



Toxicological Studies of Methanol Stem Bark Extract of *Eucalyptus camaldulensis* on Wister Albino Rats

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MSA and YI designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Author AYD managed the analyses of the study. Author SAS managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The aim is to evaluate the toxicological profiles of methanol stem bark extract of *E. camaldulensis* (MSEEC) on Wister albino rats.

Methods: Acute toxicity study was conducted according to OECD, 2001. The rats were grouped into six groups of one rat each and were given single oral dose 5000 mg/kg of the extract. A total of 30 albino rats of both sex were used for the toxicological study. The rats were divided into five (5) groups of six (6) rats. Control group (group 1) received distilled water orally 1 ml/kg. Groups (2-5) received doses of 500, 1000, 1500 and 2000 mg/kg of the extracts. The experiment lasted for 28 days. Data analysis was done using SPSS version 20.0.

Results: The LD₅₀ of MSEEC was greater than 5000mg/kg. The sub-chronic doses of 500-2000 mg/kg of the extract shows no significant (P>.05) difference of the hematological parameters when compared to the control. The Serum biochemical parameters were no significant (P>.05) compared to the control. However, there was an increase in creatinine level at doses 500, 1500 and 200 mg/kg.

Conclusion: The results from this study indicate that administration of methanol stem bark extract of *Eucalyptus camaldulensis* did not produce significant toxic effect.

Keywords: Acute toxicity; eucalyptus; camaldulensis; toxicity; albino rat.

1. INTRODUCTION

Herbal medical remedies have been abundantly used for several diseases in most endemic regions. Most of these preparations have been used extensively by several generations and knowledge about them has been accrued from experience, trial and error. About 80% of some African and Asian countries population depend on traditional medicine for their primary health care needs [1]. The WHO in 2008 report that inappropriate use of traditional medicines may have negative or dangerous effects, as such, further research is needed to confirm the efficacy and safety of several practices and medicinal plants used by traditional medicine systems. Most medicinal plants have not been thoroughly evaluated for their toxicity profiles. However, it is generally agreed that medicinal plants and their products are relatively safer than their synthetic counterpart drugs. The reasons for this is because medicinal plant constituents mimic more closely the natural constitution of the human somatic system, and following the lock and key hypothesis, it is expected that they will fit better into such system [2].

Eucalyptus camaldulensis belongs to the order myrtales and myrtaceae. It is a large genus of aromatic trees indigenous to Australia, Tasmania and the neighboring Island, but today, it can be found growing in subtropical regions of the world. The genus consists of about 700 species of evergreen trees and shrubs [3]. The tree can grow to 375-480 feet (125-160 meters). The name originates from the Greek word eucalyptol which means well covered. *Eucalyptus* trees thrive in environments that maintain average temperatures of about 40°C. The plants have been considered as sources of medicinal agents for the treatment of many diseases [4]. Due to this, it is imperative that its toxicological profile be assessed so as to know its safety in medicinal formulations if used.

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

All chemicals and reagents used were of analytical grade.

2.2 Plant Sample Collection and Identification

Eucalyptus camaldulensis stem bark was collected from Kalgo Town, Kalgo Local Government, Kebbi State, Nigeria. The plant was identified by a Taxonomist from the Plant Science and Biotechnology Department, Kebbi State University of Science and Technology Aliero and a Voucher specimen was deposited at the Herbarium of the same Department for future reference.

2.3 Experimental Animals

Albino rats weighing 150-200g of both sexes were used for the study. The rats were purchased from the Animal House of the Department of Biological Sciences, Usmanu Danfodio University Sokoto, Nigeria. The animals were allowed to acclimatize to laboratory conditions for two weeks. The rats had access to growers mash (vital feeds Ltd, Nigeria) and clean water *ad libitum*.

2.4 METHODS

2.4.1 Preparation of plant sample

The stem bark of *Eucalyptus camaldulensis* were dried at room temperature for two weeks and were cut into smaller pieces. Two hundred (200g) grams of the plant material was macerated with two litres of methanol left in an air-tight aspirator for seventy two hours. The mixture was then filtered using sterile muslin cloth. The filtrate was evaporated using a rotary evaporator at forty five degree Celsius and subsequently dried in a drying cabinet at forty five degree Celsius and labelled methanol extract. The weight of the dried extract was recorded for the calculation of yield and stored in an air-tight bottle in a refrigerator until required for analysis.

2.4.2 Acute oral toxicity test (LD₅₀ determination)

The acute oral toxicity study was conducted according to the guideline of Organization for Economic and Cultural Development for testing of chemicals (OECD, 2001) using fixed limit test dose. The rats were divided into six groups of one rat each. They were fasted overnight providing only water. The first group received distilled water orally and serves as normal control

group. The remaining five groups (2-6) were administered single oral doses of 5000mg/kg body weight of the extract. Observation was made on each group and recorded systematically at first 8hrs, 48hrs and up to 14days after the administration of the extract. The rats were observed for toxic symptom such as weakness, aggression, and food refusal, loss of weight, skin changes, hair removal, slow breathing and mortality.

2.4.3 Experimental design for sub-chronic toxicity

The sub-chronic toxicity studies was done according to OECD (407). In this experiment Thirty (30) rats of both sex were used. The rats were divided into five (5) groups of six rats each. Group I was given distilled water and serve as control. Group II III IV and V: received the methanol stem bark extract of *Eucalyptus camaldulensis* (500, 1000, 1500 and 2000mg/kg), respectively once a day for twenty eight days. Group two was given 500mg/kg b.w for 28 days. Group three was given 1000mg/kg b.w for 28 days.

2.4.4 Biochemical and Haematological analyses

Twenty four hours (24hrs) after the last oral administration of the extract, blood samples were collected via cardiac puncture. Blood samples collected in plain containers were used for biochemical analysis. Blood samples collected in EDTA containers were used for haematological analysis.

2.4.5 Liver Function Test

The following parameters were analyzed in the sera: Alanine aminotransferase (ALT) (Reitman and Frakel, 1957), Alkaline phosphatase (ALP) (Rec, 1972), Aspartate aminotransferase (AST) (Reitman and Frankel, 1957), Total protein (Dumas, 1975), Albumin (Reitman and Frakel, 1957), Total and Direct Bilirubin (Koch and Dumas, 1982), Electrolytes and Creatinine (Rec, 1972), and Urea (Dumas, 1975).

2.4.6 Haematological assessment

Erythrocyte (RBC), hemoglobin (Hb), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count, (PLC), monocyte count (MONO), neutrophil (NEUT) lymphocyte count (LYMP)

white blood count (WBC) were determined using SYSMEX KX-21N auto analyzer; Sysmex Corporation, Kobe, Japan. A small volume of blood was collected into a heparinised capillary tube, one end of which was sealed with plasticine and then spun for 5 min in a micro-haematocrit centrifuge.

2.4.7 Statistical analysis

Results are express as the Mean \pm Standard Error of the Mean (SEM). Statistical analysis of data was done using GraphPad The data was subjected to one-way analysis of variance (ANOVA) and differences in mean would be considered significance when ($P < .05$).

3. RESULTS

3.1 Acute Toxicity Assay of *Eucalyptus camaldulensis*

A single oral dose of *Eucalyptus camaldulensis* stem bark extract did not cause any death neither did the rats show any signs of toxicity at dose level of 5000mg/kg. The LD50 was therefore estimated to be greater than 5000mg/kg body weight as there was no mortality in all the treated rats.

3.2 Effect of Sub-chronic Administration of MSEEC on Serum Liver Function Parameters

As shown in (Table 1), the liver biochemical parameters (ALT, AST, ALP, TP ALB, TB, DB) were within normal range and were not elevated even at a concentration of 2000mg/kg b.wt of the extract.

3.3 Effect of Sub-chronic Administration of MSEEC on Kidney Indices

Table 2; showed the effect of sub-chronic administration of MSEEC on kidney parameters (urea, K⁺, Na⁺, Cl⁻, UA and Cr). There was no significant difference in urea, K⁺, Na⁺, and Cl⁻ and UA levels compared with the control. However, there was a significant increase on Cr level compared with the control.

3.4 Effect of Sub-chronic Administration of MSEEC on Hematological Parameters

The effect of sub- chronic administration of MSEEC on hematological parameters (Table 3)

showed no significant difference on the levels of (PCV, HB, RBC, MCHC, WBC, MCH, MCV, PLT, MONO, NEUT and LYMP) compared with control.

4. DISCUSSION

Medicinal plants have been used for centuries for human diseases because they contain

components of therapeutic value. Many traditional African plants are used in traditional medicine, but not all are documented. The fact that herbal medicines are natural does not mean that they do not contain toxic substances which could be dangerous when consumed by humans. Herbal medicine can also cause undesired effects. Therefore the common belief that

Table 1. Effect of Sub-chronic Administration of MSEEC on Liver Function parameters

Parameter	Distilled water (2ml/kg)	MSEEC 500mg/kg	MSEEC 1000mg/kg	MSEEC 1500mg/kg	MSEEC 2000mg/kg
AST(u/l)	10.60±0.24	10.20±0.37	9.20±0.37	10.20±0.37	9.80±0.37
ALT(u/l)	7.20 ± 0.20	6.80 ± 0.37	7.60 ± 0.55	8.40 ± 1.34	7.00 ± 1.00
ALP(u/l)	119.26 ± 1.99	120.48 ± 1.73	121.44 ± 0.84	109.82 ± 1.31	121.56 ± 0.36
TP(g/dl)	6.05 ± 0.20	6.30 ± 0.13	6.03 ± 0.11	6.79 ± 0.13	6.73 ± 0.03
ALB(g/dl)	4.74 ± 0.34	4.42 ± 0.13	5.01 ± 0.03	5.22 ± 0.10	5.00 ± 0.07
TB (umol/l)	5.05 ± 0.03	4.65 ± 0.02	4.67 ± 0.02	5.16 ± 0.02	5.08 ± 0.01
DB (umol/l)	3.26 ± 0.08	2.50 ± 0.12	3.14 ± 0.01	2.95 ± 0.02	3.52 ± 0.01

Values are expressed as Mean ± SEM. (n = 5) *significantly different compared to control group (P<.05). MSSEEC-Methanol Stem Bark Extract of *E. camaldulensis*.

Table 2. Effect of sub-chronic administration of MSEEC on kidney indices

Parameter	Distilled water (2ml/kg)	MSEEC 500mg/kg	MSEEC 1000mg/kg	MSEEC 1500mg/kg	MSEEC 2000mg/kg
UREA (mmol/l)	5.12±0.27	5.08±0.33	4.72±0.28	5.36±0.29	6.19±0.06
K ⁺ (mmol/l)	5.11±0.18	4.96±0.12	5.05±0.08	4.18±0.23	4.78±0.20
Na ⁺ (mmol/l)	138.47±0.85	140.40±0.25	139.12±0.70	138.41±0.94	141.80±1.19
Cl ⁻ (mmol/l)	107.68±1.91	112.80±1.28	109.60±0.60	107.50±1.30	113.73±1.03
Cr(umol/l)	42.60±0.88	43.92±0.42	47.30±0.29*	55.96±0.25*	50.54±0.20*
UA(Mmol/l)	4.88±2.16	5.56±0.24	4.86±2.13	5.45±0.67	5.34±1.08

Values are expressed as Mean ± SEM. (n = 5) *significantly different compared to control group (P<.05). MSSEEC-Methanol Stem Bark Extract of *E. camaldulensis*.

Table 3. Effect of Sub-chronic Administration of MSEEC on Hematological parameters

Parameter	Distilled water (2ml/kg)	MSEEC 500mg/kg	MSEEC 1000mg/kg	MSEEC 1500mg/kg	MSEEC 2000mg/kg
PCV (%)	41.44 ± 0.86	41.14 ± 0.72	39.52 ± 0.26	40.45 ± 0.35	41.18 ± 0.32
HB (g/dl)	12.54 ± 0.41	12.62 ± 0.34	11.54 ± 0.22	11.90 ± 0.31	11.74 ± 0.27
RBC (μ/l)	6.58 ± 0.14	6.57 ± 0.14	6.35 ± 0.18	5.84 ± 0.10	6.50 ± 0.91
WBC (μ/l)	7.62 ± 0.37	8.12 ± 0.12	7.83 ± 0.40	6.44 ± 0.25	6.70 ± 0.17
MCH (pg)	18.32 ± 0.04	17.66 ± 0.13	18.04 ± 0.38	18.38 ± 0.10	18.28 ± 0.18
MCHC(g/dl)	29.78 ± 0.68	29.70 ± 0.68	28.48 ± 0.40	28.16 ± 0.25	29.48 ± 0.78
MCV (fL)	54.66±0.06	53.50±0.36	54.73±0.55	53.44±0.34	54.28±0.43
NEUT (%)	18.36±2.01	17.99±3.02	18.49±2.35	18.22±2.34	17.83±2.56
LYMP (%)	66.28±1.63	64.58±3.78	65.98±2.34	66.33±2.76	64.57±3.54
MONO (%)	5.30±1.44	4.80±1.20	5.50±1.30	5.12±1.34	5.03±1.55
PLT(X103/μl)	702.11±11.23	711.02±23.11	698.53±21.11	706.45±34.12	678.34±11.45

Values are expressed as Mean ± SEM. (n = 5) *significantly different compared to control group (P<.05). MSSEEC-Methanol Stem Bark Extract of *E. camaldulensis*.

anything “natural is safe” is not correct [5]. Many herbal additives have some toxic side effects, and may be fatal in some doses. Toxicity related to herbal medicine is becoming more widely recognized as these remedies become popular in most parts of the world [6]. The toxic effect of herbal medicine ranges from allergic reactions to cardiovascular, hepatic, renal, neurological and dermatological toxic effects [7]. The increasing use of plant extracts in the food, cosmetics and pharmaceutical industries suggest that in order to find active compounds, a systematic study of the medicinal plants is important. Therefore plants should be investigated for better understanding of their properties, safety and efficiency [8].

The acute toxicity study of *E. camaldulensis* was found not to be acutely toxic because there was no mortality recorded even at the highest dose of 5000mg/kg bodyweight, thus indicating the safety of the extract [9], although there were visible signs of fatigue, shortness of breath, loss of appetite with consequent reduction in feeding (anorexia) and decreased activity in the first 24 hours. All these signs were reversed on the second day and the animals remained normal thereafter.

Elevated liver enzymes indicate inflammation or damage to cells in the liver [10]. Inflamed or injured liver cells may leak higher than normal amounts of certain chemicals, including liver enzymes, into the bloodstream, resulting in elevated liver enzymes on blood tests [10]. The specific elevated liver enzymes most commonly found are: Alanine Amino transferase (ALT) and Aspartate transaminase (AST).

In most cases, liver enzyme levels are elevated mildly and temporarily. Most of the time, elevated liver enzymes don't signal a chronic, serious liver problem. Low levels of ALT are normally found in the blood. But when the liver is damaged or diseased, it releases ALT into the bloodstream, which makes ALT levels go up. Most elevated ALT levels are caused by liver damage. In this study, there was no significant difference ($P < .05$) between ALT activities in the control and test groups. Similarly, the activities of AST in the control and test groups were not significantly different. AST levels fluctuate in response to the extent of cellular necrosis (cell death) and therefore may be temporarily and minimally elevated early in the disease process, and extremely elevated during the most acute phase. Depending on when the initial sample was drawn, AST levels can rise indicating increasing

disease severity and tissue damage or fall indicating disease resolution and tissue repair. Thus, the relative change in AST values serves as a reliable monitoring mechanism [10].

The extract of *Eucalyptus camaldulensis* (stem bark) does not cause any significant increase ($P < .05$) in serum ALP level. The alkaline phosphatases (ALPs) constitutes a large group of isoenzymes that play important roles in the transport of sugar and phosphates and are derived primarily from liver and bones (Schwartz and Garrison, 2008). Though ALP is present in the liver only in small quantities, the enzyme is secreted into the bile and substantial elevation of serum ALP is seen with mild intrahepatic or extrahepatic biliary obstruction [10] and early bile duct abnormalities leads to elevated ALP even before increases in serum bilirubin is observed, while bilirubin is a breakdown product of haemoglobin derived from senescent red blood cells [11] and because some bilirubin are also excreted into the bile (Schwartz and Garrison, 2008) its level rises in hepatobiliary obstruction secondary to gallstone or malignancy [11]. Hepatic damage involving the bile canalicular systems is referred to as cholestatic injury and is described as disturbance of the subcellular actin filaments around the canaliculi which prevent the movement of bile through the canaliculi system [12].

The inability of the liver to remove bile causes intrahepatic accumulation of toxic bile acids and excretion products [13]. There were no significant ($P < .05$) changes in total protein in rats treated with the plant extract, which may likely indicate that there was no sign of impaired liver synthetic function. Total protein measurements can reflect nutritional status and may be used to screen for and help diagnose kidney and liver diseases and many other conditions. [14]. Albumin is quantitatively the most important protein in plasma synthesized by the liver and is useful indicator of hepatic function. Albumin synthesis is affected not only in liver diseases but also by nutritional status, hormonal balance and osmotic pressure [15]. The result of this study have revealed no significant difference ($P < .05$) in the serum albumin and total protein of the extract treated groups as compared to the control. Bilirubin is a useful index of the excretory function of the liver. However, there was no significant difference in bilirubin levels of the treated groups compared to the control group.

Serum concentrations of Electrolytes, urea and creatinine could give an insight into the effect of the plant extract on the tubular and or glomerular part of the kidney. There was no significant difference ($P < .05$) observed on the levels of K^+ , Na^+ , Cl^- , uric acid and Urea when compared with the control group. This indicates that the kidney was not affected by the extract in terms of maintaining the electrolyte balance. However, there was a significant increase in creatinine levels (group 3, 4 and 5) when compared with the control group. This may be indicative that the extract may have adverse effect on the clearance profile of the kidney. This assertion may be due to the fact that creatinine is usually a more accurate marker of kidney function than urea. Although elevated levels of creatinine and urea are positive risk of renal impairment, a lower blood level of creatinine does not indicate impairment [16].

Assessment of hematological parameters can be used to determine the extent of deleterious effect of foreign compound including plant extract on blood. It can also be used to explain blood relating functions of chemical compound/plant extract. Such laboratory investigations have been reported to be highly sensitive, accurate and reliable and it remains the bedrock of ethical and rational research diseases diagnosis, prevention and treatment [17]. Administration of methanol stem bark extract of *Eucalyptus camaldulensis* to rats for 28 days did not produced any significant difference ($P < .05$) on hematological parameters PCV, WBC, HB, RBC, MCHC, MCH, MCV, PLT, LYMP, MONO, and NEUT when compared to control. These results suggest that the plant extract has no effect on erythropoiesis and leucocytosis [18].

5. CONCLUSION

The results from this study indicate that the administration of methanol stem bark extract of *Eucalyptus camaldulensis* did not produce significant toxic effect. From the acute and sub chronic toxicity studies carried out, *Eucalyptus camaldulensis* can be used in for varied medicinal purposes as it did not exhibit adverse effects on the albino rats. These findings support its safe ethno medicinal use.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as

specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee

DISCLAIMER

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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