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Acute and Subacute Toxicity Studies of Aqueous Extract of *Morinda lucida* Stem Bark

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ABSTRACT

Morinda lucida is used as a remedy for diabetes and some other diseases in African folk medicine. In an acute toxicity study, *Morinda lucida* extract was administered orally at doses ranging between 2-20 g kg⁻¹ to experimental mice and observed for any toxic symptoms up to 14 days. In the sub-acute toxicity, *Morinda lucida* stem bark extract was tested at dose levels of 0.1, 1 and 5 mg kg⁻¹ on physical (body weight and organ weight), biochemical parameter and histopathological examination in adult male Albino rats. The *Morinda lucida* extract was well tolerated at the acute administration. No mortality was observed even at the highest dose of 20 g kg⁻¹. In the sub-acute administration, *Morinda lucida* extract significantly (p<0.05) prevented an increase in body weight in a dose dependent manner and this reflected a significant (p<0.05) increase in the relative organs (liver, heart, kidney and spleen) weights. The biochemical parameters showed a significant (p<0.05) increase in ALT and AST at the dose level of 5 g kg⁻¹ in both two weeks and four weeks examination. Extract had a significant (p<0.05) dose reducing effect on creatinine and triglycerides at 2 weeks administration while at four weeks extract had significant reduction effect on glucose creatinine, cholesterol and triglyceride at dose level of 5 g kg⁻¹. The histopathological examination revealed steatosis in the liver at 5 g kg⁻¹ *Morinda lucida* extract administration. Thus *M. lucida* aqueous extract is well tolerated at low dose administration but may be toxic at dose level of 5 g kg⁻¹ at sub-acute administration.

Key words: *Morinda lucida*, toxicity, biochemical parameter, histopathology

INTRODUCTION

Plant derived products have been used for medicinal purposes since the creation of man. Approximately about 80% of the world population today, relies on botanical preparations as medicines to meet their health needs (Polasa and Nirmala, 2003). The problem with the botanical preparations is that most of the plants are been used indiscriminately without adequate information on associated safety/toxicity risks. Thus for proper knowledge and guidance of these natural products, there is need for scientific documentation on the safety /toxicity profile on these acclaimed medicinal plants (Deng, 1994).

Morinda lucida Benth. (Rubiaceae) is a tropical tree found in the Africa rainforest and commonly known as Brimstone tree. In the South and Central Regions of Cameroon, *Morinda lucida* is commonly known as “akeng” and it is one of the most widely used plants in this environment for medicinal purposes (Zapfack and Ngobo, 2002). *Morinda lucida* Benth. (Rubiaceae) is an evergreen shrub of small to medium-sized tree measuring up to 18-25 m tall, with bole and branches often crooked or gnarled; bark smooth to roughly scaly, grey to brown, often with some distinct purple layers. From the wood and bark of *Morinda lucida* 18 anthraquinones, tannins, flavonoids and saponosides have been isolated (Zimudzi and Cardon, 2005). Different parts of *Morinda lucida* Benth have been reported to possess medicinal properties. The leaf extract of the plant possess trypanocidal (Asuzu and Chineme, 1990), antimalarial activities (Makinde and Obih, 1985; Tona *et al.*, 1999) and aortic vasorelaxant effect (Ettarh and Emeka, 2004). Oliver-Bever (1986) documented the use of a weak decoction of the stem bark to treat severe jaundice. The leaf extract of *Morinda lucida* has also been reported to have a strong oral hypoglycemic property (Olajide *et al.*, 1999; Adeneye and Agbaje, 2008) by increasing the utilization of peripheral glucose. The leaf extract of *Morinda lucida* has also been associated with some reversal toxicity such as the reversible antispermatogenic activities in rats (Raji *et al.*, 2005).

The bark of *Morinda lucida* is widely used in Cameroon as a decoction for treating Diabetes mellitus. The absence of information on the toxicity profile of the aqueous extract of the bark necessitated the present investigation of its acute and sub-acute toxicity in animal model.

MATERIALS AND METHODS

Plant materials: Fresh bark of *Morinda lucida* Benth was harvested from natural habitat in the outskirts of Yaoundé, Cameroon in the month of September, 2008. Plant identification and voucher specimen No. 2528SRFK referencing was done at the national herbarium of Cameroon. This was then chopped into tiny bits of about 2 cm and subsequently dried in a hot air oven and pulverized using a grinding machine. The pulverized sample was then immersed in distilled water for 48 h. The extract was filtered with a sieve of 80 µm pore size and the filtrate concentrated in a freeze dryer.

Experimental animals: Male mice and Wistar albino rats obtained from the animal house of the Institute of Medical Research and Medicinal Plant Studies, Yaoundé were used for the acute and sub-acute toxicity studies, respectively. They were housed in wire mesh cages in a well ventilated room, 12 h natural light and 12 h darkness, with free access to water and food (standard rat feed). They were allowed to acclimatize for 1 week before experimentation.

Acute toxicity study: The experimental design earlier described by Agbor *et al.* (2004) was applied in this study with some modifications. Thirty male mice (25-30 g) distributed in to 5 groups of six were accommodated in wire mesh cages. Group 1 served as the control and received water only while group 2-5 were administered single doses by oral intubations of plant extract (2.5, 5, 10 and 20 g kg⁻¹) dissolved in 1 mL of distilled water. The animals were monitored for 14 days for any change in activity such as excitation, fatigue, diarrhoea, itching, curved tail, shivering, falling of hair and mortality. All the animals had regular supply of food and water until the end of the experiment.

Sub acute toxicity study: Four groups of 8 rats each (32 rats) were used for this study. Group 1 served as the normal control animals and was administered distilled water by oral intubation

while the other three groups (2, 3 and 4) served as the test groups and were administered three graded doses (0.1, 1 and 5 g kg⁻¹) of the plant extracts daily by oral intubation. The experiment lasted 4 weeks during which the animals received food and water *ad libitum* and weight taken weekly. After two weeks of administration the animals were fasted for 12 h and blood samples collected from experimental animals (under ethyl ether anesthesia) into EDTA tubes through the retro-orbital sinus. At the end of 4 weeks (28 days) the animals were sacrificed after an overnight fast and blood collected for analysis of biochemical parameters through the jugular vein. Blood collected from animals at 2 weeks and at the end of the experiment were transformed to plasma and used for determination of plasma concentration of glucose, cholesterol, triglyceride, creatinine, urea and aspartate aminotransferase (AST) and aniline aminotransferase (ALT) activities. All plasma biochemistry was performed using the respective analytical kits obtained from Fortress diagnostics Ltd, UK. The heart, liver, kidney and spleen were harvested cleaned of blood using distilled water and weighed. The liver and kidney were fixed in 10% formalin for histopathological examination. The fixed tissues were then dehydrated with 100% ethanol solution and embedded in paraffin. It was then processed into 4-5 µm thick sections and then stained using hematoxylin-eosine and observed under microscope as earlier described by Gabe (1968).

Statistical analysis: Data obtained were expressed as Mean±standard deviation. The statistical analysis was performed using one-way analysis of variance and Dunnett post test was conducted to determine significant differences between groups. The SigmaStat (Systat software, Richmond, CA) version 3.01 was employed in these analyses. The significant difference between the mean of the control and treated groups was considered at p<0.05.

RESULTS

Acute toxicity study: The plant extract was well tolerated by the by experimental animals even at higher dosages. Apart from the weak appearance observed at the dose levels of 5 g kg⁻¹ upward, shivering and lose of stability which lasted 3 h at dose levels of 10-20 g kg⁻¹ no death was registered.

Sub acute toxicity study: Table 1 presents the effect of 2 weeks administration of aqueous extract of *Morinda lucida* on plasma biochemical parameters of albino rats. After two weeks of administration of *Morinda lucida* extract, a significant (p<0.05) increase in the ALT and AST activities in group 4 animals was observed. Equally a significant (p<0.001) decrease was observed on the concentrations of triglyceride and creatinine in a dose dependent manner. Meanwhile, the rest of parameters did not change considerably.

The effect of 4 weeks (28 days) administration of the aqueous extract of *Morinda lucida* on plasma biochemical parameters of albino rats are presented in Table 2. After 4 weeks of administration of the *Morinda lucida* extract on experimental animals, a significant (p<0.001) decrease was observed in the concentration of cholesterol, triglyceride, glucose and creatinine. A significant (p<0.05) increased ALT and AST activity were observed.

The effect of *Morinda lucida* on the percentage body weight gain and organs weight of experimental animals is presented in Table 3. Administration of *Morinda lucida* extract to experimental animals induced an increase in the animals' organs weight in a dose responsive

Table 1: Plasma biochemical parameters of experimental animals after two weeks of *Morinda lucida* administration

Parameters	Group 1 (normal control)	Group 2 (0.1 g kg ⁻¹)	Group 3 (1 g kg ⁻¹)	Group 4 (5 g kg ⁻¹)
ALT (U mL ⁻¹)	42.37±2.61	38.50±2.54	40.11±2.13	54.04±1.55*
AST (U mL ⁻¹)	88.69±14.69	90.61±15.88	87.94±19.68	114.57±13.77*
Cholesterol (mg dL ⁻¹)	51.34±10.59	47.39±6.87	55.49±11.57	54.22±8.75
Triglyceride (mg dL ⁻¹)	105.12±18.17	103.22±13.97	80.16±7.24**	49.45±4.33**
Glucose (mg dL ⁻¹)	86.59±7.78	101.88±18.99	90.48±14.53	101.42±9.06
Creatinine (mg dL ⁻¹)	0.51±0.09	0.49±0.11**	0.47±0.09**	0.35±0.09**
Urea (mg dL ⁻¹)	73.44±14.54	71.01±10.65	81.19±14.93	67.70±13.81

The data represent the Mean±SD for each group of rats, n = 8 (number of animals per group), *p<0.05 significant difference compared to control (group 1), **p<0.001

Table 2: Plasma biochemical parameters of experimental animals after four weeks of *Morinda lucida* administration

Parameters	Group 1 (normal control)	Group 2 (0.1 g kg ⁻¹)	Group 3 (1 g kg ⁻¹)	Group 4 (5 g kg ⁻¹)
ALT (U mL ⁻¹)	50.95±2.51	45.02±2.45	49.63±2.17	58.17±2.44*
AST (U mL ⁻¹)	72.55±7.52	73.62±7.45	72.64±8.08	103.66±3.91*
Cholesterol (mg dL ⁻¹)	54.99±12.38	55.99±7.54	65.01±12.32	34.61±8.71**
Triglyceride (mg dL ⁻¹)	91.12±13.03	97.55±18.39	88.93±6.77	62.26±7.15**
Glucose (mg dL ⁻¹)	92.84±5.96	88.79±4.12	83.29±9.89	75.76±4.86**
Creatinine (mg dL ⁻¹)	0.73±0.09	0.59±0.10**	0.54±0.07**	0.59±0.13**
Urea (mg dL ⁻¹)	93.37±7.34	99.65±15.49	106.34±17.72	96.43±19.22

The data represent the Mean±SD for each group of rats, n = 8 (number of animals per group), *p<0.05 significant difference compared to control (group 1), **p<0.001

Table 3: Effect of *Morinda lucida* on percentage body weight gained and organ weight (mg g⁻¹ weight×100) of experimental animals

Organs	Group 1 (normal control)	Group 2 (0.1 g kg ⁻¹)	Group 3 (1 g kg ⁻¹)	Group 4 (5 g kg ⁻¹)
Liver	2.62±0.29	2.63±0.21	3.11±0.28	2.70±1.15
Heart	0.16±0.03	0.24±0.03	0.29±0.02	0.39±0.10
Kidney	0.50±0.06	0.48±0.05	0.51±0.05	0.65±0.14
Spleen	0.18±0.03	0.2±0.03	0.24±0.05	0.26±0.07
%weight gain at 2 weeks	14.1	10.6	2.7	1.40
%weight gain at 4 weeks	11.9	15.6	10.3	6.02

manner. This increase in organs weights correspond with decrease in percentage body weight gained across the table. Only the 1 and 5 g kg⁻¹ extract had an effect on the weight of experimental animals by reducing the percentage weight gain to 10.3 and 6.2% as compared to 11.9% in the control group, respectively.

Figure 1 presents the effect of sub-acute administration of the aqueous extract of *M. lucida* on the histopathology of liver. At 0.1 (Fig. 1b) and 1 g kg⁻¹ (Fig. 1c) administration *M. lucida* extract did not cause any morphological changes on the liver and kidney organs. On the other hand, steatosis (Fig. 1d) was observed on the liver of the rats that were administered 5 g kg⁻¹ of the extract.

DISCUSSION

Acute oral administration of the aqueous extract of *M. lucida* bark produced no mortality in experimental rats even at a dose of 20 mg kg⁻¹ body weight. In acute toxicity testing doses higher than 5 g kg⁻¹ body weight are generally not considered as dose related toxicity (Hayes, 1987). Also in accordance with the Organization for Economic Corporation and Development (OECD)

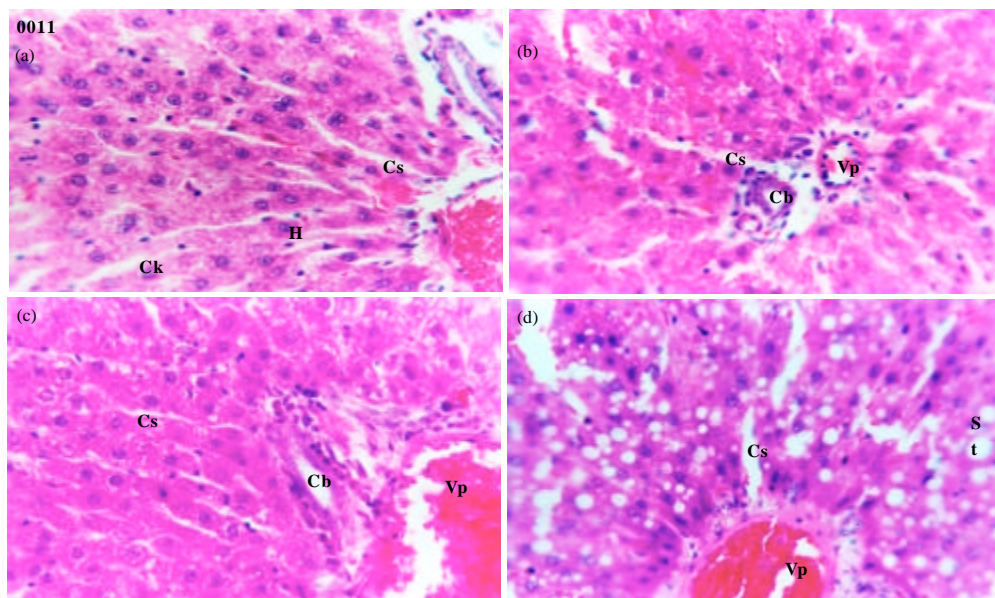


Fig. 1(a-d): Liver of a normal rat, (a) Normal architecture despite vascular congestion observed at the portal vein (Vp), normal hepatocytes (H), capillary sinusoids (Cs), biliary canals (Cb), kupffer cell (Ck), (b) Liver of a rat administered 0.1 g kg^{-1} of the aqueous extract of *M. lucida* bark. Normal architecture with capillary sinusoids (Cs), a biliary canal (Cb) and a portal vein (Vp), (c) Liver of a rat administered 1 g kg^{-1} of the aqueous extract of *M. lucida* bark. Normal architecture with biliary canal (Cb) and the capillary sinusoids (Cs), Vascular congestion at the portal vein (Vp), (d) Liver of a rat administered 5 g kg^{-1} of the aqueous extract of *M. lucida* bark. Observed steatosis (St), a sign of tissue invasion by fats. Slight dilation of the capillary sinusoid (Cs) and the beginning of degeneration

guidelines for oral acute toxicity, an LD_{50} of 2 g kg^{-1} and above is categorized as unclassified and hence declared relatively safe. Thus the aqueous bark extract of *M. lucida* was well tolerated and is relatively not toxic at acute administration. Thus *Morinda lucida* can be declared non toxic at acute administration.

Change in body weight is used as an assessment to the response of an individual to therapeutic drugs (Winder *et al.*, 1969) and as an indication of the adverse effect of a drug (Teo *et al.*, 2002; El-Sanusi and El-Adam, 2007). In the present study *Morinda lucida* had a decreasing effect on the body weight in a dose depend manner which may be associated to the general discomfort which may have led to a low feeding rate in the treated rats as earlier suggested (Oyewole *et al.*, 2007; Adeneye and Agbaje, 2008) or it could be that *Morinda lucida* interferes with the lipid metabolism of experimental animals. The relative organ (liver, heart, kidney and spleen) weight increased with increasing dose of *Morinda lucida* extract and decrease in weight gain. This was expected since the relative weight of the organs was based on the weight of experimental animals. That is the weight of organ divided by decreasing animal weight. Thus an inverse relationship does exist between the organ weight and animal weight. Other researchers believe that increase in the organ weight of animals could be associated to adaptive response (inflammation or hyperactivity) of the organs to

an accumulation of the extract (Jimoh *et al.*, 2008). However, this can only be the case if the weight was not altered.

Creatinine and urea are two serum metabolites that are indicative of the renal function. Though these metabolites are the end products of protein metabolism, their concentrations remain fairly constant under normal conditions unless renal function changes (Whitby *et al.*, 1988). In the present study, the decrease of creatinine and unalteration of urea nitrogen is an indication that *Morinda lucida* interferes with the protein oxidation and may affect the functioning of the kidney at high dosage or concentration. A number of factors have been identified as contributing to the formation of atherosclerotic plaques and the resulting impairment of coronary arterial blood flow. Among these, blood levels of lipids and lipoproteins play an important role (Shaila *et al.*, 1997). Sub-acute administration of *M. lucida* at 0.1 and 1 g kg⁻¹ did not significantly ($p > 0.05$) affect the plasma level of the cholesterol and triglycerides. This indicates that the extract did not present a risk of hypercholesterolemia and hypertriglyceridemia. However, the decreasing effect at dose level of 5 g kg⁻¹ is an indication of the plant extract as a hypolipidemic agent and may be interesting in weight loss research.

Impaired of insulin action and/or inadequate insulin secretion (Bailey, 2000) leads to hyperglycemia. The management of hyperglycemia is an important observation in cases of diabetes and often this is carried out by oral administration of hypoglycemic agents. Many hypoglycemic agents of plant origin are being used in traditional medicine and some have been investigated. *Morinda lucida* leaves and roots have earlier been reported to be hypoglycemic (Olajide *et al.*, 1999; Kamanyi *et al.*, 2006). The ability of *M. lucida* at 5 g kg⁻¹ to significantly reduce plasma glucose concentration of normal albino rats is indicative of a possible hypoglycemic activity.

The liver is one of the most important organs in the body and it is responsible for metabolism and detoxification of all toxins that enter the body. Liver diseases resulting from liver damage is a global problem. Liver function test conducted through blood assays give information about the state of the liver and cellular integrity. Chemical and drugs are known to induced lipid peroxidation, cause the swelling and necrosis of liver cells, resulting to the release of cytosolic enzymes such as ALT, AST, ALP (Agbor *et al.*, 2005; Singh *et al.*, 1998). Thus, ALT and AST increases in plasma are an indication of liver damage. ALT is the most sensitive marker of the liver and this enzyme leaks out into the blood stream when there is a liver damage. Toxicants (stanozolol) and drugs (antiretrovirals, Paracetamol) have been reported to increase plasma level of ALT and AST as a measure of hepatotoxicity (Mosallanejad *et al.*, 2011; Umar *et al.*, 2008; Basu *et al.*, 2009). An increase in the activity of ALT and AST was observed in this study at high dose administration of 5 g kg⁻¹ of the extract compared to the control group. This observation was confirmed in the histopathological examination which reveals the presence of steatosis in the hepatic cells of animals administered 5 g kg⁻¹ *Morinda lucida* extract. Steatosis is the appearance of fatty liver due to toxicity which may obstruct the lipid metabolism. In fatty liver, large droplets of fat, containing mostly triglycerides, collect within cells of the liver. The most common cause of steatosis is alcoholism. In an earlier study, Fakurazi *et al.* (2008) reported the development of steatosis in ethanol toxicity.

CONCLUSION

The aqueous extract of *Morinda lucida*, may not be toxic at low dosage in sub-acute administration. *Morinda lucida* reduces plasma glucose and lipid concentrations, it may find

application as antidiabetic and hypolipidemic agent. However, further research is needed to substantiate this claim.

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