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Acute toxicity, biochemical and haematological study of *Aframomum melegueta* seed oil in male Wistar albino rats ☆

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ABSTRACT

Ethnopharmacological relevance: *Aframomum melegueta* is a popular medicinal plant in Nigeria believed to have many agents acting in different ways to bring about human health benefits. This study aimed to determine the acute toxicity, identify some phytochemicals known to be present in this plant and the possible effects on lipid profile, haematological indices and biomarker of prostate and cardiac dysfunction.
Materials and methods: Twenty four Wistar rats (284–326 g) were used in four groups of six animals. Group 1 (control) received normal saline; groups 2, 3 and 4, received intraperitoneal injection of 27.39, 54.77 and 82.16 mg/kg body weight of the extract respectively for 7 days. Haematological and biochemical parameters were measured.
Results: Alkaloids, flavonoids, saponins, tannins, cardiac glycosides, terpenoids and steroids were identified in this plant extract. The LD_{50} was 273.86 mg/kg body weight. Prostate Specific Antigen (PSA) decreased significantly in group 2. Testosterone increased significantly in all the test groups compared to the control. Cardiac troponin I (0 ng/dl) was recorded for the test groups while the control had 1.69 ± 0.12 ng/dl. Lipid profile results showed increase in HDL and decrease in total cholesterol and LDL-cholesterol. Haemoglobin (Hb) and Red Blood Cells count (RBC) decreased significantly in group 4. White Blood Cells count (WBC), Mean Cell Volume (MCV), Mean Cell Haemoglobin (MCH) and Mean Cell Haemoglobin Concentration (MCHC) did not change significantly.
Conclusion: *Aframomum melegueta* seed oil has the potential of ameliorating benign prostatic hyperplasia (BPH) and cardiac dysfunction as indicated by testosterone, PSA, lipid profile and troponin I levels. The LD_{50} of 273.86 mg/kg body weight is indicative of mild toxicity. The lower than normal Hb, RBC confirms the possibility of toxicity.

1. Introduction

Medicinal plants are the most common natural sources of human medicine and their wide use in traditional medicine is related to alleviation of health care burden worldwide. Furthermore, the use of medicinal plants and their bioactive agents in drug design and development has increased progressively in recent decades. Medicinal plants, bioactive agents, and their derivatives have been used in the management of cancer, hypertension, diabetes, and cardiovascular diseases. It is therefore obvious that in the 21st century medicinal plants and their bioactive agents/derivatives offer opportunities for disease management, especially where current orthodox treatment methods have often failed (Denmeade and Isaacs, 2004; Wang et al., 2006; Richter et al., 2007; Pucar et al., 2008). Some secondary plant-derived molecules used as medicinal agents include vinca alkaloids, camptothecin, terpene paclitaxel, artesunate and the lignin podophyllotoxin (Bolk, 2001; Efferth, 2006). There is therefore a strong likelihood that as research tools advances, more bioactive agents will be discovered, not only in new medicinal plants but in those that have been investigated and their bioactive agents reported.

We have rich literature on the pharmacology of herbal medicines from almost all parts of the world (Buck, 2004; Saeed et al., 2004; Tsai et al., 2006; Akpanabiatu et al., 2009a, 2009b, 2012; Bisong et al., 2012; Nwankpa et al., 2012). Research contributions are also available

☆Compounds present in plant material: 6-gingerdione SID 12642, 6-gingerol CID: 442793, 6-paradol CID: 94378, 8-gingerol CID:168114, 6-shogaol CID: 5281794, Alkaloids CID: 7288, Saponin SID: 135348245, Flavonoids SID: 135332484, Tannins SID: 53790482, and Terpenoids SID: 160644576.

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on the chemical composition of some lesser-known tropical plants that may have long been used in traditional medicine (Essien et al., 1995; Demo et al., 2005). Plants generally contain a variety of photochemicals such as phytosterols, phytoestrogen, terpenoids, flavonoids, oils, lectins, polysaccharides, glycosides, fatty acids, and amino acids (Wang et al., 2006; Li and Jiang, 2007; Yuh-Shyan et al., 2007; Akpanabiatu et al., 2009a, 2009b; Sharma et al., 2009). The application of bioactive agents of plant origin in disease management is a well known aspect of African traditional and orthodox medicine. The medicinal use of plants such as *Rauwolfia vomitoria* is dated back to BC 300 but it was not until the 21st century that its bioactive agent was discovered to have significantly suppressed growth and cell cycle progression of LNCaP cells *in vitro* and *in vivo* (Bemis et al., 2006; McLarty et al., 2009). The search for new therapeutic agents of plant origin is a global concern in disease management. Looking back on available body of literature evokes or generates further insight on the benefits of plant resources in drug development.

Aframomun melegueta (Rose), K. Schum (Zingiberaceae (AM)) is a tropical herbaceous perennial plant of the genus *Aframomum,* belonging to the family zingiberaceae (ginger family) of the angiosperms in the Kingdom plantae. This fruit bearing plant known as grain of paradise, Guinea grains, alligator pepper, melegueta pepper or Guinea pepper used in West African traditional medicine (Okolia et al., 2007; Ukeh et al., 2009; Okwu et al., 2010) produces edible spicy seed with pungent peppery taste due to aromatic ketones and essential oils such as: gingerol, shagaol, paradol, and alkaloids (Lachman-White et al., 1992; Dokosi, 1998; Iwu et al., 1999). The essential oils, polyphenol profile and antioxidant activity of *Aframomum melegueta*, have been reported (Iwu, 1993; Ajaiyeoba and Ekundayo, 1999; Gabriel et al., 2003; Jazet Dongmo et al., 2008; Juliani et al., 2008). It is used medicinally to treat many diseases including measles, leprosy; to stop lactation and post-partum haemorrhage, as antidiarrhea and antiinflammatory activity which may be due to prostaglandin inhibition, and membrane stabilizing activity respectively (Umukoro and Ashorobi, 2003, 2005).

Despite the numerous medicinal application and scientific reports on *Aframomum melegueta*, there is still no report on some vital biochemical markers of clinical significance. This study is therefore aimed at determining the acute toxicity of *Aframomum melegueta*, its effects on lipid profile, haematological indices and some biomarkers of prostate dysfunction.

2. Materials and methods

The dried fruits of *Aframomum melegueta* were bought from vendors in a market located in Ekpri Ikang, Akpabuyo Local Government Area of Cross River State, Nigeria. The botanist in the botanical garden of University of Uyo authenticated the fruit of the plant. A voucher specimen numbered MIA 2011 was submitted to the herbarium of the same school. The fruit was exfoliated to remove the seeds. The seeds were processed and extracted with 80% ethanol according to the method of Ugochukwu et al. (2003). The filtrate was concentrated using open water bath at 45 °C overnight.

Wistar albino mice and rats obtained from the animal house, Biochemistry Department, University of Uyo, were used in this study. The animals were maintained under standard laboratory conditions with rat chow (Guinea Feed Ltd., Nigeria) and water *ad libitum*. All animal experiments were carried out in line with the guidelines of Institutional Animal Ethical committee as approved by the graduate School, University of Uyo, Nigeria. Median lethal dose (LD_{50}) of *Aframomum melegueta* seed oil was determined using male albino mice according to the method of Lorke (1983). A total of 27 mice weighing between 30 and 35 g were used in three experiments of 9 mice each. Three groups of 3 mice were used in each experiment to determine the LD_{50}. Animals were fasted overnight before seed oil was administered intraperitoneally (ip). Dosages administered ranged from 100 to 2000 mg/kg body weight. Fraction and percentage of mortality were computed and recorded (Table 1). From the outcome of the three experiments the LD_{50} was calculated. The Lorke method determined the LD_{50} as a geometrical means of the maximum dose producing 0% mortality (a) and the minimum dose producing 100% mortality (b) using the formula: $LD_{50} = ab$ (Lorke, 1983). Twenty four adult albino Wistar rats (236–266 g) were used in four groups of six animals. Group 1 (control) received normal saline; groups 2, 3 and 4, received intraperitoneal injection of 27.39, 54.77 and 82.16 mg/kg body weight of the seed oil, representing 1/10, 2/10 and 3/10 of the LD_{50} respectively for 7 days.

Table 1
Results of acute toxicity test (LD_{50}) on albino mice treated with ethanol extract of *Aframomum melegueta* seed oil.

Experiment	Dose (mg/kg body weight)	Fraction of death	Percentage mortality (%)
1	100	0/3	0
	250	0/3	0
	2000	3/3	100
2	270	1/3	33
	290	2/3	67
	1500	3/3	100
3	300	3/3	100
	500	3/3	100
	1000	3/3	100

2.1. Animal sacrifice

All experimental animals were anaesthetized using chloroform fumes 24 h after the last administration of the extract. Blood samples were collected by cardiac puncture using a sterile needle and syringe into EDTA sample bottles for haematological studies while serum was extracted by centrifugation of the whole blood at 2000 rpm using a bench top centrifuge (MSE, England, United Kingdom). Sera were stored in the refrigerator until analyses were carried out. All the analyses were conducted with 48 h of sample collection.

2.2. Determination of biochemical parameters

BC-23400 haematological analyzer (Shenzhen Mindray, Bio-Medical Electronics Co., Ltd., China) was used in the determination of haematological indices. Lipid profile was determined by the enzymatic colorimetric methods using TECO diagnostic kits reagents (TECO Diagnostic, USA). The absorbance was measured using an Optima 3000 nano-UV/vis scanning spectrophotometer (Optima, USA). Cardiac troponin I was determined using an Oxis Research reagent kit (Oxis Intl' Inc., USA) and the absorbance was read using a TECO micro-well reader (TECO Diagnostic, USA). PSA and testosterone were determined using the ELISA method (TECO diagnostic micro-well kit reagents, TECO Diagnostic, USA). Quantification was carried out using a micro-plate reader (TECO Diagnostic, USA). Statistical analysis was carried out using the SPSS 11.0 statistical software (SPSS Inc., Chicago, IL).

3. Results

The effects of *Aframomum melegueta* seed oil on acute toxicity of albino mice (Table 1); haematological indices (Table 2), lipid profile (Table 3) and PSA, testosterone and troponin (Fig. 1) are reported.

Table 2
Effects of *Aframomum melegueta* seed oil on haematological indices of male Wistar albino rats.

Group	Hb (g/dl)	RBC × 10^6/μl	WBC × 10^3/μl	MCV (fl)	MCH (pg)	MCHC (g/dl)
1 (Control)	13.30 ± 1.02	7.93 ± 0.69	12.28 ± 2.54	55.28 ± 1.82	16.80 ± 0.78	30.38 ± 0.90
2 (27.39 mg/kg body weight)	12.94 ± 0.45	7.89 ± 0.38	10.74 ± 1.62	55.76 ± 1.40	16.42 ± 0.49	29.44 ± 1.03
3 (54.77 mg/kg body weight)	13.14 ± 0.73	7.90 ± 0.43	12.70 ± 1.92	54.34 ± 0.54	16.56 ± 0.29	30.46 ± 0.14
4 (82.16 mg/kg body weight)	11.70 ± 0.75[a,b]	6.93 ± 0.62[a,b]	10.32 ± 1.33	56.06 ± 1.20	16.90 ± 0.65	30.18 ± 0.76

Values are expressed as mean ± S.D., $n=6$. Hb=Haemoglobin, RBC=Red Blood Cell, WBC=White Blood Cell, MCV=Mean Cell Volume, MCH=Mean Cell Haemoglobin and MCHC=Mean Cell Haemoglobin Concentration.

[a] $p<0.05$ (test groups compared with control).
[b] $p<0.05$ (test group 4 compared with group 3).

Table 3
Effects of *Aframomum melegueta* seed oil on lipid profile of male Wistar albino rats.

Group	Total Chol (mg/dl)	Triglycerides (mg/dl)	HDL-Chol (mg/dl)	LDL-(mg/dl)
1 (Control)	69.20 ± 12.35	145.23 ± 12.61	10.44 ± 1.36	40.21 ± 10.98
2 (27.39 mg/kg Body weight)	64.35 ± 2.96	81.32 ± 9.56[a]	11.39 ± 1.29	30.78 ± 5.91
3 (54.77 mg/kg body Weight)	66.61 ± 6.82	62.71 ± 1.85[a]	12.33 ± 1.94	35.17 ± 4.82
4 (82.16 mg/kg Body weight)	43.66 ± 9.93[a,c]	100.74 ± 11.57[a,b]	13.99 ± 1.53[a]	22.54 ± 1.49

Values are expressed as mean ± S.D., $n=5$. Chol=Cholesterol, HDL=High Density Lipoprotein, and LDL=Low Density Lipoprotein.

[a] $p<0.05$ (test groups compared with control).
[b] $p<0.05$ (test group 3 compared with group 4).
[c] $p<0.05$ (test group 4 compared with groups 2 and 3).

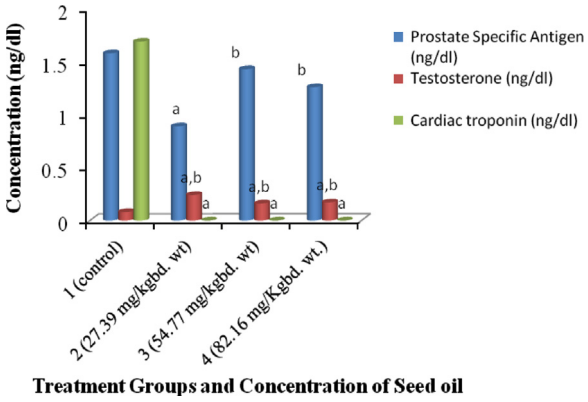

Fig. 1. Effect of *Aframomum melegueta* seed oil on serum prostate specific antigen, testosterone and cardiac troponin I levels of male Wistar albino rats. Values are expressed as mean ± S.D., $n=6$; $a=p\leq 0.05$ (test groups compared with control), and $b=p\leq 0.05$ (test groups 3 and 4 compared with group 2).

Saponin, tannin, alkaloid, steroid, cardiac glycosides, flavonoid, and terpenoids are already known phytochemicals in seed extract of this plant and some of these have been isolated and characterised (Okwu and Njoku, 2010; Gröblacher et al., 2012).

3.1. Acute toxicity (LD_{50}) determination

The LD_{50} determined in the acute toxicity study carried out using albino mice in this investigation was calculated to be 273.86 mg/kg body weight. Table 1 shows the percentage mortality in the acute toxicity study.

3.2. Biochemical parameters

The effects of exposure of male Wistar albino rats to *Aframomum melegueta* seed oil extract (concentrations: 27.39, 54.77, and 82.16 mg/kg body weight for 7 days), selected based on LD_{50} of 273.86 mg/kg body weight, were determined using haematological indices, troponin I, testosterone, prostate specific antigen (PSA), lipid profile. The seed oil of *Aframomum melegueta* caused significant ($p<0.05$) decrease in PSA levels of experimental animals and a significant increase in testosterone (Fig. 1), though these changes were not completely dose dependent. Cardiac troponin I was completely absent in all the test groups or lower than the detection limit of the method used in this experiment (Fig. 1). This is an indication that the cardiac muscle of the experimental animals was sensitive to the different doses of the seed oil of *Aframomum melegueta*.

4. Discussion

In this study, we described some biochemical effects of the seed oil of *Aframomum melegueta* on Wistar albino rats. We also examined the effects of *Aframomum melegueta* seed oil on acute toxicity using the albino mice model and some biochemical indices of adult male Wistar albino rats were investigated as an attempt to ascertain its medicinal significance. The result of acute toxicity study shows that the LD_{50} of *Aframomum melegueta* seed oil is 273.83 mg/kg body weight. The LD_{50} value obtained in this work is low compared to other medicinal plants and is an indication of a possibility of this plant being toxic. Okokon and Nwafor (2009) have reported LD_{50} level in this range as being moderately toxic.

The effects of *Aframomum melegueta* seed oil on the male endocrine system showed a decrease in the level of PSA and an increased testosterone level (Fig. 1). Decreased PSA reported in this investigation is indicative of a non-enlarged/cancerous prostate since increase level of PSA is often associated with prostate cancer or BPH. The seed oil of *Aframomum melegueta* may protect against cancer and BPH. Equally, increase in testosterone levels of male experimental animals reported in this study is a clear indication of decreased dehydro-testosterone (DHT) whose precursor is testosterone. A decrease in the expression of 5-alpha reductase, an enzyme with the primary duty of converting testosterone to DHT has resulted in a high level of testosterone in this work. This is in agreement with the report on the androgenic effect of *Mondia whitei* roots in male rats (Watcho et al., 2004). Tannins, a protein inhibitor present in the seed oil of *Aframomum melegueta* maybe

implicated in the inhibition of 5-alpha reductase activity (Qian and Wang, 1984).

Troponin I was completely absent, indicating the cardiac protective effect of the extract. This is further confirmed by the low cholesterol level reported in this study. Cholesterol is not only an important biomolecule, but also a marker of cardiovascular disease. Increase of cholesterol has been implicated in hypertention and other cardiovascular diseases (atherosclerosis, coronary artery disease, myocardial infarction, stroke, congestive heart failure, *etc*.) and in diabetes. In this work, value of the lipid profile study showed significant changes in all parameter in group 3 animals. The reduction in the total cholesterol, triglycerides (TG), and LDL-cholesterol is an indication that the seed oil of *Aframomum melegueta* has some hypolipdaemic properties at the concentration of 82.16 mg/kg body weight. The increased HDL and decreased LDL are of great significance in cardiovascular diseases management. The reverse cholesterol transport (RCT) pathway is complex and the precise mechanisms, receptors and functions have not been fully elucidated. However, high level HDL-cholesterol suggests that the RCT pathway is the major cardioprotective function of HDL (Kontush and Chapman, 2006). It is therefore not unlikely that the bioactive agent/s in the seed oil of *Aframomum melegueta* may have positive influence in the reverse transport of cholesterol.

The haematological indices: haemoglobin, PCV, WBC, RBC Hb, MCV, MCH, and MCHC were estimated to establish the haematotoxicity of the seed oil of *Aframomun melegueta*. The results of this investigation showed that seed oil of *Aframomun melegueta* did not improve the haematological indices of experimental animals. However, Hb and RBC decreased significantly in group 4; implying that the seed oil of this plant may be haematotoxic at a certain concentration. The low Hb and RBC in this study may be as a result of iron deficiency or chemically induced anaemia (Akpanabiatu et al., 2012). Iron deficiency may have resulted from the effect of iron chelators presence in the extract.

5. Conclusion

We observed that seed oil of *Aframomum melegueta* seed oil is a potential hypolipidaemic and cardioprotective substance and may provide a bioactive agent(s) for biopharmaceutical applications. It is also capable of ameliorating benign prostate hyperplasia and it may contain inhibitors of 5-alpha reductase since increased testosterone level is observed in this study. More investigations on this plant seed extract are ongoing in a collaborating laboratory in the USA.

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