential toxic principles in the extract. In general, reduction in body weights and internal organ weights are a simple and sensitive index of toxicity after exposure to potentially toxic substances (Shrinath *et al*.).[13]

Liver is the major organ responsible for metabolism of toxic substances that enter the body (Alisi *et al*.)[14] and

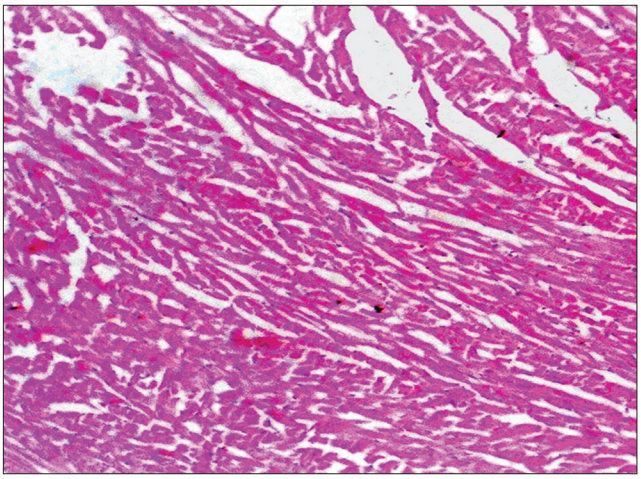

Figure 3: Group 4 heart section showing mild congestion (H and E, ×70)

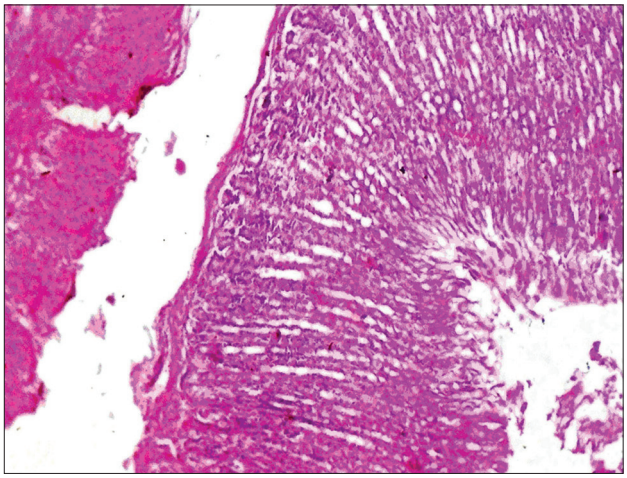

Figure 4: Group 4 testis showing interlobular edema and severe necrotic changes in seminiferous tubular epithelial cells (H and E, ×70)

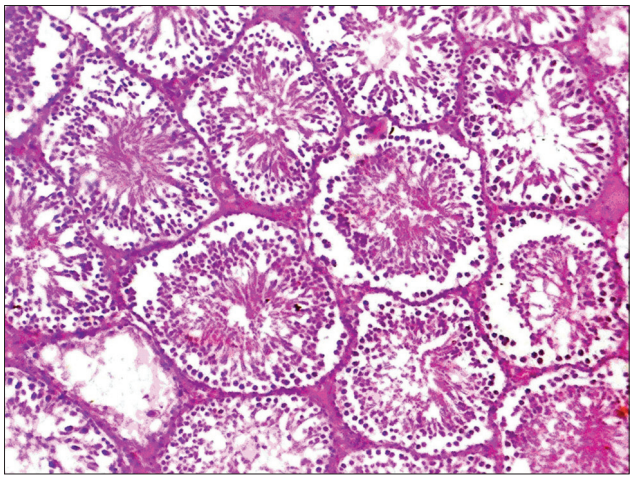

Figure 5: Group 4 stomach showing the desquamation of lining epithelial cells

the functions of the liver can be detrimentally altered by liver injury resulting from acute or chronic exposure to toxicants or by situations affecting both ß-oxidation and the respiratory chain enzymes (Alisi *et al*.).[14] Further, hepatotoxicity has been viewed as liver injury associated with impaired liver function caused by exposure to drug or other noninfectious agents or herbs (Navarro;[15] Oduola *et al*.[1]) Serum enzyme activities are used as indicators of chemical-induced liver damage (Drotman and Lawhorn).[16] The study on the activities of different biomarker enzymes such as AST and ALT, and the concentration of total protein have been found to be of great value in the assessment of clinical and experimental liver damage. Membrane damage releases the enzyme into circulation and therefore they can be measured in serum (Teo *et al*.).[17] In the present study, the plant extract did not alter the activities of AST, ALT and total protein levels indicating no potential liver damage [Table 3].

Non-protein nitrogenous (NPN) substances such as urea and serum creatinine are increased only when renal function is below 30% of its original capacity in animals (Kaneko *et al*.).[18] In the present study, there was no significant difference in the creatinine levels in all of the alcoholic extract treated groups.

The activity of creatine phosphokinase (CPK) has been used to assess cardiac damage as it is a biomarker enzyme (Adeneye *et al*.).[19] The CPK levels were not altered in the present study using alcoholic extract of the herb indicating non-toxic implications to the heart.

The hematopoietic system is very sensitive to the toxic effects of chemicals and serves as an important indicator of the physiological and pathophysiological status of both animals and humans (Hashemi *et al*.).[20] After 28 days of treatment using the alcoholic extract of *B. ovalifoliolata*, there were no treatment-related changes in hematological parameters. The study revealed that the orally administered doses are non-toxic and did not interfere with erythropoiesis and leucopoiesis in rats. This shows that the plant is safe for use because some plants are known to cause destruction of red blood cells leading to anemia (Blood and Radostits;[21] Adedapo[22,23]).

Increased levels of lipid peroxides and reduced glutathione activity reflect the hepatic toxicity of the compound (Adeneye *et al*.).[19] In the present study, the levels were not altered indicating that there are no potential toxic compounds in the extract that can cause oxidative damage.

The gross and histopathological changes in liver, kidney, heart and gastric mucosa revealed no abnormalities in the groups 2 and 3 which were administered 100 mg and 500 mg/kg of the extract. However, in group 4 which was given higher dose of the extract (1000 mg/kg) showed bile duct proliferation, degeneration of tubular epithelial cells in kidney, congestion of heart and desquamation of gastric epithelial lining indicating that the extract is not safe beyond 500 mg/kg upon repeated oral administration for 28 days.

In conclusion, the safety study on stem-bark extract of *B. ovalifoliolata* revealed no adverse effects of toxicological importance at doses of 100 and 500 mg/kg b.wt whereas at the dose level of 1000 mg/kg revealed mild histopathological changes on repeated 28 day oral toxicity study in rats. Hence, it is concluded that the drug is safe for use with a no observed adverse effect level (NOAEL) of 500 mg/kg/day when administered orally for 28 consecutive days. However, as the higher dose (1000 mg/kg) of the extract revealed mild histopathological changes, it is recommended that chronic toxicity, mutagenicity and carcinogenicity studies are further warranted to support the safe and sound use of the herb.

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