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Full Length Research Paper

Toxicity of four herbs used in erectile dysfunction;*Mondia whiteii*,*Cola acuminata*,*Urtica massaica*, and *Tarenna graveolens*in male rats

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In Sub-Saharan Africa, herbal medicines are commonly used for prevention or treatment of illnesses, including erectile dysfunction. Contemporary medicines used to manage erectile dysfunction are not only inaccessible to local populations, but also impose significant out-of-pocket expenditure on patients. Herbal medicines offer alternatives for alleviating erectile dysfunction, which has clinical, psychological and societal consequences. Regardless, there are increasing concerns about the safety and/or toxicity of herbal medicines. In this study, the toxicity of aqueous extracts of four herbs, commonly used in south-western Uganda, to manage erectile dysfunction, was investigated. Acute and sub-chronic toxicity studies were conducted following the Organization for Economic Cooperation and Development (OECD) guidelines for toxicity study. All four plants extracts were found safe at single dose exposure up to the limit dose of 5000 mg/kg. Extracts of *Cola acuminate* reduced the weights of the experimental animals, *Tarenna graveolens* and *Cola acuminata* indicated low level liver toxicity and *Tarenna graveolens, Cola acuminata* and *Urtica massaica* indicated low level renal toxicity following multiple exposures for 90 days. Three of the four herbs studied have shown low level toxicity on multiple exposure for 90 days.

Key words: Toxicity, *Mondia whiteii*,*Cola acuminata*,*Urtica massaica*, and *Tarenna graveolens.*

INTRODUCTION

In Sub-Saharan Africa, there is an increase in the use of herbal medicine with prevalence rate varying among different countries. In Uganda, about 80 to 90% of the population is reported to use herbal medicines (Kamatenesi-Mugisha et al., 2005; Ijeoma et al., 2014). Herbal medicines are derived from parts of the plant,

including leaves, stems, flowers, roots, and seeds. Herbal extracts contain active ingredients including fatty acids, sterols, alkaloids, flavonoids, glycosides, saponins, among several others (Rotblatt and Ziment, 2002).

Despite the increased use of herbal medicines, not much has been done to investigate the toxicity on vital organs such as the liver, or kidneys, and herbal medicines continue to be consumed by the local population with less regard for safety. Herbs though perceived to be natural and safe by most of the population, they are not without harm, including side effects (Kamatenesi-Mugisha and Oryem-Origa, 2005).

An investigation into the disclosure and adverse effects of complementary and alternative medicine (CAM) used by hospitalized patients in North East England reported that nearly half of patients (45.8%) who used CAM within two years experienced various CAM side-effects that tended to resolve after discontinuation (Bello et al., 2012).

Erectile dysfunction which is the inability to achieve or maintain an erection sufficient for satisfactory sexual performance requires using herbs for a long time as there is no cure for it. Several herbal medicines are commonly used for the treatment of erectile dysfunction in South-western Uganda including; *Citropsis articulata* roots, *Mondia whiteii* roots, *Cola acuminata* fruits, *Urtica massaica* leaves, and *Tarenna graveolens* roots (Kamatenesi-Mugisha and Oryem-Origa, 2005). Literatures reviewed indicated that *Mondia Whitei* is used traditionally as an antacid and to treat indigestion; as a tonic; to stimulate appetite; and infusions of the root are used in Zimbabwe for treating anorexia and bilharzia.

Fits in children and stress and tension in adults are apparently also treated with this plant. The roots are used as an aphrodisiac and for the treatment of erectile dysfunction and impotence (http://www.plantzafrica.com accesses 6.6.2015) and for appetite and libido, as a galactagogue, fertility medication, and as an anti-depressant (Oketch-Rabah, 2012). Urtica massaica is reportedly used for treatment of diarrhea in Rwanda and commonly eaten by Mountain Gorillas (Nahayo et al., 2008). *Cola acuminata* is reported to have stimulant action apart from the caffeine content, valuable nervine, heart tonic, and a good general tonic. (www.botanical.com) and no other medicinal use of *Tarenna graveolens* was found other than its use in the management of erectile dysfunction in south-western Uganda (Kamatenesi-Mugisha and Oryem-Origa, 2005).

However, there is no documented scientific evidence to suggest that herbs or their products are safe either for short or long term use. This study was conducted to determine the safety of the extract of four herbs used for the treatment of erectile dysfunction. Specifically the herbal extracts were evaluated for their; (i) acute toxicity, (ii) effects on weight (ii) effects on renal function and (iv) effects on liver function.

MATERIALS AND METHODS

A total of 120 male Wistar rats were used to test the four herbal extracts (i.e. 30 rats per herbal extract). For each extract, the rats were put into 4 groups of 6 rats each and 6 other rats were used for the acute toxicity test. The dry powders of aqueous extracts of *Mondia whiteii* roots, *Cola acuminata* fruits, *Urtica massaica* leaves, and *Tarenna graveolens* roots were used, 99% chloroform was used for anesthesia. Dissecting kits, needles, and syringes were utilized for sample removal. EDTA- containing vacutainers were used to store the samples before analysis.

Collection, identification and preparation of plant materials

All the four herbs were collected from areas of south-western Uganda. Samples of each plant material were taken for botanical identification at the Science and Biology departments of Mbarara University of Science and Technology, where they were authenticated by Dr. Eunice Apio Olet.

They were then transported to the University's pharmaceutical science laboratory for analysis. All herbs were initially washed under running water, prior to extraction. A reasonable quantity of *Cola accuminata* fruits and *Mondia whiteii* roots were extracted fresh, while *Urtica massaica* leaves and *Tarenna graveolens* roots were air dried at room temperature for two weeks before extraction.

Extraction and drying

All plant materials were warm macerated by boiling, strained using muslin cloth and the resulting extract was filtered using Whatman filter paper number 1. The extracts were dried in the incubator at 60°C for 6 days in a large open container, stored in the fridge at ±4°C before and while the experiment was going on.

Animal handling and preparation

Male Wistar Albino rats 3 to 4 month old were used in this study. They were obtained from the pharmacology and toxicology departments of Kampala International University-Western Campus, transported in well ventilated, wooden cages and acclimatized for two weeks in the animal house facility at Mbarara University of Science and Technology before use.

Housing

The animals were kept in a well-ventilated animal house facility at Mbarara University of Science and Technology, in well-spaced cages, which were lined with soft wood shavings. The cages were

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cleaned twice weekly and the animals had free access to feed and water *ad libitum.* Throughout the study duration, the animals were fed on standard NUVITA® mice pencils.

Experimental procedures

Grouping and dosing of animals

All animals were put into 4 groups A, B, C and D, with each consisting of 6 animals. Groups A, B, and C were administered the extract by the oral route using an oral cannular at doses of 125, 250 and 500 mg/kg. Care was taken to ensure that no animal received more than 2ml of the prepared extract at each dose.

Acute toxicity study

The acute toxicity study was conducted using the limit test dose of 5,000 mg/kg body weight. The animals were fasted overnight for 12 h; food was withdrawn, but drinking water maintained. The animals were observed for signs of toxicity (hypoactivity, urination, priapism, fatique, coma and death) for 6 h after treatment, and after every 30 min for another 3 h. They were then observed daily for 14 days.

Sub-chronic toxicity

Animal grouping

Animals used in the study were in 4 broad groups of *Tarenna graveolens, Urtica massaica, Cola acuminate and Mondia whiteii.* Each of these groups was subdivided into subgroups; 'A' for the dose level 125 mg/kg, 'B' for 250mg/kg and 'C' for 500 mg/kg. One group was kept as the control for all the animals under treatment by the four plants extracts and was treated with distilled water at a dose of 10 mls/kg.

Sub-chronic toxicity was conducted following the OECD (organization for economic co-operation and development) guidelines (OECD 423, 2001). The study was conducted for 90 days with daily administration of the extracts at 125, 250 and 500 mg/kg. Parameters investigated as a function of chronic toxicity included effects on body weight and laboratory markers for liver function and renal function.

Termination of the experiment

At the end of the 90th day of the administration of the extracts, all animals were deeply anaesthetized using chloroform, an abdominal incision made, a thoracotomy performed and 3 mls of blood sample removed by Cardiac puncture for analysis. Blood samples were taken, and plasma analysed for aspartate transaminase (AST) and alanaine aminotransferase (ALT) to assess liver function while Creatinine and urea were examined as markers of renal function.

Statistical analysis

Graphpad prism version 5 was used to analyse the data obtained. Results of all parameters; renal function test (RFT) and liver function test (LFT) was tested by Oneway ANOVA, followed by Turkey Multiple comparison test at P = 0.05.

Ethical consideration

Ethical approval was granted by the Mbarara University of Science and Technology Institutional Review Committee (MUST-IRC), given approval number MUIRC 01/02-13 and Uganda National Council for Science and Technology (UNCST), given approval number, HS 1557. The animals were handled following the National Institute of health (NIH) guidelines for animal handling in teaching and research (NIH, 2011).

RESULTS

Acute toxicity studies

At the limit test dose of 5000 mg/kg, none of the four herbal extracts induced any observable signs of toxicity (hypo activity, urination, priapism, fatigue, coma and death).

Subchronic toxicity studies

Effects on body weight

Comparison of three doses of the extract indicates that *cola acuminata* at the dose of 500 mg/kg caused reduction on body weight from week 9 through week 14. Followed by 250 mg/kg and finally the dose of 125 mg/kg (Figure 1). Three dose levels of the extracts of *Tarenna graveolens* and *Mondia whiteii* 125, 250 and 500 mg/kg did not affects the weight gain by the animals.

Figure 2 compares the effects of three dose levels of the extracts of *Urtica massaica* on growth and indicated that the extract had negative effects on weight gain by the animals during the 90 days of treatments. All had weight curves below the control group, with the dose of 250 mg/kg showing greater effects than 500 and 125 mg/kg. Figure 3 compares all the extract at 500 mg/kg and shows that *Cola acuminata* at the dose of 500 mg/kg caused much reduction on body weight of the animals during the 90 days of treatment compared to the other three extracts.

Effects of herbal extracts on liver function

Results of analysis indicated that there was significant effect of oral administration of the four extracts AST levels at $p < 0.05$, [$F (12, 65) = 3.290$, $p = 0.0009$]. Turkey HSD post hoc test however did not reveal any significant difference between or within groups (Table 1). It was noted that there was no significant effect of oral administration of the four extracts on Alanine aminotransferase (ALT) levels at $p < 0.05$,[$F (12, 65) = 1.865$, $p = 0.0557$] (Table 2).

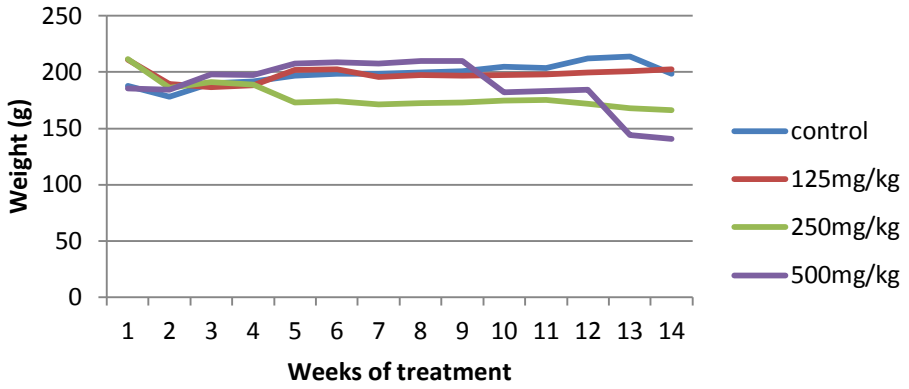

Figure 1. Effects of *Cola acuminata* extract on body weight following treatment for 90 days. *Cola acuminata* at the dose of 500 mg/kg had a greater effect on body weight from week 9 through 14 followed by 250 mg/kg, while the dose of 125 mg/kg almost had similar results to that of the control groups treated with distilled water.

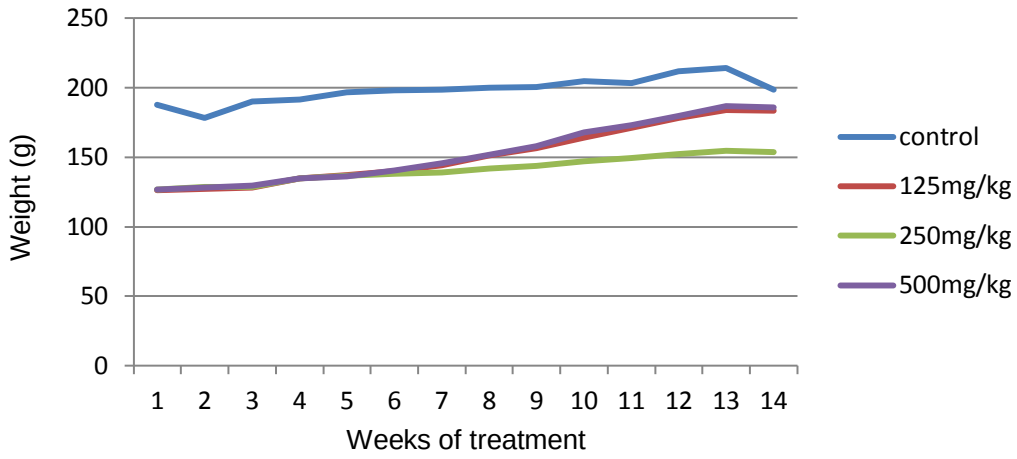

Figure 2. Effects of *Urtica massaica* extract on body weight following treatment for 90 days. *Urtica massaica* had no effects on weight gain by the animals during the 90 days of the treatments. All had weight curves below the control group, starting from week one, but showed normal increase in weight over the 90 days of treatment.

ALT levels were however higher in *Cola acuminata* treated group wile AST levels were higher in *Tarenna graveolens, Urtica massaica* and *Cola acuminata* treated groups, respectively.

Effects of herbal extracts on renal function

Results indicated that there was no significant effect of oral administration of the four extracts on Creatinin levels at $p < 0.05$, [$F(12, 65) = 0.8321$, $p = 0.6175$] (Table3). *Tarenna graveolens* and *Urtica massaica* increased levels of creatinin above that of the control group. No significant effect was noted on oral administration of any of the four extracts on urea levels at $p < 0.05$ level, [$F(12, 65) = 1.483$, $p = 0.1536$] (Table 4). *Urtica massaica, Tarenna graveolens* and *Cola acuminate,* respectively increased levels of urea above that of the control groups.

DISCUSSION

This current study was conducted to determine the toxicity of the aqueous extracts from four plants; *Tarenna*

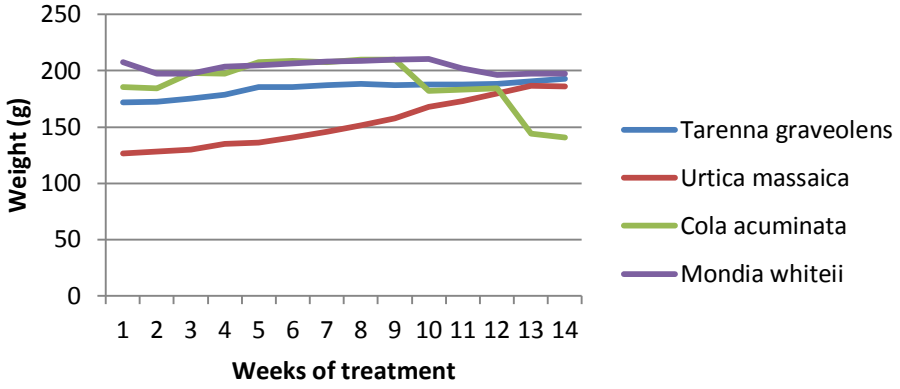

Figure 3. Effects of crude aqueous extract of the four herbs at 500 mg/kg on body weight following treatment for 90 days.*Cola acuminata* at the dose of 500 mg/kg caused much reduction on body weight of the animals during the 90 days of treatments compared to the other three extracts.

Table 1. Effects of crude extracts of *Tarenna graveolens, Urtica massaica, Cola acuminata* and *Mondia whiteii*on AST levels in Wistar rats.

Extract and dose (mg/kg)	No. per group	Mean AST levels (U/l)	Std dev	95% CI		Min	Max
				Lower	Upper		
Control	6	118	55.41	59.85	176.1	69.0	210.0
Tarenna (125)	6	232.2	111.3	115.4	348.9	69.00	361.0
Urtica (125)	6	195.7	54.99	138.0	253.4	124.0	268.0
Cola (125)	6	122.8	83.93	34.76	210.9	58	280.0
Mondia (125)	6	108.8	44.21	62.44	155.2	80.0	198.0
Tarenna (250)	6	203.3	107.1	90.93	315.7	48.0	132.0
Urtica (250)	6	216	94.40	116.9	315.1	61.0	293.0
Cola (250)	6	132.5	55.23	74.54	190.5	57.0	206.0
Mondia (250)	6	93.67	21.57	71.03	116.3	70.0	117.0
Tarenna (500)	6	207.8	93.46	109.8	305.9	114.0	379.0
Urtica (500)	6	201.5	39.10	160.4	242.5	145.0	261.0
Cola (500)	6	117.8	44.32	71.32	164.3	39.0	162.0
Mondia (500)	6	94.83	18.10	75.83	113.8	74.0	122.0

Tarenna = *Tarenna graveolens*, Urtica = *Urtica massaica*, Cola = *Cola acuminata*, Mondia = *Mondia whiteii*. Table 1 above indicates that there was significant effect of oral administration of the four extracts AST levels at $p < 0.05$, [$F (12, 65) = 3.290$, $p = 0.0009$] (Table1). Turkey HSD post hoc test however did not reveal any significant difference between or within groups. *Tarena graveolens* elevated AST levels higher than the other three extracts, followed by *Urtica massaica* and *Cola acuminata* while *Mondia whitei* was not toxic.

graveolens, *Urtica massaica*, *Cola acuminate* and *Mondia whiteii,* some of the most commonly used herbs for the treatment of erectile dysfunction in men in South-western Uganda. Effects were monitored on weight gain, liver and renal functions. All test performed were on the assumption that, extracts from the four herbs are not toxic. Acute toxicity study was conducted following the OECD 423 guidelines at the limit test of 5000 mg/kg body weight and indicated that the extracts of the four extracts are not toxic. The dose of 5000 mg/kg was chosen based on the fact that no prior toxicological information is available and the fact that doses consumed by humans are not well known, because none of the abnormal activities which were monitored such as hypo activity, urination, priapism, fatique, coma, death and others which could be attributed to extracts administered within a reasonable time were not observed, this extracts classifications falls in the unclassified category. In the

Table 2. Effects of crude extracts of *Tarenna graveolens, Urtica massaica, Colaacuminata* and *Mondia whiteii*on ALT levels in Wistar rats.

Extract and dose (mg/kg)	No. per group	Mean ALT levels (U/l)	Std dev	95% CI		Min	Max
				Lower	Upper		
Control	6	140.0	54.61	82.69	197.3	72.0	266.0
Tarenna(125)	6	77.33	26.55	49.48	105.2	37.0	114.0
Urtica(125)	6	113.7	33.41	78.60	148.7	78.0	171.0
Cola(125)	6	195.8	181.0	5.836	385.8	63.0	552.0
Mondia(125)	6	171.8	82.34	85.43	258.2	115.0	337.0
Tarenna(250)	6	76.17	22.48	52.57	99.76	33.0	98.0
Urtica(250)	6	142.8	89.07	49.36	236.3	20.0	276.0
Cola(250)	6	174.2	58.31	113.0	235.4	89.0	258.0
Mondia(250)	6	150.5	46.59	101.6	199.4	82.0	207.0
Tarenna(500)	6	90.83	32.67	56.55	125.1	58.0	153.0
Urtica(500)	6	107.0	45.57	59.18	154.8	38.0	166.0
Cola(500)	6	186.3	70.35	112.5	260.2	74.0	252.0
Mondia(500)	6	156.3	54.60	99.03	213.6	96.0	256.0

Tarenna = *Tarenna graveolens*, Urtica = *Urtica massaica*, Cola = *Cola acuminata*, Mondia = *Mondia whiteii*. Table 2 above shows that there was no significant effect of oral administration of the four extracts on Alanine aminotransferase (ALT) levels at $p < 0.05$, [$F(12, 65) = 1.865$, $p = 0.0557$] (Table 2). *Cola acuminata* extract indicated more toxicity to the liver by elevating ALT levels above that of the control group than the other three extracts.

Table 3. Effects of crude extracts of *Tarenna graveolens, Urtica massaica, Colaacuminata* and *Mondia whiteii* on creatinin levels in Wistar rats.

Extract and dose (mg/kg)	No. per group	Mean creatinin levels (mg/dl)	Std dev	95% CI		Min	Max
				Lower	Upper		
Control	6	0.3217	0.1559	0.1581	0.4852	0.1800	0.5200
Tarenna (125)	6	0.4417	0.1129	0.3232	0.5601	0.2700	0.5500
Urtica (125)	6	0.3417	0.08353	0.2540	0.4293	0.2400	0.4500
Cola (125)	6	0.2900	0.08462	0.2012	0.3788	0.1400	0.3700
Mondia (125)	6	0.5900	0.7801	0.2287	1.409	0.1300	2.170
Tarenna (250)	6	0.3683	0.1692	0.1908	0.5459	0.0600	0.5300
Urtica (250)	6	0.4233	0.09913	0.3193	0.5274	0.2800	0.5900
Cola (250)	6	0.4933	0.3787	0.09589	0.8908	0.2300	1.220
Mondia (250)	6	0.2183	0.06242	0.1528	0.2838	0.1100	0.2800
Tarenna (500)	6	0.4133	0.1244	0.2828	0.5438	0.1800	0.5300
Urtica (500)	6	0.3833	0.07033	0.3095	0.4571	0.3000	0.4900
Cola (500)	6	0.3683	0.1631	0.1971	0.5395	0.1600	0.6500
Mondia (500)	6	0.2700	0.08602	0.1797	0.3603	0.1800	0.4300

Tarenna = *Tarenna graveolens*, Urtica = *Urtica massaica*, Cola = *Cola acuminata*, Mondia = *Mondia whiteii*. Table 3 above indicates that there was no significant effect of oral administration of the four extracts on Creatinin levels at $p < 0.05$, [$F(12, 65) = 0.8321$, $p = 0.6175$] (Table1). The extract of *Tarenna graveolens* raised creatinin levels in treated rats higher than the other extracts.

region, the herbs are used by males with suspected cases of erectile dysfunction, a reason for which toxicity study was conducted using male animals. Biochemical indicators of toxicity within twenty four hour (24 h) to forty eight hour (48 h) period, such liver and renal function tests were not done however in this case. This result indicated that aqueous extract of the four herbs are safe compared to that of *Assa-foetida L* in rats which were

Table 4. Effects of crude extracts of *Tarenna graveolens, Urtica massaica, Cola acuminata* and *Mondia whiteii* on urea levels in Wistar rats.

Extract and dose (mg/kg)	No. per group	Mean urea levels (mg/dl)	Std dev	95% CI		Min	Max
				Lower	Upper		
Control	6	34.50	10.62	23.36	45.64	21.00	50.00
Tarenna (125)	6	47.50	16.63	30.04	64.96	31.00	79.00
Urtica (125)	6	50.17	17.61	31.68	68.65	36.00	77.00
Cola (125)	6	40.83	13.89	26.26	55.41	29.00	64.00
Mondia (125)	6	40.33	8.042	31.89	48.77	30.00	51.00
Tarenna (250)	6	44.50	10.31	33.68	55.32	32.00	59.00
Urtica (250)	6	51.67	12.04	39.03	64.31	39.00	66.00
Cola (250)	6	44.33	8.802	35.10	53.57	32.00	55.00
Mondia (250)	6	35.67	18.70	16.04	55.30	19.00	69.00
Tarenna (500)	6	41.00	4.604	36.17	45.83	33.00	46.00
Urtica (500)	6	48.17	6.555	41.29	55.05	41.00	59.00
Cola (500)	6	32.83	6.795	25.70	39.96	20.00	40.00
Mondia (500)	6	40.83	10.57	29.74	51.93	27.00	54.00

Tarenna = *Tarenna graveolens*, Urtica = *Urtica massaica*, Cola = *Cola acuminata*, Mondia = *Mondia whiteii.* Table 4 above indicates no significant effect of oral administration of any of the four extracts on urea levels at $p < 0.05$ level, [$F (12, 65) = 1.483$, $p = 0.1536$]. Extract of *Urtica massaica* elevated urea levels to a greater extent followed by *Tarenna graveolens, Cola acuminata* and finally *Mondia whiteii.*

found to have LD50 of 5 g/kg in rats (El-Kassis et al., 2009). Effects on weight indicate that *Cola acuminate* generally affected weight gain by the animals in a dose dependant manner (Figure 1 and 3). This could be attributed to its traditional use in the suppression of appetite in most parts of West Africa and thereforecausing appetite suppression in the animals (Lowe et al., 2014; Endrini et al., 2011). A 90 day sub-chronic toxicity study was then conducted based on results of acute toxicity study and using doses of 125, 250 and 500 mg/kg which were administered orally on a daily basis. These doses were chosen to somehow reflect what a person would most likely take to a greater level as there is no accurate information as to the exact quantity taken at any one point.

A one-way ANOVA test on the effects of the four extracts on liver function and specifically on aspartate aminotransferase levels indicated significant effects ($P < 0.0009$). Turkey HSD post hoc test however did not indicate any significant difference between or within groups. This could be due to the fact that data generated from the laboratory analysis varied, notwithstanding the F-statistics of 3.290.

The increase in AST level in the *Tarenna graveolens, Urtica massaica* and *Cola acuminata* treated groups above those of the control indicates low level toxicity of these three plants extracts to the liver and only *Cola acuminata* showed a larger increase in ALT levels $p = 0.0557$.

One-way ANOVA test on the effects of the four extracts on creatinin and urea levels did not yield any significant results at $P < 0.05$ with P-values of, $p = 0.6175$ and $p = 0.1536$ (Table 2, 3 and 4), respectively. This current study was conducted using dose levels as comparative to studies on *Ferula harmonus* oil (El-Thaher et al., 2001) which was conducted using doses of 0.05, 0.5 and 2 g/kg, respectively. Results from this current study however, indicates higher values at the dose of 500 mg/kg on both AST and ALT levels, a possible indication that these extracts could be more toxic to the liver as compared to *Ferula harmonus* oil. The extracts of the four plants in this current study has also demonstrated safety as compared to that of combination infusion of *Piper retrofractum* L., *Centella asiatica* and *Curcuma domestica* in rats (Rahmawati and Saiful, 2012).

This result generally shows that extracts of *Tarenna graveolens*, *Urtica massaica*, *Cola acuminata* at lower doses of up to 500 mg/kg are slightly toxic on repeated exposure in rats. It has also indicated that extracts of *Mondia whiteii* are safer. Studies with higher doses above these dose levels or even repeats using similar doses are thus warranted for effective classification of their safety profiles.

Conflict of Interest

The authors have not declared any conflict of interest.

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