Acute and Subacute Toxicological Study of the Aqueous Extract of the Stem Bark of *Khaya Grandifoliola* (Meliaceae) in Wistar Rats

D.S.M. Essama¹*, G.L.N. Otto², G.E. Enow³, P. Amand⁴, P.V. Tan¹

¹Department of Animal Biology and Physiology, Faculty of Sciences, University of Yaoundé I, P.O. Box 812, Yaoundé, Cameroon.
²Department of Life Science, Higher Teachers’ Training College, University of Ngaoundéré, P.O. Box 652, Bertoua, Cameroon.
³Regional Hospital of Bafoussam, P.O. Box 980, Bafoussam, Cameroon.
⁴Department of Biological Sciences, Faculty of Science, University of Maroua, Maroua, P.O. Box 814, Cameroon.

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**ABSTRACT**

This study was carried out to investigate the possible toxic effects of the water extract from *Khaya grandifoliola* stem bark in Wistar rats. The acute assay used 9 females distributed into 3 groups of 3 rats each. A control group received distilled water and the two test groups received by oral gavage a unique dose of the extract at 2000 mg/kg. In subacute assay, 60 rats both sexes were distributed into 6 groups of 10 rats each (5 males and 5 females) and received the extract by oral gavage for 28 days consecutively. The tests groups received extract at 250, 500 and 1000 mg/kg. The controls and satellite test groups were realized. LD₅₀ was superior to 2000 mg/kg in acute assay. In subacute toxicity assay, *Khaya grandifoliola* stimulated the haematopoetic and immune function, showed a significant decrease of alanine transaminase, aspartate transaminase and hypocholesterolaemic effects. Histopathology showed the presence of disturbances at the dose of 1000 mg/kg especially. *K. grandifoliola* stem bark could possess moderate toxicity at high doses and adequate caution should be exercised in its use in ethnomedicine.

1. Introduction

Plants which are commonly used in traditional medicine are frequently promoted as natural and, therefore, harmless. This assessment is based on their usage in the treatment of diseases over centuries [1, 2]. The increasing cost, non-availability of modern drugs and limited access to adequate health care have compelled about 80 % of the world population to use traditional pharmacopoeia for primary health care [3]. Therefore, it should be emphasized that the traditional use of any plant for medicinal purposes, by no means, guarantees the safety of such plant. This raises concern about the potential toxic effects resulting from the short-term and long-term use of such medicinal plants. The data of the acute and subchronic toxicity studies on medicinal plants or preparations derived from them should be obtained in order to increase the confidence in their safety to humans, particularly for use in the development of pharmaceuticals [4]. Consequently, in response to public health concerns, research that focuses on deficiencies in the knowledge about medicinal plants and their potential toxicities is highly encouraged by many official medical and scientific organizations [5, 6] and by complementary and alternative medicine (CAM) researchers and practitioners [7]. Therefore, evaluating the toxicological effects of any medicinal plant extract intended to be used in animals or humans is a crucial part of its assessment for potential toxic effects.

*Khaya grandifoliola*, family of Meliaceae, also called African mahogany, Benin Mahogany, Large-leaved Mahogany, or Senegal Mahogany. It is found in Benin, The Democratic Republic of the Congo, Ivory Coast, Ghana, Guinea, Nigeria, Sudan, Cameroon, Togo and Uganda. It is used in the form of concoction for the treatment of convulsion, cough, stomach ache, fever, threatened abortion, rheumatism, dermatomyositis and malaria fever in Nigeria [8-10]. The stem bark of this plant has been scientifically evaluated for some activity. The anti-malaria activity of the stem bark was reported [11-14]. The stem bark was also found to possess anti-inflammatory property [15], antimicrobial potentials against both gram positive and gram negative bacteria especially on some resistant strains of *Staphylococcus* [16], anti-inflammatory activity [17], anti-anemic [18, 19], hypoglycaemic, hyporoteinaemic and hypochondroselective effects [20]. *Khaya grandifoliola* extract was also reported as possessing the antioxidant activity and hepatoprotective effect [21, 22]. The phytochemicals tests showed the presence of limonoids, saponines, tannins, alkaloids, anthraquinones, flavonoids, reducing sugars and phlobatannins in these plants [23-25]. Proximate analysis showed that carbohydrate and proteins were higher in *K. grandifoliola*, and lower concentration of minerals such as magnesium, calcium, sodium, potassium, magnesium, iron and manganese [23]. In spite of the wide ethnotherapeutic applications of the plant, there is no literature information related to the safety limits of *Khaya grandifoliola* aqueous extract in traditional medicine. Thus, in the present study, we evaluated the oral acute and subacute toxicity of the water extract of the aerial parts of *K. grandifoliola* in rats.

2. Experimental Methods

2.1 Plant Material

The plant material, fresh stem bark *Khaya grandifoliola*, was collected in Mbockam village (Jaktiri) in the North-West Region of Cameroon (6° 06' North and 10° 39' East). Botanical identification was done at the National Herbarium in Yaoundé by comparison with existing herbarium specimen No. PM 09/95/95.

2.2 Animals

Adult female Wistar rats (140-150 g) were used for acute toxicity and young Wistar rats of both sexes (85-90 g) were used for subacute toxicity. The female rats were nulliparous and non-pregnant. The animals were raised in the Animal house of the Animal Physiology Laboratory, Faculty of Science, University of Yaoundé I. They were fed with a standard laboratory diet and tap water ad libitum. Each cage contained 3 to 5 rats of the same sex with a bedding of wood shavings, and natural day/night cycles were provided. Environmental conditions were maintained at a temperature of 26 °C ± 2 °C and a relative humidity of 60% ± 10%. Prior
2.3 Preparation of Plant Extract

The dried ground stem bark was extracted in water by boiling 1 kg in 5 liters of water for 2 minutes. The fresh stem bark of K. grandifoliola was cut, dried and ground to a powder. One kilogram of dried material was boiled in 5 liters of distilled water for 30 minutes. The extract solution was filtered through Whatman filter paper No. 3. The resulting filtrate was evaporated at 40 °C using a ventilated oven (Jencons-PLS, UK) to obtain 66.35 g of a red powder. The extract re-dissolved readily in distilled water which was used as the vehicle.

2.4 Acute Toxicity Study

Acute toxicity assay was carried out according to the Organization of Economic Co-operation and Development (OECD) guideline No. 423 for testing of chemicals [26]. The overnight fasted (water ad libitum) female rats were divided into 3 groups of 3 animals each. Animals in the control group received distilled water. The first test group received by oral gavage a single dose of the extract at 2000 mg/kg and the second test group (the confirmation group), received the same dose of extract 48 hours later. Neither food nor water was given up to 4 h after extract administration and the animals were observed closely during this time for any toxicity manifestations. Body weight change, signs of toxicity, behavior and mortality were observed for the initial 24 h after extract administration and once daily for 14 days. At the end of the experimental period, all rats were sacrificed using an overdose of ether. The animals were quickly dissected and the liver, kidneys, stomach, spleen, lungs, heart and ovaries were excised, weighed and prepared for gross anatomy.

2.5 Subacute Toxicity Study

The repeated doses (28 days) procedure for oral toxicity study was carried out in rats according to the OECD test guideline No. 407 [27]. Sixty rats of both sexes were distributed into 6 groups of 10 rats each (5 males and 5 females) as follows: Control group I and II received distilled water, while Groups III to Group VI received, respectively, 250, 500, 1000 and 2000 mg/kg of extract daily for 28 days. The animals were fasted overnight (water ad libitum) during the treatment period and once daily for 14 days. At the end of the experimental period, all rats were sacrificed and the liver, kidneys, stomach, spleen, lungs, heart and ovaries were excised, weighed and prepared for gross anatomy.

Statistical analysis was done by one-way analysis of variance (ANOVA) followed by the Dunnett’s test for multiple comparisons and p values less than 0.05 were considered as significant. The results are expressed as mean ± standard error of mean (S.E.M.).

3. Results and Discussion

3.1 Acute Toxicity

The limit dose of 2000 mg/kg did not cause death or any toxic signs in treated rats (females). All rats were normal throughout the study and survived until the end of the 14-days experimental period. No behavioral changes such as tremor, convolution, self-mutilation, salivation, lethargy or sleep were observed during the first four hours. No change in body condition and reactivity to noise and touch were observed. The eating and drinking habits of all the animals remained normal, and there were no significant differences in body and organs weights of rats treated with the extract compared with the controls. Macroscopic examination did not reveal any changes in organ condition.

3.2 Subacute Toxicity

No behavioural changes (in locomotor activity, no ataxia, and no signs of intoxication) and death were observed at the end of the treatment period. Similarly, no significant differences in food intake and weight gain (Table 1) were observed between control and treated groups during this period. The relative organs weights showed no significant differences between treated and control groups (Table 2). The macroscopic observation of the target organs (liver, lung, heart, spleen, kidney and sex organs) of the treated animals did not show significant changes in color and texture when compared with the controls.

### Table 1 Effects of K. grandifoliola on the body weight (g) in subacute assay

| Dose (mg/kg) | Day 1 | Day 7 | Day 14 | Day 21 | Day 28 | Day 35 | Day 42 |
|-------------|-------|-------|--------|--------|--------|--------|--------|
| **Male**    |       |       |        |        |        |        |        |
| Control I   | 131.9 ± 9.72 | 145.3 ± 8.01 | 156.2 ± 8.07 | 175.3 ± 10.6 | 180.8 ± 11.3 | -      | -      |
| Control II  | 151.1 ± 11.3 | 180.4 ± 12.2 | 189.1 ± 12.4 | 195.8 ± 11.0 | 210.3 ± 12.7 | 219.6 ± 13.2 | 225 ± 12.2 |
| Group III   | 147.7 ± 8.00 | 155.0 ± 6.55 | 174.6 ± 0.23 | 183.1 ± 0.92 | 195.1 ± 0.87 | -      | -      |
| Group IV    | 141.0 ± 13.4 | 152.1 ± 13.8 | 163.4 ± 15.9 | 177.4 ± 19.7 | 186.7 ± 18.4 | -      | -      |
| Group V     | 149.2 ± 10.3 | 160.5 ± 0.83 | 169.5 ± 0.68 | 178.4 ± 0.63 | 174.6 ± 0.91 | -      | -      |
| Group VI    | 131.1 ± 15.7 | 158.7 ± 18.8 | 162.3 ± 18.9 | 175.2 ± 1.75 | 186.8 ± 15.8 | 203.6 ± 15.9 | 211 ± 14.4 |
| **Female**  |       |       |        |        |        |        |        |
| Control I   | 118.0 ± 6.2 | 123.2 ± 7.3 | 130.1 ± 6.2 | 141.3 ± 9.3 | 151.8 ± 8.5 | -      | -      |
| Control II  | 101.5 ± 2.2 | 124.7 ± 2.2 | 136.9 ± 2.2 | 143.1 ± 1.7 | 157.0 ± 1.9 | 166.7 ± 5.9 | 166.6 ± 9.0 |
| Group III   | 119.2 ± 5.4 | 130.8 ± 5.2 | 140.8 ± 5.8 | 154.3 ± 5.8 | 169.0 ± 4.7 | -      | -      |
| Group IV    | 124.6 ± 7.9 | 126.9 ± 7.7 | 134.4 ± 9.4 | 144.5 ± 7.0 | 157.2 ± 6.4 | -      | -      |
| Group V     | 132.0 ± 4.7 | 142.0 ± 4.6 | 147.3 ± 4.4 | 154.1 ± 5.4 | 162.5 ± 3.0 | -      | -      |
| Group VI    | 1064.6 ± 6.3 | 125.1 ± 7.6 | 127.9 ± 8.3 | 134.1 ± 9.8 | 141.1 ± 10 | 151.8 ± 10.8 | 153.6 ± 1.0 |

Values are expressed as mean ± S.E.M. (n=5)
### Table 2: Effects of K. grandifoliola on the relative organ weights (g/100 g of b.w.) in subacute assay

|                     | Control I | Control II | 250 mg/kg | 500 mg/kg | 1000 mg/kg | 1000 mg/kg |
|---------------------|-----------|------------|-----------|-----------|------------|------------|
| Heart               |           |            |           |           |            |            |
| Lungs               | 0.35 ± 0.02 | 0.32 ± 0.01 | 0.35 ± 0.01 | 0.35 ± 0.02 | 0.34 ± 0.01 | 0.33 ± 0.03 |
| Liver               | 0.93 ± 0.12 | 0.86 ± 0.06 | 0.77 ± 0.06 | 1.12 ± 0.16 | 0.90 ± 0.13 | 0.91 ± 0.04 |
| Spleen              | 2.86 ± 0.13 | 2.71 ± 0.18 | 2.79 ± 0.15 | 2.94 ± 0.08 | 2.71 ± 0.25 | 2.88 ± 0.15 |
| Kidneys             | 0.79 ± 0.04 | 0.82 ± 0.04 | 0.86 ± 0.03 | 0.88 ± 0.05 | 0.90 ± 0.02 | 0.85 ± 0.05 |
| Testis/Ovaries      | 0.41 ± 0.08 | 0.33 ± 0.02 | 0.46 ± 0.03 | 0.36 ± 0.02 | 0.29 ± 0.00 | 0.31 ± 0.03 |

### Table 3: Effects of K. grandifoliola on hematological parameters in subacute toxicity

|                     | Control I | Group I | Group II | Group III | Control II | Group IV |
|---------------------|-----------|---------|----------|-----------|------------|----------|
| RBC (10^6/μl)       | 5.83 ± 0.06 | 7.62 ± 0.16* | 6.38 ± 0.17 | 5.83 ± 0.60 | 5.48 ± 0.08 | 5.04 ± 0.36 |
| WBC (10^3/μl)       | 4.27 ± 0.09 | 3.05 ± 0.03 | 3.5 ± 0.67 | 3.57 ± 0.28 | 4.67 ± 0.13 | 4.57 ± 0.09 |
| Lymphocyte (%)      | 90.1 ± 0.06 | 86.53 ± 1.42 | 79.37 ± 5.14 | 82.47 ± 5.38 | 90.7 ± 0.94 | 93.7 ± 1.91 |
| Monocyte (%)        | 6.8 ± 0.06 | 6.57 ± 0.72 | 10.10 ± 1.78 | 10.13 ± 2.95 | 6.13 ± 0.09 | 6 ± 0.81 |
| Platelets (10^3/μl) | 3.2 ± 0.09 | 6.9 ± 0.12** | 10.5 ± 1.11*** | 10.0 ± 0.8*** | 3.2 ± 0.21 | 4.67 ± 0.55 |
| Normolysis (%)      | 590.4 ± 0.6 | 546.7 ± 7.70 | 462.7 ± 45.5 | 397.8 ± 399 | 545 ± 843* | 534 ± 854* |
| Hb (g/dL)           | 13.4 ± 0.13 | 9.3 ± 1.37 | 11.23 ± 1.34 | 13.73 ± 0.02 | 8.53 ± 2.4 | 13.17 ± 0.74 |
| Hct (%)             | 32.8 ± 0.06 | 48.0 ± 4.97* | 36.27 ± 2.30 | 34.57 ± 2.11 | 31.86 ± 1.62 | 34.09 ± 2.92 |
| MCHC (g/dL)         | 23.57 ± 0.03 | 18.47 ± 0.72 | 20.13 ± 1.8 | 24.37 ± 2.05 | 23.6 ± 0.04 | 31 ± 0.78** |
| MCH (pg)            | 55.7 ± 0.33 | 65.67 ± 5.49 | 85.67 ± 17.33 | 53.67 ± 3.76 | 71.46 ± 6.66 | 705 ± 3.75 |
| MCV (fL)            | 5.83 ± 0.06 | 7.26 ± 0.16* | 6.38 ± 0.17 | 5.83 ± 0.60 | 5.48 ± 0.08 | 5.04 ± 0.36 |

### Table 4: Effects of K. grandifoliola on biochemical parameters in subacute toxicity

|                     | Control I | Group I | Group II | Group III | Control II | Group IV |
|---------------------|-----------|---------|----------|-----------|------------|----------|
| ALAT (IU/L)         | 55.95 ± 10.49 | 40.47 ± 3.38 | 34.68 ± 3.54 | 11.70 ± 4.42** | 73.20 ± 44.3 | 95.15 ± 38.45 |
| ASAT (IU/L)         | 195.10 ± 2.74 | 156.30 ± 9.32 | 149.20 ± 22.50 | 117.80 ± 22.99* | 208.8 ± 13.2 | 268.20 ± 24.13 |
| Total Chol (mg/dL)  | 91.82 ± 1.54 | 111.40 ± 7.86 | 81.02 ± 6.51 | 85.03 ± 3.77 | 119.6 ± 14.3 | 99.38 ± 5.71 |
| Triglyceride (mg/dL)| 48.80 ± 0.61 | 53.40 ± 0.67 | 53.2 ± 1.17 | 54.71 ± 10.14 | 48.17 ± 2.48 | 39.2 ± 6.64 |
| HDL-Chol (mg/dL)    | 51.52 ± 4.68 | 72.75 ± 3.57* | 45.68 ± 0.96 | 45.30 ± 7.81 | 41.87 ± 5.21 | 48.9 ± 4.91 |
| LDL-Chol (mg/dL)    | 30.52 ± 5.10 | 28.09 ± 4.97 | 28.87 ± 4.81 | 30.79 ± 9.00 | 63.52 ± 11.4 | 42.59 ± 6.80 |
| Atherogenic index   | 1.84 ± 0.21 | 1.53 ± 0.04 | 1.78 ± 0.16 | 1.66 ± 0.11 | 2.59 ± 0.20 | 2.06 ± 0.19 |
| Creatinine (mg/dL)  | 0.87 ± 0.20 | 0.36 ± 0.06 | 0.34 ± 0.03 | 0.50 ± 0.10 | 0.65 ± 0.20 | 0.60 ± 0.23 |
| Total bilirubin (mg/dL) | 1.38 ± 0.44 | 1.21 ± 0.09 | 0.89 ± 0.33 | 1.00 ± 0.08 | 3.51 ± 1.68 | 1.69 ± 0.63 |
| Total protein (mg/dL) | 1.90 ± 0.11 | 2.56 ± 0.11* | 1.88 ± 0.11 | 1.48 ± 0.17 | 2.03 ± 0.12 | 1.82 ± 0.53 |

Values are expressed as mean ± S.E.M. (n=5) **p<0.01; ***p<0.001; †††p<0.0001; statistically significant compared to Control I, *p<0.05; **p<0.01; ††p<0.001; statistically significant compared to control II, †††p<0.001; statistically significant compared to control II

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Hematological parameters such as WBC, HGB, lymphocyte, monocyte and MCH in both control and experimental rats, were not significantly different. Except granulocytes counts whose increase significantly in all the animals to treat of extract at different dose. Also, in male rats, platelet counts showed a significant increase at the dose of 250 mg/kg and 1000 mg/kg (group VI). At the same, the parameters like RBC, HCT and MCV also showed a significant increase at 250 mg/kg compared with the control (group I) and MCHC at the dose of 1000 mg/kg (group VI). In female, all the other parameters didn’t show a significant variation, except platelet counts that showed significant decrease at the dose 1000 mg/kg (Table 3).

The results of biochemical parameters in rats treated with various doses of the aqueous extract of K. grandifoliola for 28 days are shown in Table 4. In the extract-treated rats, the parameters like ALAT and ASAT decrease significantly only at the dose 1000 at the males; while at the females, ALAT decrease very significantly at all the dose and ASAT only at the dose of 250 mg/kg of K. grandifoliola respectively. The male rats showed at the dose of 250 mg/kg a light increase of HDL-cholesterol and total protein values, while the female showed a significant decrease of triglycerides (at the dose of 1000 mg/kg of extract) and LDL (at the dose of 500 and 1000 mg/kg).

Histology of the lung sections of control rats and of all the extract-treated groups revealed a normal architecture with bronchioles, thin-walled alveoli and alveolar sacs. At dose 250 mg/kg, the male and female lung shown any reactive lesion at this dose. Female lung shows alveolar coalescence and male lung shows congestion shown by dilated blood–filled vessels is present in the lungs of animals at 500 mg/kg dose. At 1000 mg/kg dose, lung congestion persists and is exaggerated and complicated by interstitial hemorrhagic foci in both sexes. There is a marked reversal of congestion and hemorrhage to near normal in male and female lungs with satellite control at 1000 mg/kg dose (Figs. 1 and 2).

Histology of the liver sections of control (I & II) rats showed normal hepatic architecture and normal liver lobular structure with portal triad, prominent nucleus and well-preserved cytoplasm. At 250 and 500 mg/kg dose no effect on the lesions in the liver. The 1000 mg/kg dose shown centrilobular chronic persistent inflammatory reaction is seen in the liver in both sexes by presence of inflammatory cells limited by limiting plates to the centrilobular area. Satellite control reverses the pathological changes in the liver of the both sex at 1000 mg/kg dose, because has no effect on the lesions in the liver at 1000 mg/kg dose (control II) (Figs. 1 and 2). There are no significant histological lesions observed in the kidney of both male and female rats at 250, 500 and 1000 mg/kg doses (Figs. 1 and 2).

Toxicological investigation of an unknown substance. The index for the acute toxicity is the LD50. The results in this study showed that the acute administration of the aqueous extract of K. grandifoliola at the dose of 2000 mg/kg did not produce any sign of acute toxicity or instant death in rats tested during the period of observation. This, however, suggest that the LD50 of the extract is greater than 2000 mg extract/kg of body weight. There were no significant differences in organ and body weights in the extract-treated groups compared with the control. In line with the chemical labelling and classification of acute systemic toxicity. The aqueous extract of K. grandifoliola can be assigned to the lowest toxicity class (class 5; no label; unclassified) [26] and to be considered nontoxic at acute administration since the extracts were well tolerated and there was no observed adverse effect.

Acute toxicity data are of limited clinical application since cumulative toxic effects do occur even at very low doses. Hence multiple dose studies are almost always essential in evaluating the safety profile of phytomedicines. Thus, sub-acute toxicity study was carried out for evaluation of long-term effects of the water extract of K. grandifoliola. The study revealed that no adverse clinical sign or toxicity sign or death was observed throughout the treatment duration of 28 days in the rats. This is in line with the acute toxicity studies where experimental animals treated orally with the extract doses up to 2000 mg/kg body weight showed

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neither toxicity sign nor death in mice. This may be an indication that long-term administration of the extract will not result in toxicity. Changes in body weight (especially weight loss) have been used as an indicator of adverse effects of drugs and chemicals [29]. There were no significant changes in animal behaviour, food and water consumptions and in body weight gain in K. grandifoliola-treated group at any dosage. Macroscopic observation of the major organs showed no abnormalities in morphology, consistency and appearance in the rats treated for 28 days with the extract.

Assessment of hematological parameters can be used to determine the extent of deleterious effect of foreign compounds present in plant extracts on the blood constituents of an animal. It can also be used to explain blood relating functions of chemical compounds and plant extracts [30]. Such analysis is relevant to determine the evaluation of biological function and toxicity of a compound. Therefore, the increase in the size of RBCs is a sign that the extract has a haemopoietic activity and can be expected to exert therapeutic effects of this extract. The haemopoietic effects could also be the consequence of the hepatotoxicity of the extract. In fact, the liver is the main seat of the synthesis of blood cholesterol. Any violation of liver function may therefore inhibit the synthesis and subsequently reduce blood cholesterol levels. The increase (in this study not significantly at 1000 mg/kg dose) in RBCs may be due to the haemopoietic effects of the extract. The haemopoietic effects may be also be expected to exert therapeutic effects of this extract. The haemopoietic effects could also be the consequence of the hepatotoxicity of the extract. In fact, the liver is the main seat of the synthesis of blood cholesterol. Any violation of liver function may therefore inhibit the synthesis and subsequently reduce blood cholesterol levels. The increase (in this study not significantly at 1000 mg/kg dose) in RBCs may be due to the haemopoietic effects of the extract. The haemopoietic effects may be also be expected to exert therapeutic effects of this extract.

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