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Intraperitoneal and Oral Acute Toxicity Studies of Aqueous Leaf Extract of *Chrysophyllum Albidum* in Swiss Albino Rats

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Abstract

The acute toxicity of aqueous leaf extract of *Chrysophyllum albidum* was evaluated in Swiss albino rats. The rats were randomly distributed into four groups of three animals each for the first phase of treatment. The groups were respectively administered both intraperitoneally and orally aqueous leaf extract of *Chrysophyllum albidum* at 0, 10, 100 and 1000 mg/kg body weight in a single dose. In the second phase of the experiment for intraperitoneal administration, the albino rats were randomly distributed into four groups of three animals each and the groups were administered single doses of the extract at 0, 1000, 2900 and 5000mg/kg body weight. For oral administration, the rats were also divided into four groups of 3 animals each and were administered single doses of the extract at 0, 1600, 2900 and 5000 mg/kg body weight and monitored frequently for 24h and 14 days respectively in both phases. The number of deaths in each group was recorded. The intraperitoneal LD50 of the aqueous leaf extract of *Chrysophyllum albidum* was calculated to be 1265 mg/kg. The results indicate that the extract may be very toxic at a high dose and short term exposure when administered intrapeitoneally. For the oral intubation, no mortality was observed in the albino rats. All the animals showed a positive gain in body weight throughout the study. The oral LD50 of aqueous leaf extract of *Chrysophyllum albidum* was estimated to be above 5000 mg/kg body weight and the plant extract was said to be safe and non-toxic when taken through the oral route.

Keywords: *Chrysophyllum albidum*; aqueous extract; albino rat; acute toxicity

Introduction

Generally, medicinal plants contain bioactive compounds which demonstrate both intra- and inter-species variation in type and content. Plants by virtue of their chemical constituents are potentially toxic; thus, some plants used in traditional medicine are intrinsically toxic. Some plants well known in traditional medicine to be toxic or poisonous include *Atropa belladonna*, *Datura spp*., *Digitalis spp*. [1].

Many plants used in traditional medicine or used as food have demonstrated some toxicity (mutagenic and carcinogenic) effects [2]. The issue of the possible toxic, genotoxic and/or mutagenic effects of plants used in traditional medicine has been highlighted in the review by Fennell et al. [3]. However, some of the toxic plants are useful to man as medicines and also as poisons for hunting and for use as pesticides, for example, Datura (tropane alkaloids), Digitalis (cardiac glycosides) and Pyrethrum (pyrethrin insecticides). Well-known medicinal plants have demonstrated toxicity in laboratory studies and field observations. For example, Lantana camara used in the management of malaria and other diseases has been reported to be hepatotoxic in several animal species which could be of concern regarding its chronic use in man. Similarly, Momordica charantia, a known anti-diabetic and anti-malarial plant but also used in Ghana as an abortifacient, has reportedly caused deadly hypoglycemia in children [4].

Chrysophyllum albidum, commonly known as African Star Apple belong to family sapotacea, a plant species commonly found throughout tropical Africa [5]. The roots, barks, fruit pulp and seeds of *albidum* have different medicinal uses. The bark of C. *albidum* has been used in treatment of yellow fever, fibroids and malaria while the leaf is used as emollient and for the treatment of skin eruption, stomach ache and diarrhea [6]. Okwu and Morahfni, 2007 suggested that [7]. *C. albidum* is used as therapeutic, antiseptic, antifungal, bacteriostatic agent due to the phenolic content in this plant. The antioxidants properties of *C. albidum* has improved health by protecting the body against harmful radical which has been implicated in the origin of many ailments or diseases such as cancer, cardiovascular diseases, diabetes mellitus, neural disorder and arthritis. Therefore, this present study is aimed at investigating the acute toxicity effects of aqueous leaf extract of *C. albidum* following oral and intraperitoneal administration in Swiss albino rats and the effects on their weight.

Materials and Method

Plant material and extract preparation

The leaves of *chrisophyllum albidum* were obtained from Eziobodo elu, Ihiagwa, Owerri, Imo State, Nigeria and identified by a Taxonomist, Dr. Faruwa Francis at the department of Forestry and Wildlife Technology, School of Agriculture and Agricultural Technology, Federal University of Technology Owerri (FUTO). The voucher number of the plant as deposited in the Herbarium section of the department of Forestry and Wild life is FUTO/FWT/HERB/2021051.

The leaves of *Chrysophyllum albidum* were air dried under the shade, inside the laboratory for four weeks and blended into powdered form. The powdered sample was stored in airtight polythene bags to protect the sample from sunlight. The aqueous extract of the leaf powder was prepared by quantitative extraction i.e. 100g of this powder was soaked in 800 ml of methanol in a 1000 ml conical flask sealed air tightly with cotton wool and foil for 72 hours and thereafter filtered

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with whatman no 1 filter paper. The decoction liquid obtained was concentrated in a water bath at 45°C to produce a semi solid residue. The extract was stored in the refrigerator at 40c until it was used for evaluation.

Experimental animals

The male Swiss albino rats used for the acute toxicity study of African Star Apple (*Chrysophyllum albidum*) were purchased from the Department of Vertinary Medicine, Michael Okpara University of Agriculture Umuahia, Abia state. The rats which weighed between 60-100 grams were used and maintained under laboratory conditions; humidity, temperature (23-25°C) and light 12 hrs light/ dark cycle. They were kept in standard cages in the animal house of the Department of Biochemistry, Federal University of Technology Owerri, Imo State. The animals were allowed to acclimatize for two weeks before commencement of the acute toxicity study, and were fed with commercial feed (Vital Grower's Pellets) and tap water ad libitum. Meanwhile, they were fasted for about 12 hrs before the commencement of first and the second phases of the study.

Acute toxicity evaluation/determination of median lethal dose

The acute toxicity study of aqueous leaf extract of *Chrysophyllum albidum* was conducted in accordance with Lorke's method [8]. Two different routes of administration were used for this study, the intraperitoneal route of administration and the oral intubation. The method involved two phases for each route of administration.

For the first phase, 12 rats were randomly distributed into four groups of three animals each. The groups were respectively administered both intraperitoneally and orally single doses of leaf extract of *Chrysophyllum albidum* at 10, 100 and 1000 mg/kg body weight, the fourth group which was the control was administered normal saline only. The animals were observed closely for the first one hour and then every 30 minutes for the first 24 hours for the onset of any immediate signs of toxicity and daily during the 14 day observation period to record any delayed acute effects. During this period, their weights were recorded daily and clinical signs of toxicity such as loss of appetite, immobility, convulsion, etc. were observed. The mortality in each group were also recorded.

In the second phase of the experiment, 12 rats were also randomly distributed into four groups of three animals each. The groups were respectively administered both intraperitoneally and orally single doses of aqueous leaf extract of *Chrysophyllum albidum* at 1600, 2900 and 5000 mg/kg body weight, the fourth group which was the control was administered normal saline only. The second phase doses were chosen based on the result of the first phase treatment. The animals were observed frequently as previously described in the first phase and the mortality in each group were equally recorded. The surviving animals were weighed daily and monitored for two weeks for clinical signs of acute toxicity such as; writhing, gasping, palpitation increased or decreased respiration rate, loss of appetite, etc.

The result of the first and second phase of the experiment were used to calculate the LD50 of the plant extract. The LD50 was calculated according to the method outlined by Geometric mean of the highest dose for which there was no mortality X the lowest dose for which mortality occurred= X mg/kg [8].

Statistical analysis

All data generated during the course of the research were expressed as mean ± standard deviation (SD) and analyzed statistically by analysis of variance (ANOVA). Means were compared using LSD post hoc test and differences between treatment and control groups accepted as significant at $p \leq 0.05$.

Results

Result of quantitative extraction

$$\% \text{ Plant yield} = \frac{\text{Weight of dry extract} \times 100}{\text{Weight of dry plant} \quad 1}$$

$$\% \text{ Plant yield} = \frac{21.7 \times 100 = 21.7\%}{100 \quad 1}$$

Results of the intraperitoneal acute toxicity evaluation of aqueous leaf extract of chrysophyllum albidum

In the first phase of treatment, rats intraperitoneally administered with the aqueous leaf extract of *Chrysophyllum albidum* did not develop any clinical sign of toxicity (loss of appetite, loss of stimuli sensitivity, loss of agility, change in the color of faces and convulsion) after 30 minutes of treatment period or during the post treatment period with 10 mg/kg, 100 mg/kg, and 100 mg/kg of the extract. There was no mortality in these groups immediately or during the 14 days of observation period (Table 1).

In the second phase of the experiment, rats administered with the aqueous leaf extract of Chrysophyllum albidum developed clinical sign of toxicity (loss of appetite, loss of stimuli sensitivity, loss of agility, and convulsion) after 20 minutes of treatment period and during the post treatment period with 1600 mg/kg, 2900 mg/kg, and 5000 mg/kg of the extract (Table 1). No clinical sign of toxicity or mortality was observed in the control groups injected with normal saline, either immediately or during post treatment period. In the second phase of treatment, two-third of the rats in the groups, 2900 mg/kg and 5000 mg/kg died while all the rats in the group, 1600 died after 24 hours of treatment (Table 1).

From the result of the intraperitoneal acute toxicity study of aqueous leaf extract of african star apple (*chrysophyllum albidium*), the intraperitoneal LD50 of the African star apple (*chrysophyllum albidium*) was calculated to be 1264 mg/kg using Lorke's formula;

$$\sqrt{\text{geometric mean of the maximal dose without mortality} \times \text{mean of the minimal dose with mo}}$$

LD50 of *Chrysophyllum albidum* = 1264 mg/kg

Figures 1, 2, 3 and 4 show the body weight distribution and changes of the animals treated with aqueous leaf extract of *Chrysophyllum albidum* and the control groups treated with normal saline only.

In the first phase of the treatment, a decrease in body weight

Table 1: Intraperitoneal Acute Toxicity Studies (Ld50) Aqueous Leaf Extract Of Chrysophyllum Albidum.

Plant	Experiment	Dose (mg/kg)	Proportion of death	
			After 24 hours	After 2 weeks
Chrysophyllum albidum (aqueous leaf extract)	Phase 1	10 100 1000 Control	0/3 0/3 0/3 0/3	0/3 0/3 0/3 0/3
Chrysophyllum albidum (aqueous leaf extract)	Phase 2	1600 2900 5000 Control	3/3 2/3 2/3 0/3	3/3 2/3 2/3 0/3

was observed during the first few days in the experimental animals treated with 10 mg/kg, 100 mg/kg and 1000 mg/kg of the extract when compared with the control which was seen as a clinical sign of toxicity. Subsequently there was a significant increase in body weight of the experimental animals when compared to the control, which was seen as a sign of recovery. This shows that aqueous leaf extract of *Chrysophyllum albidum* has potentials to support weight gain at the dosages given.

In the second phase of the treatment, a decrease in body weight was observed during the first few days in the experimental animals treated with 1600 mg/kg, 2900 mg/kg, 5000 mg/kg, of the extract when compared with the control. This was seen as a clinical sign of toxicity. Subsequently there was a significant increase in body weight of the experimental animals which survived when compared to the control, which was seen as a sign of recovery. This shows that aqueous leaf extract of *Chrysophyllum albidum* has potentials of supporting weight gain at the dosages given. (Figures 1-4)

Results Of The Oral Acute Toxicity Evaluation Of Aqueous Leaf Extract Of *Chrysophyllum Albidum*

The results of the oral LD50 determination of aqueous leaf extract of *Chrysophyllum albidum* is presented on table below. No mortality was recorded in both the control and the treated groups during the two phases of treatments. No clinical signs of toxicity were observed in all the animal groups during the phase one treatment. During the phase two treatments, the animals treated with 2900 mg/kg and 5000 mg/kg body weight of the plant extract showed signs of irritability and weakness after 1 hour of administration. However, the animals recovered within two hours. The lacks of mortality during the study indicate that the LD50 is above 5000 mg/kg body weight. (Table 2)

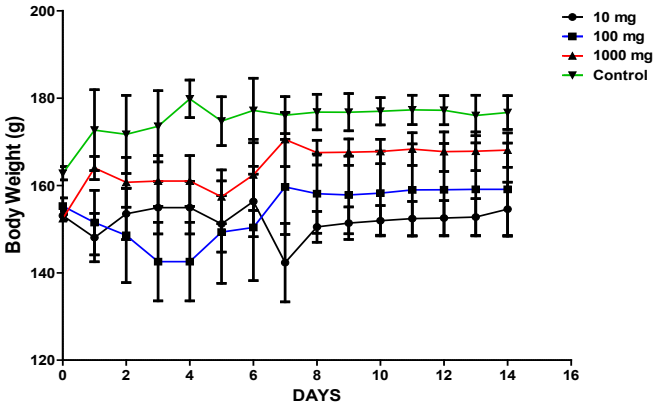

Figure 1: Body weight (g) distribution of animals in phase one administered intraperitoneally with 0, 10, 100, 1000 mg/kg body weight of aqueous leaf extract of *Chrysophyllum albidum.*

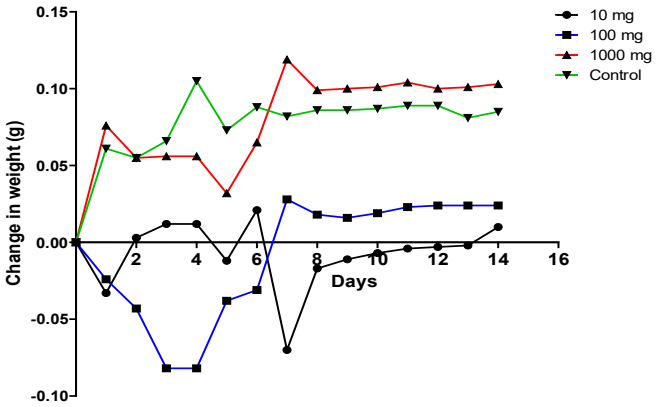

Figure 2: Change in body weights (g) of animals in phase one administered intraperitoneally with 0, 10, 100, 1000 mg/kg body weight of aqueous leaf extract of *Chrysophyllum albidum.*

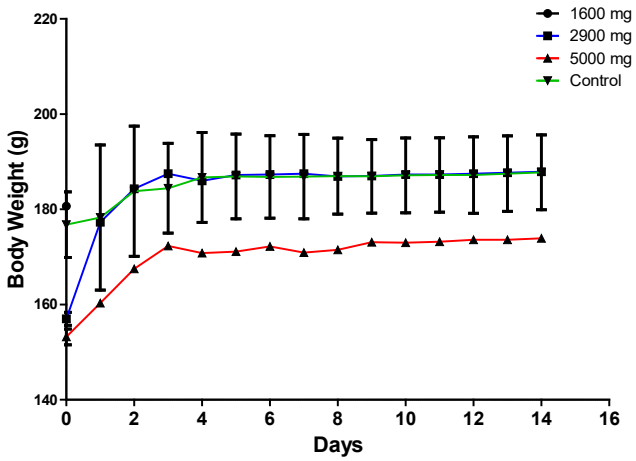

Figure 3: Body weight (g) distribution of animals in phase two administered intraperitoneally with 0, 1600, 2900, 5000 mg/kg body weight of aqueous leaf extract of *Chrysophyllum albidum.*

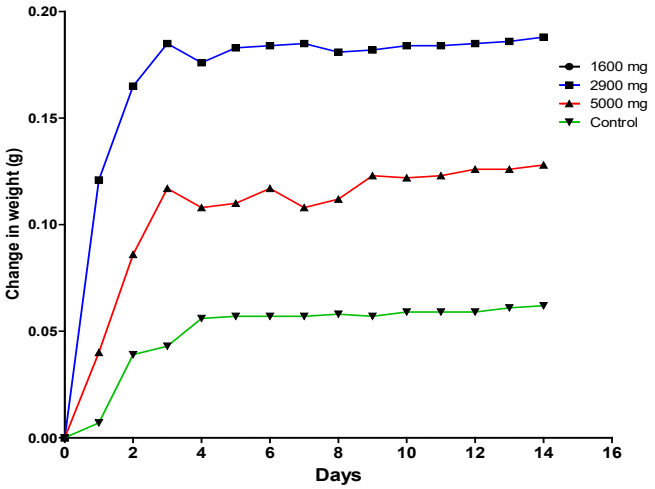

Figure 4: Change in body weight (g) of animals in phase two administered intraperitoneally with 0, 1600, 2900, 5000 mg/kg body weight of aqueous leaf extract of *Chrysophyllum albidum.*

The results of the 14 days weight measurement of the animals during the phase 1 is presented in figure 5. The change in body weight of the animals during the phase 1 is shown in figure 6. No significant changes ($p<0.05$) in body weights were observed among all the groups except on day 8. A significant difference in the body weight of the animals treated with 100 mg/kg body weight of the extract was observed when compared with the control animals on day 8. All the groups showed an increase and positive change in body weight during the first 8 days of measurement followed by a decline from day 8 to day 14 (Figure 6).

The body weight distributions of the animals in phase 2 are

Table 2: Oral Acute Toxicity (Ld50) Determination of Aqueous Leaf Extract of Chrysophyllum Albidum.

Experiment	Dose (mg/kg)	No of mortality
Phase 1	Control	0/3
	10	0/3
	100	0/3
	1000	0/3
Phase 2	Control	0/3
	1600	0/3
	2900	0/3
	5000	0/3

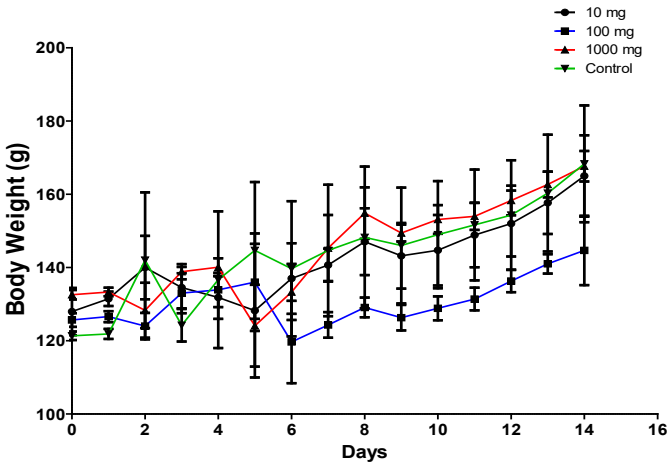

Figure 5: Body weight (g) distribution of animals in phase one administered orally with 0, 10, 100, 1000 mg/kg body weight of aqueous leaf extract of *Chrysophyllum albidum*.

presented in figure 7. There was a significant change ($p<0.05$) in the body weight of the treatment groups from day 6 to day 11 compared to the control animals. From day 12 to day 14, significant difference was only observed between the animals treated with 2900mg/kg body weight and the control group. The change in body weight of the animals during the phase 2 is shown in Figure 8. The groups treated with 1000mg/kg, and 5000 mg/kg body weight of the extract and the control group showed a positive change in body weight of the animals throughout the study. The group treated with 2900mg/kg body weight of the extract maintained a positive change in body weight until day 11 before declining to a negative change in body weight from day 11 to day 14 (Figure 8). (Figures 5-8)

Discussion

The toxicological evaluation of any plant extract helps in assessing the efficacy of the extract at different doses, to ensure the safety of its use and to determine the possible collateral effects of the extract [9]. Some factors such as the part of the plant, the age of the plant, route of exposure, genetic differences, amount of sunlight and soil quality that the plant has grown in, are capable of interfering with the toxicity of medicinal plant. The toxicity can be inherent in the plant or may happen during the process of extract preparation [10]. The toxicity of a plant could be attributed to its active components or not [11].

According to Egharevba, the presence of secondary metabolites in *Chrysophyllum albidum* may be responsible for its potential use as drug such as in the treatment of skin eruptions, diarrhea and stomach ache [5]. It has been recognized that therapeutic bioactive products from plants may also contain substances which act as poisons in humans. Several researches demonstrated that the sites and number of hydroxyl

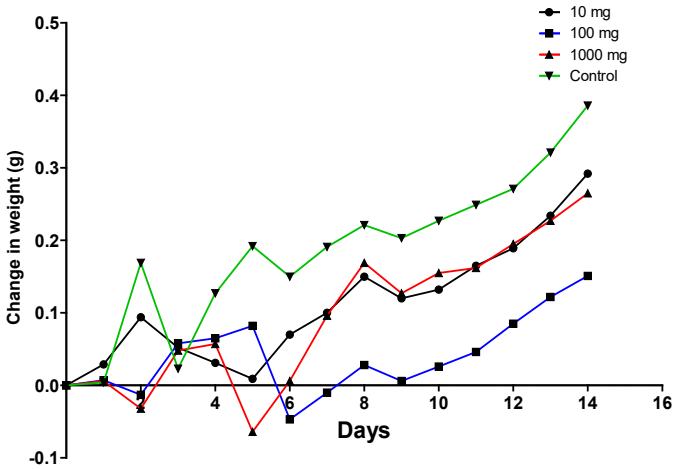

Figure 6: Change in body weights (g) of animals in phase one administered orally with 0, 10, 100, 1000 mg/kg body weight of aqueous leaf extract of *Chrysophyllum albidum*.

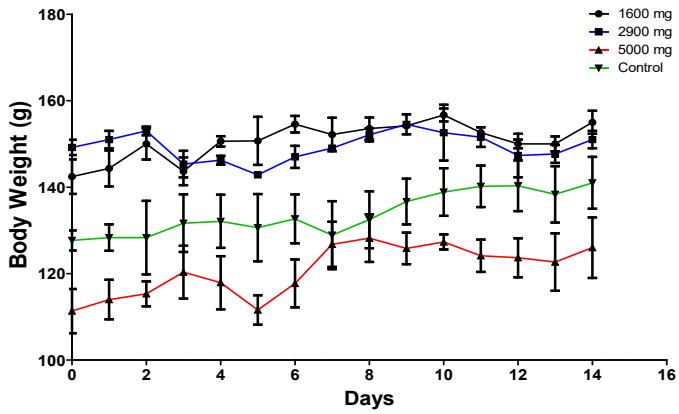

Figure 7: Body weight (g) distribution of animals in phase two administered orally with 0, 10, 100, 1000 mg/kg body weight of aqueous leaf extract of *Chrysophyllum albidum*.

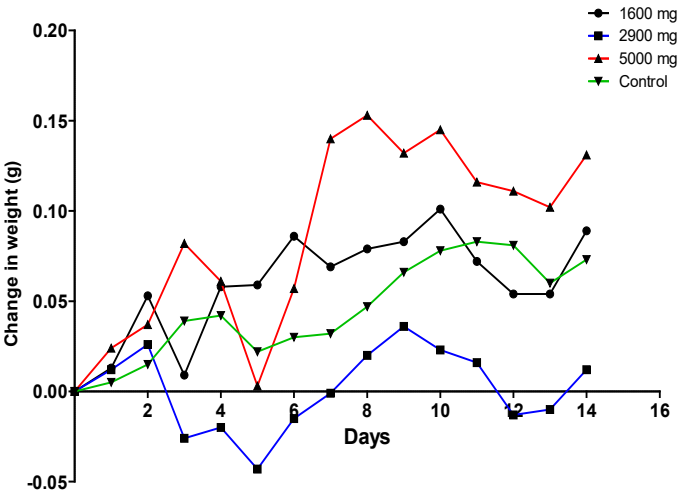

Figure 8: Change in body weights (g) of animals in phase two administered orally with 0, 10, 100, 1000 mg/kg body weight of methanol leaf extract of *Chrysophyllum albidum*.

groups on the phenols are thought to be responsible for their toxicity to organisms, with the evidence that increased hydroxylation results to an increased toxicity [12].

There was a significant (P≤0.05) increase in the body weight of the treated animals in both phase 1 and phase II when compared to the untreated control. This indicates the ability of the extract to stimulate the appetite of the rats and enhance weight gain at the dosages given. In a similar study, Ekene and Odigie reported a significant increase in body weight of rats treated with *Chrysophyllum albidum* when compared to the control as a result of tannins present in the extract, as tannins have been implicated in stimulating increase in body mass [13]. A study by Marcus et al., 2003 revealed that tannins present in medicinal plants are potent in increasing body mass [14]. Also, a phytochemical analysis of *C. albidum* has shown the presence of small quantities of tannins, among other components as one of its active components [15]. This could be responsible for the increased body weight observed in this study.

There were no major clinical signs of toxicity observed in the animals intraperitoneally administered 10 mg/kg, 100 mg/kg, and 1000 mg/kg b.wt of the aqueous extract. There was no mortality in these groups immediately or during the 14 days of observation period.

In the second phase of the experiment, the rats intraperitoneally administered 1600 mg/kg, 2900 mg/kg, and 5000 mg/kg of aqueous leaf extract of *Chrysophyllum albidum* developed clinical signs of toxicity (loss of appetite, loss of stimuli sensitivity, loss of agility, and convulsion) after 20 minutes of treatment period and during the post treatment period. No clinical sign of toxicity no mortality was observed in the control groups administered normal saline, either immediately or during post treatment period. In the second phase of treatment, two-third of the rats intraperitoneally administered with 2900 mg/kg and 500 mg/kg of the aqueous extract died while all the rats in the group administered with 1600 mg/kg of the extract died after 24 hours of treatment. The acute toxicity of the aqueous leaf extract of *Chrysophyllum albidum* was established. The acute toxicity study indicates that the aqueous leaf extract of *Chrysophyllum albidum* is toxic when administered through the intraperitonial route to the experimental animals at dose greater than 1265 mg/kg (1.3 g/kg) body weight (ip).

In a similar study, Adedoyin et al. reported the toxic effects of methanolic seed cotyledons of *Chrysophyllum albidum* in swiss albino rats and the LD50 was calculated to be 750 mg/kg body weight [16].

In another study Ene et al reported the toxic effects of chloroform leaf extract of Artemisia maciverae and the LD50 was calculated to be 566 mg/kg body weight (i.p.) in mice [11]. These studies indicated that the plant extract was toxic to the experimental animals at higher doses and safe at lower doses. In the first phase of treatment, they used the doses of 10, 100 and 1000 mg/kg and the result of the first phase determined the doses used in the second phase. This is in agreement with the methodology of this present study.

For the oral acute toxicity evaluation, The LD50 of the extract of was estimated to be more than 5000 mg/kg. The dose produced no mortality after 24 hours and 14 days observation period. It also had no adverse effects on the behavioral responses of the tested rats after 14 days of observation. It has been suggested that any substance with an oral LD50 of above 5000 mg/kg should be regarded as safe [17]. It can therefore be inferred that, the plant under study is non-toxic and safe when taken orally. Although, the extract can be deduced to be safe, some dose dependent toxic manifestations were observed in the groups treated with 2900 mg/kg and 5000 mg/kg body weight of the extract following oral administration. This may be due to the effect of one or more of the chemical constituents present in the extract. The non-toxic observation that was made in the current studies following the evaluation of the acute toxicity aligns very well with other studies on toxicity of *Chrysophyllum albidum*. Adewoye et al. reported a non-toxic LD50 of methanol bark extract of *Chrysophyllum albidum* while Bada reported that the seed extract are non-toxic following both oral and intraperitoneal administration to albino rats [6,18]. The non-toxic effect of the plant could be due its rich content of nutritional molecules. Adisa reported that the whole plant is rich in Vitamin C, protein and mineral contents [19].

Available evidence has shown that body weight changes are important and sensitive indices of toxic effects [20]. The monitoring of body weight of the experimental animals is important while studying the toxicity and safety of a natural product since it hints at the physiological and metabolic status of the animals and gets rid of the researcher from deriving any "false" observations due to nutritional abnormalities of the rats. In the current study, the positive change in body weight shown by all the rats was comparable and followed a general trend. The slight increase in body weight after the 14-day treatment can be ascribed to normal growth of the animals over the period [21]. None of the experimental groups suffered loss in weight or gained overweight which suggested that the plant extracts did not induce significant changes in the appetite and did not exert any deleterious effects on the general health status and metabolic growth of the rats. The animals in the control group showed a negative change in body weight towards the end of the observations. This change could be merely as a result of environmental factors as the control group only received water and food. The pattern of body weight was altered after day 8 during the phase 1 experiment. However, this change was also observed with the control group and is therefore not caused by the administration of methanol extract. This suggested that the plant extracts did not induce any deleterious effects on growth and development of the rats. A positive change in body weight of animals has also been reported by various works Adewoye et al. reported a positive change in body weight after oral administration of non-toxic plant extracts [6].

Conclution

A single dose of 10 mg/kg b.w, 100 mg/kg b.w, and 1000 mg/kg b.w of aqueous leaf extract of *Chrysophyllum albidium* intraperitoneally administered to the rats were not able to induce mortality and other clinical signs of toxicity in the rats during the 14 days of observation, while a single higher dose of 1600 mg/kg b.w, 1900 mg/kg b.w, and 5000 mg/kg b.w of the extract were able to induce mortality and other clinical signs of toxicity including, sluggishness, convulsion, loss of appetite, loss of motility. And a single dose of 10 mg/kg b.w, 100 mg/kg b.w, 1000 mg/kg b.w, 1600 mg/kg b.w, 1900 mg/kg b.w, and 5000mg/kg b.w of aqueous leaf extract of *Chrysophyllum albidium* orally administered to the rats were not able to induce mortality and other clinical signs of toxicity in the rats during the 14 days of observation, This indicates that aqueous leaf extract of *Chrysophyllum albidium* is safe at lower doses when administered intraperitoneally and can be used for the various medicinal purposes such as antimicrobial, anti-malarial, antioxidant, ant diabetic, anti-inflammatory, anticancer, anti-fungi, antibacterial, antithrombotic and among others with which it is attributed, but toxic and can cause severe harm at higher doses. While the aqueous leaf extract of *Chrysophyllum albidium* is safe at lower and higher doses when administered orally.

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