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Use of the Leaf-Aqueous Extract of *Pseudopanax Arboreus* (*Araliaceae*) (L.F. Phillipson) is Void of Toxic Effects

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ABSTRACT

Although plants may be effective in treating some ailments, they may contain potent chemical compounds that could cause adverse effects and toxicity. It is therefore essential to ensure the clinical efficacy, quality and safety of any medicinal plant preparation before making it available to consumers. *Psudopanax arboreus* (*Araliaceae*) has scientifically been proven to have sex-enhancing potentials and is capable of reversing male sexual dysfunction; but its toxicological profile has never been assessed. The present study focused on evaluating the toxicological effect of its leaf-aqueous extract in rats. In acute toxicity, a total of 21 rats were divided into 3 groups of 7 rats each, with animals of group 1 administered 10 ml/kg distilled water, while groups 2 and 3 received 2000 and 5000 mg/kg of the aqueous extract, respectively. In sub-acute toxicity, a total of 40 rats of either sex were divided into 4 groups of10 animals each. Animals of group 1 received 10ml/kg of distilled water, while groups 2, 3, 4 were given the aqueous extract at 250 mg/kg, 500 mg/kg and 1000 mg/kg, respectively. Single oral administration provoked no clinical signs of toxicity and death in the tested doses; hence, the LD50 value of the extract was found to be greater than 5000mg/kg. Similarly, the 28 days treatment did not cause any significant difference in body weight, water/food intake, organ weights, hematological and biochemical parameters between the extracted-treated animals and the control group. It can be concluded that the leaf-aqueous extract of *P. arboreus* is well tolerated.

Abbreviations: ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; HMG-CoA: Hydroxyl Glutanyl Co-Enzyme A; Kg: Kilograms; LD: Lethal Dose; mg: Milligrams; NOAEL: No Observed Adverse Effect Level; OECD: Organization for Economic Co-Operation and Development; P: *Pseudopanax*, SGOT: Serum Glutamic Oxaloacetic Transaminase; SGPT: Serum Glutamic Pyruvic Transaminase; WHO: World Health Organization

Introduction

Over the past two decades, there has been an increase in the use of plant-based medicine worldwide. It is estimated that three-quarters of the world's population use herbal medicine for their healthcare [1]. Interestingly, the World Health Organization (WHO) has encouraged this alternative medicine for the prevention and treatment of diseases and according to estimates put up by this organ (WHO), more than 80% of the population in Africa uses the doctor's

plants to meet their need for care and health [2]. The toxicity of chemical products, the high cost of chemical drugs, the remoteness and /or insufficiency of health centers, especially in rural settings, which limits the genuine handling of public health problems, have favored the use of such drugs [3]. As a result, traditional medicine can be considered an integral part of primary healthcare and is used to improve access to healthcare [4]. Unfortunately, because plants are natural, they are considered to be non-dangerous, and the population use them in many and very different contexts. The products used are often the mixture of plants whose knowledge and requirements of preparation and consumption are not controlled. Thus, although plants may be effective in treating some ailments, they may contain potent chemical compounds that cause adverse effects and toxicity, especially when administered at high doses and for a long period [5,6]. For instance, Peganum harmala is a plant with scientifically proven analgesic, hypoglycemic, anti-nociceptic and anti-parasitic properties, but whose prolonged administration leads to hepatotoxic and nephrotoxic abnormalities. Also, Astragalus hamosus is effective in the treatment of gastrointestinal diseases, respiratory problems and headache, but causes liver and kidney dysfunction at higher doses and following long term administration [7].

It is therefore essential to ensure not only the clinical efficacy and the quality, but especially the safety of any medicinal herbal preparation before making it available to consumers. Toxicity tests are therefore indispensable and accompany the biological activity test in the course of the selection of new molecules [8]. For this, a renewed interest has been brought to phytotherapy to deepen the analysis of its therapeutic efficacy and especially its toxicity aspect. *P. arboreus* is, belonging to the Family *Araliaceae*, is commonly used in traditional medicine in the treatment of many ailments such as hypertension, male infertility and male sexual dysfunction. It has already been the subject of several scientific studies in which the sex-enhancing properties of the aqueous [9] and methanol [10] extracts of its leaves have been demonstrated. In other investigations, its potentials to reverse clinically induced male sexual dysfunction (MSD) have been proven [11]. Further studies have evaluated the time-response activity of the leaf-methanol extract of the plant [10]. However, till date, no study has been conducted in relation to its toxicological effect, hence the question of whether the aqueous extract of *P. arboreus* would have toxic effects in the body. This would suggest that in addition to its proven biological efficacy, the aqueous extract of *P. arboreus* would be devoid of toxic effects. This work therefore had as aim to evaluate the toxicological effect of aqueous extract of *P. arboreus* in rats.

Materials and Methods

Plant Collection and Preparation of the Aqueous Extract

Fresh leaves of *P. arboreus* were collected from Ntenako village, Manyu Division, South-West Region of Cameroon, under the guide of a local tradi-practitioner who confirmed the plant's identity. Its authentication, processing and production of the aqueous extract were done following the same procedures as outlined in our previous study [9].

Chemical Products or Reagents

Products or reagents used in this study included assay kits for triglycerides and total cholesterol (IVD DIALAB, Austria), Creatinine, AST (aspartate aminotransferase), ALP (alkaline phosphatase), ALT (alanine amino transferase) (Elabscience, USA) and Albumin (BioVision Inc, USA). All were purchased and stored under recommended conditions until used.

Breeding of Animals

Animals used were rats of the Wistar Strain of either sex that were bred in the Animal Facility of the Department of Zoology and Animal Physiology of the Faculty of Science, University of Buea under standard conditions of temperature, humidity and light (12H cycle). They were given free access to water and a standard laboratory diet.

Acute Toxicity

In order to assess the toxic nature of a compound, acute oral toxicity is the first step to be carried out [12]. Acute toxicity testing involves the determination of lethal dose, the single dose that kills 50% of the tested group of animals within 24 hours. Acute toxicity studies of the leaf aqueous extract of P.*arboreus* were carried out in male rats by using Organization for Economic Co-operation and Development (OECD) guidelines [13]. Before oral administration of a single dose of the test substances, the rats were deprived of food for 3 hours. They were randomly divided into 3 groups of 7 rats each. Animals of group 1 were administered 10 ml/kg distilled water to serve as the control; while those of groups 2 and 3 received 2000 and 5000mg/kg of the aqueous extract, respectively. All animals were observed for general behavioral changes (somnolence, convulsion, fatigue, increase heart rate); symptoms of toxicity and mortality after treatment for the first four (critical) hours, then over a period of 24 hours and thereafter, 2 hours daily for 14 days. Meanwhile, body weights were measured daily. Abnormal findings were recorded with the time of onset and disappearance. On the 14th day, all animals were sacrificed and selected organs (lung, liver, heart and kidney) isolated and processed for macroscopic observations [12].

Sub-Acute Toxicity

When treatment related toxicity is not identified in acute toxicity, sub-acute toxicity is assessed to ensure safety after repeated exposure over a relatively long period of time. Sub-acute toxicity study can be used to determine the undesirable effects of continuous or repeated exposure of part of an average life laboratory animal to a plant extract and to provide information of target organ

toxicity. Like in the acute toxicity test, sub-acute toxicity study (28-day repeated oral toxicity study) was also carried out according to OECD 407 guidelines [14]. Eight (8) weeks old (110-120g) rats of either sex were divided into 4 groups with 10 animals (5 males plus 5 females) in each group. Animals of group 1 received 10ml/kg of distilled water and served as a control group whereas groups 2, 3 and 4 were given the aqueous extract at 250 mg/kg, 500 mg/kg and 1000 mg/kg body weight, respectively. All animals were observed for 4 hours daily for mortality and morbidity till the completion of the experiment. They were observed for clinical signs and the time of onset, duration of these symptoms, if any were recorded. Body weights of the rats in all groups were recorded once before the start of treatment, once weekly during the treatment period and finally on the day of sacrifice. The amount of food and water intake was recorded daily and expressed as an average for 7 days. Animals were treated orally once a day using the metal oropharyngeal cannula for a duration of 28 days [15].

On the 29th day from commencement of treatment, all animals were terminated for the evaluation of other signs of toxicity. To this effect, they were starved for 24hours, then anesthetized using an overdose of ethyl-ether. The thoracic region was rapidly dissected and blood samples collected through cardiac puncture. Part of it was collected in heparinized test-tubes, whereas the other part was collected in heparin-free test-tubes which allowed coagulation and the subsequent collection of serum. The animals were then sacrificed through cervical dislocation and selected organs including the heart, kidney, liver and spleen isolated. They were freed from all connective tissue moisture, examined for morphological changes such as the presence of any kind of lesions and then weighed using an electronic balance (NVT 1601/1, OHAUS, USA). Both blood samples were preserved at 4oC±1 for hematological and biochemical tests, respectively. As regards hematological tests, red blood cell (RBC), white blood cell (WBC) and platelet numbers as well as the percentage lymphocytes, monocytes, eosinophils and neutrophils were determined using the fully automated hematology analyzer (URIT3300) (Prasanth et al. 2014). The serum was processed for biochemical parameters including creatinine, alanine aminotransferase (ALT) (serum glutamate pyruvate transaminase, SGPT), aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase, SGOT), alkaline phosphatase (ALP), albumin, total cholesterol and triglycerides [16,17].

Ethical Consideration

Animals were handled in accordance with the Organization for Economic Cooperation and Development (OECD) guidelines for testing chemicals 423 and 425 (OECD, 2008a&b) and the experimental protocol was approved by the University of Buea Institutional Animal Care and Use Committee (UB-IACUC).

Statistical Analyses

Values were expressed as Mean±standard error of mean (SEM). Mean values were calculated for each animal and quantitative comparisons between groups established from those means. One way ANOVA followed by Duncan test was used to analyse the data with the aid of the SPSS for windows version 20.0 software. Significant levels were tested at $p<0.05$.

Results

Acute Toxicity

Single oral administration of the leaf-aqueous extract of *P. arboreus* at 2000 mg/kg and 5000 mg/kg produced no behavioral changes, no signs of toxicity and no mortality in rats after treatment. Since there were no clinical signs of toxicity and death in the tested doses, LD50 value of the extract was found to be greater than 5000mg/kg.

Sub-Acute Toxicity

Following 28 days repeated oral administration of the leaf-aqueous extract of *P. arboreus* at 250, 500 and 1000mg/kg doses to rats, there were no treatment related toxicity signs and mortality observed in both sexes of rats treated. No significant ($p<0.05$) differences in weekly body weight gain were observed between the extract-treated and control rats Table 1. As presented in Table 2, repeated treatment of rats with the leaf-aqueous extract of *P. arboreus* produced a non-significant ($p<0.05$) difference in the weekly food intake of the animals, compared to their control counterparts. Like in food intake, similar results were obtained in water intake of animals following 28days repeated treatment with the leaf-aqueous extract of *P. arboreus*, compared to the control animals Table 3. Sub-acute treatment of rats with the leaf-aqueous extract of *P. arboreus* did not produce any significant ($p<0.05$) difference in the weight of organs such as the heart, kidney, liver and spleen, compared to the control animals Table 4. Results of the effects of sub-acute treatment of animals with the leaf-aqueous extract of *P. arboreus* on hematological parameters are presented in Table 5. According to the table, there were no statistically significant ($p<0.05$) differences in the hematological parameters measured between the control and extract-treated groups. Sub-acute administration of the leaf-aqueous extract of P. *arboreus* did not show any significant changes in biochemical parameters such as alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate aminotransferase (AST), creatinine, triglycerides, total cholesterol and albumin when compared to control group Table 6.

Table 1: Effects of the Sub-acute (28 days) administration of the leaf-aqueous extract of P. arboreus on the body weight of rats.

Treatment	Body Weight (G)					
	Sex	Day 1	Day 14	Day 14	Day21	Day28
DW, 10ml/kg	Males	145.09±2.17	151.21±2.66	158.00±2.41	163.18±2.33	165.25±2.63
	Females	142.48±2.78	148.55±2.35	154.61±2.17	159.71±3.21	163.43±3.17
AE, 250mg/kg	Males	138.22±2.60	143.45±2.18	151.33±3.67	157.08±2.34	160.13±2.77
	Females	133.44±2.75	140.21±2.44	147.11±2.47	153.28±2.37	158.84±2.62
AE, 500mg/kg	Males	156.53±2.38	164.76±2.31	174.49±2.72	177.29±2.21	182.68±2.17
	Females	158.41±2.83	163.26±2.33	171.65±2.74	173.40±2.61	173.00±3.18
AE, 1000mg/kg	Males	180.24±4.76	186.40±5.17	194.225.63	198.12±5.33	201.24±5.43
	Females	178.13±5.69	184.77±6.45	190.26±5.31	196.44±5.87	199.55±5.33

Values: Mean±SEM; DW: distilled water; AE: aqueous extract

Table 2: Effects of sub-acute (28days) administration of the leaf-aqueous extract of P. arboreus on weekly food intake (g) in rats.

Treatment	Weekly Food Intake (G)				
	Sex	1ST Week	2ND Week	3RD Week	4TH Week
DW, 10ml/kg	Males	35.22±4.33	36.72±3.89	38.24±4.11	40.64±4.51
	Females	35.82±3.77	34.39±4.72	36.75±4.59	39.45±4.08
AE, 250mg/kg	Males	38.15±2.67	40.77±2.43	40.23±2.79	41.56±2.38
	Females	37.18±3.11	37.73±2.40	38.44±2.60	40.55±2.13
AE, 500mg/kg	Males	40.54±3.92	40.81±3.45	42.76±3.11	43.50±3.23
	Females	39.73±3.44	40.62±2.89	42.34±2.94	41.75±2.49
AE, 1000mg/kg	Males	36.58±±4.70	38.34±4.56	40.62±4.12	40.83±4.51
	Females	36.20±3.88	37.25±4.61	39.14±4.55	40.85±4.23

Values: Mean±SEM; DW: distilled water; AE: aqueous extract; Fem.: females.

Table 3: Effects of sub-acute (28days) administration of the leaf-aqueous extract of *P. arboreus* on weekly water intake (ml) in rats.

Treatment	Weekly Water Intake (Ml)				
	Sex	1ST Week	2ND Week	3RD Week	4TH Week
DW, 10ml/kg	Males	50.25±6.93	48.75±6.33	51.34±6.47	53.40±6.52
	Females	45.63±5.48	48.24±5.17	50.67±5.41	51.78±5.64
AE, 250mg/kg	Males	48.57±5.33	50.26±5.93	50.76±5.82	51.84±5.46
	Females	48.34±5.77	47.94±5.22	49.40±5.63	50.65±5.89
AE, 500mg/kg	Males	45.37±5.66	47.34±5.71	48.70±5.82	49.23±5.43
	Females	40.67±5.14	42.23±5.48	42.37±5.44	44.60±5.72
AE, 1000mg/kg	Males	50.79±4.54	48.31±4.82	51.06±4.78	52.34±5.18
	Females	48.27±5.69	50.74±5.12	50.92±5.56	51.78±5.44

Values: Mean±SEM; DW: distilled water; AE: aqueous extract.

Table 4: Effects of sub-acute (28days) administration of the leaf-aqueous extract of arboreus on the weight of some selected organs.

Organ Weight (G)	Treatment							
	DW 10ml/kg		AE 250mg/kg		AE 500mg/kg		AE 1000mg/kg	
	Males	Fem.	Males	Fem.	Males	Fem.	Males	Fem.
Heart	0.64±0.04	0.66±0.06	0.63±0.04	0.64±0.05	0.68±0.05	0.71±0.04	0.76±0.04	0.69±0.04
Kidney	1.09±0.06	1.11±0.11	1.13±0.07	1.07±0.08	1.12±0.11	1.16±0.13	1.25±0.11	1.19±0.09
Liver	4.64±0.22	4.820.34	4.27±0.56	4.47±0.71	4.75±0.63	4.29±0.33	5.78±0.65	5.26±0.55
Spleen	0.44±0.04	0.46±0.03	0.39±0.02	0.41±0.03	0.42±0.04	0.45±0.04	0.49±0.05	0.47±0.04

Values: Mean±SEM; DW: distilled water; AE: aqueous extract.

Table 5: Effects of sub-acute (28days) administration of the leaf-aqueous extract of *P. arboreus* on hematological parameters of rats.

Hematological Parameter	Sex	Treatment			
		DW 10ml/kg	AE 250mg/kg	AE 500mg/kg	AE 1000mg/kg
RBC Count ($X10^6$/µl)	Males	5.13±0.41	4.93±0.22	5.43±0.88	4.85±0.34
	Females	5.87±0.73	6.17±0.45	6.71±0.42	6.78±0.33
WBC Count ($X10^3$/µl)	Males	9.06±1.07	9.11±0.71	9.23±0.88	8.97±0.42
	Females	10.44±0.78	9.95±0.94	10.49±1.11	10.78±1.08
Platelet count ($X10^3$/µl)	Males	811.44±37.61	813.36±41.08	815.56±41.22	809.34±38.11
	Females	835.33±38.84	846.17±50.23	830.42±43.97	821.37±42.51
Neutrophils (%)	Males	46.77±5.61	48.18±4.74	50.06±5.27	52.80±5.23
	Females	45.28±4.43	45.71±5.12	47.33±5.31	47.80±5.39
Lymphocytes (%)	Males	34.45±3.72	30.83±3.55	33.77±3.69	35.38±3.62
	Females	35.64±3.95	31.17±3.22	34.68±2.89	35.69±3.47
Eosinophils (%)	Males	3.27±0.31	3.42±0.42	2.97±0.37	3.38±0.77
	Females	2.87±0.36	3.17±0.64	3.08±0.33	2.86±0.24
Monocytes (%)	Males	5.53±0.66	5.87±0.92	5.78±0.82	5.49±0.68
	Females	3.97±0.38	4.28±0.67	3.65±0.44	3.18±0.72

Values: Mean±SEM; AE: aqueous extract; DW: distilled water %: percentage; µl: microliters.

Table 6: Effects of sub-acute (28days) administration of the leaf-aqueous extract of P. arboreus on biochemical parameters.

Biochemical Parameter	Sex	Treatment			
		DW 10ml/kg	AE 250mg/kg	AE 500mg/kg	AE 1000mg/kg
ALP (U/l)	Males	77.78±6.55	79.68±13.49	80.77±3.97	81.25±5.37
	Females	79.43±6.28	80.11±4.52	79.83±4.49	80.78±4.22
ALT or SGPT (U/l)	Males	42.21±4.11	42.97±3.41	42.69±2.75	43.14±3.07
	Females	40.80±4.54	41.71±2.82	41.47±3.18	42.79±2.46
AST or SGOT (U/l)	Males	56.28±6.79	55.33±5.63	57.30±6.25	56.35±6.50
	Females	54.31±6.11	55.206.45	56.80±5.35	54.66±6.75
Creatinine (mg/dl)	Males	1.26±0.24	1.31±0.34	1.28±0.23	1.30±0.28
	Females	1.31±0.22	1.35±0.34	1.34±0.33	1.32±0.25
Triglycerides (mg/dl)	Males	66.81±9.42	67.28±10.23	67.59±9.57	66.52±10.88
	Females	67.07±8.38	67.31±9.54	67.43±10.85	68.20±9.70
Total cholesterol (mg/dl)	Males	82.12±11.23	80.25±10.20	81.78±11.75	80.47±10.35
	Females	80.37±10.44	79.70±11.25	80.17±10.45	79.50±10.19
Albumin (g/dl)	Males	3.37±0.71	4.11±0.87	3.78±0.65	3.82±0.77
	Females	3.65±0.66	3.95±0.75	4.06±0.57	3.45±0.88

Values: Mean±SEM; AE: aqueous extract; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DW: distilled water; SGOT: serum glutamic oxaloacetic transaminase: SGPT: serum glutamic pyruvic transaminase.

Discussion

In developing countries, herbal medicines have become famous in healthcare, and some have been falsely considered as safe without understanding the possible health effects and thus commonly used as self-medication [18]. As the use of plant-based products increases, it is important to screen the toxicological profile of these plants to confirm the safety and efficacy of those natural sources. Though *P. arboreus* is popular in the Bayang folk medicine as a sex enhancer, there is lack of data on its toxicological profile and adverse effects. Therefore, toxicity studies were necessary not only to identify the further range of doses in animal studies, but also to explain the probable clinical signs evoked by its extracts. Hence the present experiment was undertaken to evaluate the possible effects of the short term and long-term administration of its leaf-aqueous extract. Throughout the 14 days of observation period, no morbidity or mortality was observed in the extract-treated rats. In the present study, the results showed no adverse events in the

dose groups 2000 mg/kg and 5000 mg/kg which indicate that the LD50 was greater than 5000 mg/kg. According to the OECD [12], a substance that does not cause mortality at the limit dose of 5000 mg/kg would have a DL50 greater than this limit dose and can be considered non-toxic. When treatment related toxicity is not identified in acute toxicity, sub-acute toxicity is assessed to ensure safety after repeated exposure over a relatively long period of time.

In the repeated dose (28-day) oral toxicity study, there were neither deaths nor treatment-related signs observed in all the groups of animals. After exposure to a few possible toxic substances, there will be changes in body weight gain and internal organ weights which would reflect toxicity [19]. The body weight changes are markers of adverse effects of drugs and chemicals and if the body weight loss occurred is more than 10% of the initial body weight it will be considered as statistically significant [20,19]. There were no significant differences in body weight gain of both control and treated groups. We can therefore deduce that leaf-aqueous extract of *P. arboreus* is almost non-toxic. Organ weight also is an important indicator of physiological and pathological status of animals. The relative organ weight is fundamental to confirm whether the organ was exposed to the injury or not. The heart, kidney, liver and spleen are the primary organs affected by metabolic reactions caused by toxicants [21]. In the present study, organ weights in all the treated groups of both sexes were not significantly different from those of control groups. Hence, it can equally be concluded that leaf-aqueous extract of *P. arboreus* is almost non-toxic.

Since proper food and water intake is necessary to the physiological status of the animal and to the achievement of a better response to test substance under investigation, these parameters were measured in our study [17,22]. Our findings revealed that both food and water consumption were not affected by the administration of the extract. Thus, this indicates that there was no interruption in the metabolism of carbohydrate, protein and fat. Analysis of blood parameters is important in the evaluation of risks associated with test compounds under investigation as the changes in the hematological system have a greater indicative value for human toxicity, when the data are converted from animal studies [18]. Repeated treatment of animals with the aqueous extract of *P. arboreus* for 28 days did not produce any changes in hematological parameters including RBC, WBC and platelet counts as well as the percentage lymphocytes, monocytes, eosinophils and neutrophils, an indication that the extract did not affect the blood cellular components or their production. Transaminases such as serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) (also called aspartate aminotransferase [AST] and alanine aminotransferase [ALT], respectively) are normally present in the heart and liver and their release into blood indicates heart or liver damage.

They are therefore well-known good indicators of liver and heart function and are used as biomarkers to predict the probable toxicity of drugs and xenobiotics [23,24]. Normally, destruction to the liver parenchymal cells will result in an increase of both these enzymes in the blood [25]. Interestingly, there were no changes in the ALT and AST levels in our investigations, which reveal that the extract did not affect the liver function/ or metabolism. Furthermore, determination of plasma proteins like albumin is required in order to assess the synthetic capacity of the liver and decrease in plasma proteins therefore tend to reflect chronic damage [26]; hence, the no alteration in the level of albumin in extract-treated animals is another indication that their liver was not affected. The extract did not equally provoke any change in the serum levels of total cholesterol and triglycerides. The action of the extract in maintaining a stable serum lipid profile could be through the induction of the inhibition of reductase hydroxyl methyl glutanyl CoA (HMG-CoA) leading to reduction of hepatic synthesis and intestinal absorption of cholesterol. Indeed, the inhibition of HMG-CoA by flavonoids which have been identified in our plant extract has been reported. This effect of the leaf-aqueous extract of *P. arboreus* on lipid profile could suggest its beneficial effects against lipid peroxidation and subsequently on oxidative stress [27]. The reduction of blood lipids is an efficient method to prevent and treat cardiovascular affections [28]. This could explain its empirical use in treating hypertension, since arterial hypertension is generally associated to dyslipidemia [29].

Conclusion

Results of our findings indicate that treatment with single oral doses of 2000 mg/kg and 5000 mg/kg of the plant extract did not result in any toxic signs or mortality in the acute toxicity studies; likewise, daily oral administration of the extract of *P. arboreus* for a period of 28 days did not cause mortality, changes in body weight and body weight gain. Hematological and biochemical examinations proved that the extract is safe. Hence, the no-observed adverse-effect level (NOAEL) of the extract was found to exceed 1000 mg/kg/day. Overall, it can be concluded that the leaf-aqueous extract of *P. arboreus* is well tolerated.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflict of Interest

No conflict of interest declared.

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