Original Article

Journal of Medicinal Herbs and Ethnomedicine 2015, 1(1): 45-49
http://scienceflora.org/journal/jmhe/
doi:10.5455/jmhe.2015-07-011

Effect of the sub-chronic administration of some commonly used herbal products on the liver enzymes, body weight, and feed intake of albino Wistar rats: Any implication for public health?

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Received: 22.07.2015
Revised: 31.07.2015
Accepted: 01.08.2015
Published: 01.08.2015

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ABSTRACT

The present study was focused to assess the effects of the administration of commonly used herbal products *viz*.: Yoyo cleansing bitters, T. angelica herbal tonic, and Bio-Strath elixir on the liver enzymes, body weight, and feed intake in adult albino Wistar rats. A total number of seventy Wistar rats were divided into three major groups. Each group received a particular herbal product and each of these groups was further subdivided into subgroups that received various dosages of each of the herbal products. The rats were acclimatized for 14 days after which they received different doses of each of the herbal products for 6 weeks. The body weight, feed intake, and modulation in liver enzymes were evaluated. The feed intake and body weights were reduced in animals that received T. angelica herbal tonic and Yoyo cleansing bitters at twice the normal dose once and twice daily, but the reverse was the case for the rats that received Bio-Strath elixir even at higher doses. The liver enzymes were increased at all doses in rats which were given Bio-Strath elixir but it was not significant ($P > 0.05$), while those of Yoyo bitters and T. angelica herbal tonic were significantly increased ($P < 0.05$), especially at higher doses. From our study results it was suggested that a higher dose than the manufacturer's recommended dose taken for a longer duration can elevate liver enzyme, thus causing abnormal liver function.

KEY WORDS: Body weight, herbal products, liver enzymes, Wistar rats

INTRODUCTION

Herbal medicines in which plants dried or in extract form are used as therapeutic substances, is one of the practices encompassed by the term "Complementary and Alternative Medicine" (Liu *et al.,* 2004). It has gained enormous popularity worldwide over the past 20 years, and several studies continue to demonstrate the amazing therapeutic benefits inherent in medicinal plants (Ekor *et al.,* 2010; Salau *et al.,* 2010). Herbal treatments not only heal, but are also the most natural ways to cure most of the diseases ranging from minor ailments to the most life-threatening ones (Sudha *et al.,* 2009).

The World Health Organization estimates that 80% of the population of some Asian and African countries presently used herbal medicine for some aspect of their primary health care (Bodeker and Kronenberg, 2002). The increased patronage of these remedies is often predicated on the assumption that they are harmless since they are prepared from natural sources. However, toxicity relating to herbal medicine is becoming widely recognized, and recent researches have highlighted the possible systemic toxicities that might be associated with high doses or due to prolonged usage of the products (Joshua *et al.,* 2001; Elvin-Lewis, 2001).

A classical example is hepatotoxicity arising from the usage of herbal drug. Drug-induced liver injury accounts for 25% of all hospital admissions and 50% of all acute liver failures with risk of death or of liver transplantation (Chitturi and Farrell, 2000; Woolf, 2003). This is mostly as a result of overdosage of herbal preparations as most people tend to misuse them, because of the belief that they are of natural origin, and as such harmless. Unfortunately, there is limited

scientific evidence regarding the safety and efficacy of these products to back up the continued therapeutic application of these remedies. The rationale for their utilization has rested largely on long-term clinical experience (Pak *et al.,* 2004).

However, with the upsurge in the usage of herbal medicines, a thorough scientific investigation of these plants will go a long way in validating their folkloric usage. Yoyo cleansing bitters, angelica herbal tonic, and Bio-Strath elixir are examples of such polyherbal formulations used for various ethnomedicinal purposes in Nigeria.

MATERIALS AND METHODS

Study Location

The study was conducted at the Faculty of Pharmacy, Madonna University, Elele, River State of Nigeria.

Herbal Drug

The selected herbal products used include: (1) Yoyo cleansing bitters; (2) Bio-Strath elixir; and (3) T. angelica herbal tonic. They were all obtained from Flowell Pharmacy Nigeria Limited, Port Harcourt.

Materials and Equipment

Weighing balance; cages with 10 compartments; animals feed (include manufacturer address); chloroform (to anesthetize the rats); spectrophotometer; and Universal bottle.

Product Evaluation

The safety stage of the product was assessed at the Department of Pharmacology of the University of Lagos, and it was found to be safe for experimental animals.

Another test (mention the test name) was conducted by Multi-consult Laboratory Limited Lagos Nigeria, and it showed that the product was sterile and microbiologically fit for human consumption. Acute toxicity studies showed that at doses above 500 mg/kg body weight, the herbal tonics did not cause mortality and produced no signs of toxicity.

Chemical

Phenolphthalein monophosphate and 2,4, dinitrophenyl hydrazine.

Methodology

The method for selecting the herbal products involved a multi-stage sampling technique. A list of all the registered pharmaceutical stores was procured from the Ministry of Health. In each of the stores, the 3 most commonly sold and patronized herbal products were identified which were then used for the project experiment.

Seventy Wister rats of both sexes weighing between 72.8 g and 270 g were obtained from the animal house of the University of Nigeria, Nsukka. These animals were acclimatized for 2 weeks during which they were fed on food and water only and were free from extremes of temperature and humidity (mention the temperature and humidity). The animals were kept in separate cages to avoid aggression and injury to each other. After the period of acclimatization, the rats were weighed daily till the end of the experiment.

Experimental Design and Necropsy

The rats were divided into 3 major groups and each group received a particular herbal product. Each of this group was further sub-divided into 3 sub-groups and the sub-groups were given various dosages of each of the herbal products.

Another group served as the controls, which were fed on food and water only throughout the duration of the experiment. The dosages of each herbal product were derived using the equivalent of the dosage given to a 75 kg adult.

The first sub-group of each group was given the normal dose of the equivalent dosage, which were; 0.4 ml of Bio-Strath elixir, 2.2 ml of Yoyo cleanser bitters, and 5.9 ml of T. angelica herbal tonic.

The second sub-group of each group was administered double the normal dose once daily which were; 0.8 ml of Bio-Strath elixir, 4.4 ml of Yoyo cleanser bitters, and 11.8 ml of T. angelica herbal tonic.

The third sub-group of each group was administered double the required dose twice daily which were 0.35 ml of Bio-Strath elixir, 2.7 ml of Yoyo cleansing bitters, and 6.5 ml of T. angelica herbal tonic. The average weights of the rats were determined at the end of every week, after which a rat from each of the sub-groups including the control group was sacrificed at the end of every 7 days for 6 weeks.

Method of sacrifice involved anesthetizing the animals with chloroform first and then collecting their blood samples through cardiac puncture. The blood was then kept in heparinized bottles to prevent clotting and sent immediately to the laboratory for analysis.

Also, the liver of the animals were harvested and put in a universal bottle containing chloroform and then sent to the lab for histopathological examination. After the 6 weeks of experiment, the remaining animals were divided into two groups and were fed with food and water without drug administration for a period of 2 weeks.

The first group of animals were given antioxidant (vitamin C) at normal dose 3 times daily while the other group of animals were not given any antioxidant but were left to allow the natural reversal of the liver function.

Thereafter, they were sacrificed and their blood samples were collected for analysis to determine if there was any reversal or improvement of any pathological defects and also to ascertain which group of animals had a faster improvement of pathological defects.

Statistical Analysis

The data were collected and entered directly into Microsoft Excel spreadsheet. Data were expressed in frequency tables and graphs. Statistical significance was set at 5% or 0.05% and values less than this were considered as statistically significant ($P < 0.05$).

Ethical Consideration

Permission was obtained from the Ethics and Research Committee of Madonna University, Elele, before the study was conducted.

RESULTS

Table 1 shows the effect of the sub-chronic administration of the 3 herbal products on rats' liver enzymes. Yoyo cleanser bitters has the most remarkable effect, followed by T-angelica and then Biostrath Elixir. In Table 2, the effects of different doses of vitamin C on the rats' liver enzymes after intake of the herbal products are shown. Marked reduction in liver enzymes is noticed in all the 3 groups especially with anti-oxidant vitamin C. Table 3 shows that administration of the herbal products brought about a consistent reduction in the body weight of the rats over a period of 6 weeks. This trend was more pronounce among the rats that were fed with Yoyo bitters and T. angelica. Furthermore, administration of vitamin C restored the baseline (week 1) weight of the rats which took Bio-Strath but could not achieve the same feat among the rats fed on the other two herbal products. Also, while the mean weights of the rats fed on Bio-Strath (+vitamin C) were higher than their baseline weights, the mean weights of the T. angelica (+vitamin C) and Yoyo bitters (+vitamin C) rats were smaller than their respective baseline weights [Figures 1-3].

DISCUSSION

The study showed that the administration of T. angelica herbal tonic and Yoyo cleanser bitters resulted in a reduction in the level of food consumption in the rats in contrast to Bio-Strath elixir.

The rats consumed less of the feeds and showed a low interest in food in an almost dose-dependent manner. This may be consolidating the manufacturers' claim that the ingestion of Yoyo cleanser bitters and T. angelica herbal

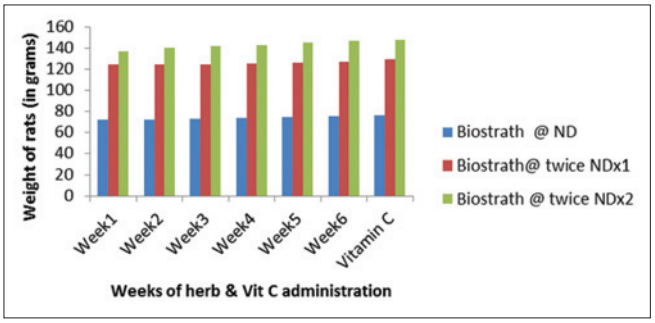

Figure 1: Effect of increasing doses of Biostrath+Vit C on weight of rats over time

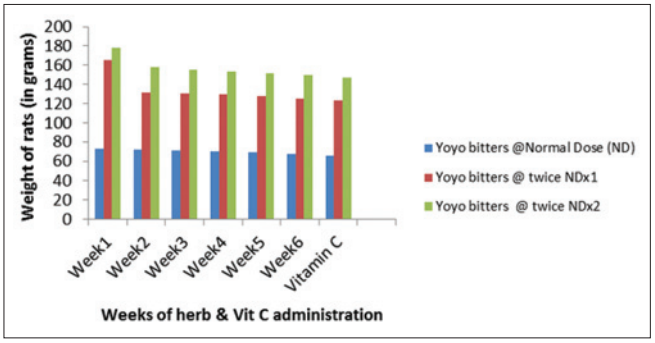

Figure 2: Effects of increasing doses of Yoyo Bitters +Vit C on weight of rats over time

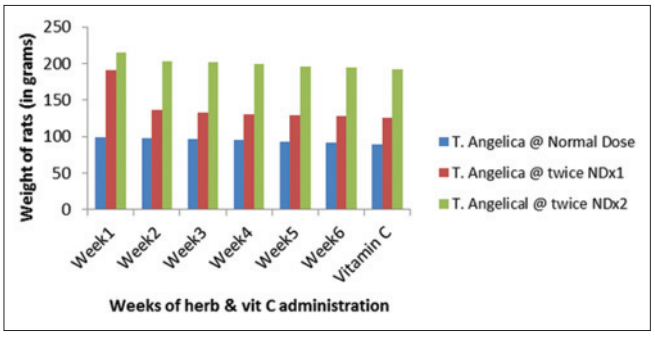

Figure 3: Effects of increasing doses of T-angelica +Vit C on weight of rats over time

Table 1: Effects of sub-chronic administration of the herbal products on rat's liver enzymes

		Herbal product dosages		
T. angelica on liver enzymes	Control	Normal dose (5.9 mg/kg)	Twice the normal dose once daily (11.4 mg/kg)	Twice the normal dose twice daily (6.5 mg/kg)
AST (U/L)	19.2±6.30	49.8±16.04	74.2±15.88	102.2±13.05
ALT (U/L)	15.8±6.85	46.8±8.93	60.5±11.05	68.2±12.06
ALP (U/L)	36.8±6.46	55.2±89.61	74.2±10.05	81.2±12.04
Yoyo cleanser bitters on liver enzymes	Control	Normal dose (2.2 mg/kg)	Twice the normal dose once daily (4.9 mg/kg)	Twice the normal dose twice daily (2.7 mg/kg)
AST (U/L)	19.2±6.30	54.0±8.02	57.2±8.23	79.0±11.09
ALT (U/L)	15.8±6.85	51.5±8.31	55.8±9.85	62.7±10.09
ALP (U/L)	36.8±6.46	50.3±7.50	51.5±8.87	64.8±11.37
Biostrath elixir on liver enzymes	Control	Normal dose (0.4 mg/kg)	Twice the normal dose once daily (0.6 mg/kg)	Twice the normal dose twice daily (0.35 mg/kg)
AST (U/L)	19.2±6.30	34.7±7.06	35.5±7.66	48.0±9.74
ALT (U/L)	15.8±6.85	33.3±7.81	31.8±8.52	41.5±8.41
ALP (U/L)	36.8±6.46	48.8±7.17	46.5±8.19	60.3±10.75

ALT: Alanine transaminase, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase

Table 2: Effects of administration of vitamin C on liver enzymes after intake of herbal products

Vitamin C administration after herbal product intake	Liver enzymes (U/L)		
	AST	ALT	ALP
Normal dose vitamin C (0.4 mg/kg)			
Anti-oxidant vitamin C after Biostrath elixir intake	22	15	32
Non-antioxidant vitamin C after Biostrath elixir intake	28	20	40
Twice the normal dose vitamin C once daily (0.6 mg/kg)			
Anti-oxidant vitamin C after Biostrath elixir intake	25	19	40
Non-antioxidant vitamin C after Biostrath elixir intake	35	28	47
Twice the normal dose twice daily (0.35 mg/kg)			
Anti-oxidant vitamin C after Biostrath elixir intake	32	25	48
Non-antioxidant vitamin C after Biostrath elixir intake	40	32	53
Normal dose vitamin C (2.2 mg/kg)			
Anti-oxidant vitamin C after Yoyo cleanser bitters intake	30	35	40
Non-antioxidant vitamin C after Yoyo cleanser bitters intake	50	40	51
Twice the normal dose vitamin C once daily (4.9 mg/kg)			
Anti-oxidant vitamin C after Yoyo cleanser bitters intake	36	40	47
Non-antioxidant vitamin C after Yoyo cleanser bitters intake	57	46	55
Twice the normal dose twice daily (2.7 mg/kg)			
Anti-oxidant vitamin C after Yoyo cleanser bitters intake	41	44	52
Non-antioxidant vitamin C after Yoyo cleanser bitters intake	62	51	60
Normal dose vitamin C (5.9 mg/kg)			
Anti-oxidant vitamin C after T. angelica intake	35	40	50
Non-antioxidant vitamin C after T. angelica intake	45	48	58
Twice the normal dose once daily (11.4 mg/kg)			
Anti-oxidant vitamin C after T. angelica intake	45	47	52
Non-antioxidant vitamin C after T. angelica intake	56	53	60
Twice the normal dose twice daily (6.5 mg/kg)			
Anti-oxidant vitamin C T. angelica intake	51	48	57
Non-antioxidant vitamin C after T. angelica intake	72	53	67

ALT: Alanine transaminase, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase

tonic will lead to weight loss, which is of benefit in the management of obesity and overweight.

There was also an associated drop in the body weight of the rats on Yoyo cleansing bitters and T. angelica. This was similar to the findings of Pond (2005), and Oyewo *et al.* (2012), they also observed that apart from body weight reduction that these bitter herbs may also affect an immune modulating action.

The study also showed that the administration of Yoyo cleansing bitters and T. angelica led to a rise in the level of liver enzymes. This was similar to the findings of Woolf (2003), who also observed that herbal remedies may lead to elevation of liver enzymes resulting to fulminant liver failure, often requiring liver transplantation.

The derangement in the liver enzymes was reversed following the administration of ascorbic acid for 2 weeks after cessation of herbal product administration.

This finding supported the hepatoprotective activity of ascorbic acid by way of modulating the antioxidant pathway. The administration of Bio-Strath elixir did not elicit any rise in the level of liver transaminases, even in higher doses.

CONCLUSION / IMPLICATION FOR PUBLIC HEALTH

The study showed that sub-chronic administration of Yoyo cleansing bitters and T. angelica herbal products led to a rise in the level of liver transaminases, with the risk of hepatotoxicity. However, the daily administration of Bio-Strath elixir, even above the recommended dose is highly encouraged since the increase in plasma liver markers is not significant, and therefore not harmful to the liver. The finding in this study supports the hepatoprotective activity of vitamin C by modulating the antioxidant pathway. The Public health implication of these findings is that even

Table 3: Effects of administration of the herbal products on the rats' body weights (grams)

Herbal products (at different doses)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Vitamin C	Baseline versus end line mean weights *t*-test/*P* value
Yoyo bitters at ND	73.2	72	71.5	70	69	67.3	66	*P*=0.12
Yoyo bitters at twice ND×1	165.73	131.7	131	129.5	127.7	125.5	123	
Yoyo bitters at twice ND×2	177.83	158.1	155.5	153.5	151.7	149.5	147	
Biostrath at ND	71.5	72	73	73.6	74	74.9	76	*P*=0.08
Biostrath at twice ND×1	123.9	124	124.5	125	126	126.8	129.2	
Biostrath at twice ND×2	136.9	140	142	143	145	146.7	148	
T. angelica at ND	98.5	97.5	96.6	95.4	93.2	91.7	89.2	*P*=0.19
T. angelica at twice ND×1	191.3	135.9	133.2	130.5	129	128.1	125	
T. angelica at twice ND×2	215.3	202.6	201.7	199.7	195.4	194	191.5	
Control	150.7	150.8	150.9	148	146.7	145.2		

ND: Normal dose

though the experiment was carried out on rats, there is a probability that the same effect might be recorded in humans.

RECOMMENDATION

More studies should be carried out, this time among the human populations in order to further evaluate the safety/ toxicity potentials of these herbal preparations in man. An observational study like descriptive cross sectional survey in a human population might be a good way to start. Such a study should be designed to establish the prevalence of use among humans. A case control and cohort studies should be next designed to study the relationship between use of the herbal products and liver toxicity among humans.

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