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Thyrotoxic Evaluation and Lipid Peroxidation in Wistar Albino Rats Exposed to *Vitellaria paradoxa* Stem Bark

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Authors' contributions

This work was carried out in collaboration between all authors. Author TO designed the study, wrote the protocol and wrote the first draft of the manuscript. Author AAN supervised the study and managed the literature searches. Authors HM and MOA performed sample and data analyses. Authors AOM and ASA review the manuscript and managed experimental process. All authors read and approved the final manuscript.

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ABSTRACT

Background: *Vitellaria paradoxa* stem bark is used by villagers because of its antimicrobial activity for treating skin diseases and wound infections in some parts of Nigeria without considering its safety.
Aim: The aim of the study was to determine the effect of ingestion of *Vitellaria paradoxa* stem bark on thyroid hormones and lipid peroxidation in Wistar albino rats.
Place and Duration of Study: The study was undertaken at the Department of Chemical Pathology, Faculty of Medical Laboratory Sciences, Usmanu Danfodiyo University, Sokoto.

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Methods: The oral acute toxicity of the extract (LD_{50}) was determined in 30 Wistar rats divided into 6 groups of 5 rats per group. Group 1 was the control and received normal saline. Different doses of 5, 50, 300, 2000, and 5000 mg/kg were administered once to the study groups (2, 3, 4, 5 and 6) respectively. A sub-chronic toxicity study was then carried out in 30 Wistar rats, divided into six groups of 5 rats per group. Group 1 served as control and was given normal saline and standard rat pellets. The remaining 5 groups were administered different doses of 50, 100, 200, 300 and 400 mg/kg *Vitellaria paradoxa* stem bark extract daily respectively for 30 days. Thyroid function test (T_3, T_4 and TSH) was carried out by the use of enzyme linked immunosorbent assay (ELISA), malondialdehyde (MDA) and total antioxidant status (TAS) determined by spectrophotometric techniques.

Results: No mortality was recorded in the rats after 24 hours and up to 14 days post-oral treatment, an indication that LD_{50} of the extract is greater than 5000 mg/kg. In the sub-chronic toxicity study, T3, T4 and TSH values of animals that received higher doses were significantly decreased ($p<0.05$) than the control groups. MDA values were significantly lower ($p<0.05$) in treated animals than the control group but there was no significant difference ($p>0.05$) in the values of TAS.

Conclusion: T3 and T4 play important roles in metabolism, growth and development among others, consumption of *Vitellaria paradoxa* may have harmful effect in the long term users. Hence, T3 and T4 should be monitored in *Vitellaria paradoxa* consumers so as to prevent induction of hypothyroidism. However, it may still be of clinical benefit in the treatment of hyperthyroidism. Consumers may not develop oxidative stress induced diseases because of reduced values of MDA in the treated animals.

Keywords: Vitellaria paradoxa; hypothyroidism; lipid peroxidation; toxicity; oxidative stress.

1. INTRODUCTION

Herbal products contribution to modern medicine is well known and life in most parts of Africa begins and ends with herbal medicine. About 65-80% of world's population relies on traditional medicine for their health care needs [1]. According to the United Nations Conference on Trade and Development, 33% of total modern drugs produced by industrialized countries are plant based [2]. In Nigeria, thousands of plant species are known to have medicinal values [3] and the use of different parts of several medicinal plants to cure specific ailments has been in vogue since ancient times [4]. As a result of better cultural acceptability and fewer side effects herbal medicine still remains the mainstay of 75-80% of the whole population in the developing countries for primary health care [5].

V*itellaria paradoxa* (previously *Butyrospermum parkii*) belongs to the Sapotaceae family indigenous to Africa and occurs in Mali, Cameroon, Congo, Cote d'Ivoire, Ghana, Guinea, Togo, Nigeria, Senegal, Sudan, Burkina Faso and Uganda. *V. paradoxa* can easily be distinguished by its very long leaf stalks, more widely spaced leaves and abundant white latex when slashed [6]. The shea fruit consists of a thin, tart, nutritious pulp that surrounds a relatively large, oil-rich seed from which shea butter is extracted. The fruits are eaten for their nutritive and medicinal values in various part of Africa. Shea butter prepared from the seed of shea tree has been marketed as a skin and hair moisturizer and as a treatment for a variety of skin conditions including acne, burns, chapped lips, dry skin, eczema, psoriasis, scars, stretch marks, and wrinkles. It has also been used as a cream in the treatment of arthritis, rheumatism, bruises and muscle sore from human study, shea butter may be effective in the treatment of nasal congestion, lowering cholesterol levels, and for blood thinning [7].

Thyroid hormones (T4 and T3) bind to intranuclear receptors that function as transcription factors and thereby regulate gene expression. Thyroid hormones have ubiquitous effects on growth and development in the foetus, child, and adolescent, and they regulate calorigenesis and metabolic rate throughout life. At a molecular level, thyroid hormones (1) increase oxygen consumption within tissues via increased membrane transport, (2) enhance mitochondrial metabolism, (3) increase sensitivity to catecholamines with increased heart rate and myocardial contractility, (4) stimulate protein synthesis and carbohydrate metabolism, (5) increase synthesis and degradation of cholesterol and triglycerides, (6) increase vitamin requirements, and (7) regulate calcium and

phosphorus metabolism. Thyroid hormones maintain the basal metabolic rate and thus regulate the metabolism of endogenous and exogenous substances. Hypothyroidism impairs the excretion of many drugs, with hyperthyroidism accelerating their clearance [8].

Thyroid hormones perform many important functions in the body, herbs or any other xenobiotics that impair thyroid functions may induce other metabolic processes in the system, and also any xenobiotic that induces lipid peroxidation may induce oxidative stress diseases, the present study was therefore designed to assess to what fashion the effect of consumption of *Vitellaria paradoxa* stem bark on thyroid hormones and lipid peroxidation in Wistar albino rats.

2. MATERIALS AND METHODS

2.1 Plant Collection and Identification

The stem bark of *Vitellaria paradoxa* was collected from Kankia local government, Katsina State, Nigeria, in the month of June, 2014. The plant was identified and authenticated at the Herbarium unit of Botany Department, Obafemi Awolowo University, Ile Ife, by comparing with established Herbarium specimen with voucher number: Benth 13689 reference number which was kept at the herbarium.

2.2 Preparation and Extraction

Fresh samples of the stem bark of *Vitellaria paradoxa* was collected and air-dried at room temperature over a period of 6 weeks. It was then crushed manually using Mortar and Pestle. Five hundred grams (500 g) of the grinded plant material was soaked in 4 Litres of methanol for 72 hours on a mixer to ensure maximum extraction by percolation method using maceration technique under room temperature. This was followed by periodic stirring. The resulting crude extract was filtered using Whatman number 1 filter paper and then the filtrate was concentrated to dryness in an oven at 48℃ to obtain 40 g brown powder extract. The dried crude extract was stored in a refrigerator at low temperature (4℃) in sterile plastic bottles, at the Faculty of Pharmaceutical Sciences, UDUS, until required for use [9].

The residual filtrate was later re-constituted [9], taking into consideration the average weight of the albino rats, the duration of extract administration, and the required volume of doses.

The crude extract was diluted in cold water to obtain varying concentrations of the extract per Kg body weight. It was then kept refrigerated at 4℃ until use.

2.3 Experimental Animals

Albino Wistar rats aged 8 to 12 weeks old, weighing between 100 g to 150 g were obtained from the animal house, of the Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria. They were allowed to acclimatize for a period of 2 weeks. They were maintained in clean metabolic cage-sand, placed in a well-ventilated room conditions with a temperature of 26℃ to 28℃, photoperiods of 12 hours light and 12 hours darkness; humidity of 40% to 60% [10].

The animals were maintained on pellet feeds (Vital®), obtained from Grand cereals oil mills limited, Jos and were supplied with drinking water *ad libitum*. Cleaning of the animal cages was carried out daily, and on regular basis. All the experimental protocols were in compliance with our Institutional Animal Ethics Committee guidelines as well as internationally accepted practices for use and care of laboratory animals as contained in US guidelines (National Institute of Health [11] and also in accordance with the recommendations of the International Association for the Study of Pain (IASP) [12].

2.4 Experimental Design

2.4.1 Acute toxicity study

Acute toxicity study was performed in accordance with the procedures outlined by the Organization for Economic Co-operation and Development guidelines 420 [13]. Thirty (30) Wistar albino rats of both sexes were used for this study. The rats were randomly divided into 6 groups composing of 5 animals each, with the first group as the control. The extract was administered to rats in groups 2 - 6 in single oral doses of 5 mg/kg, 50 mg/kg, 300 mg/kg, 2000 mg/kg and 5000 mg/kg body weight respectively, dissolved in 1 ml of distilled water by intra gastric gavage using oral cannula (a feeding needle). The control group (Group 1) received an equal volume of distilled water. Observations of toxic symptoms were made and recorded within the first hour, four hours and subsequently for 24 hours after administration of the extract. Behavioural parameters and mortality were also monitored closely for 14 days. Lethal

dose in 50% of the total population (LD_{50}) was interpolated using OECD method [10].

2.4.2 Sub-chronic toxicity test

Sub-chronic toxicity study was carried out in accordance with OECD 407 [13] guidelines. Thirty (30) rats of both sexes, were divided into six (6) groups of five (5) rats each. Group 1 served as the control and received normal saline as vehicle. Graded doses of the extract were administered orally to the rats in groups 2, 3, 4, 5 and 6. The doses given to the groups were 50 mg/kg, 100 mg/kg, 200 mg/kg, 300 mg/kg and 400 mg/kg body weight respectively daily for 30 days. All the rats had free access to food and water throughout the duration of the experiment and were observed daily for general symptoms of toxicity and mortality [10].

At the end of the 30 days period, the animals were fasted overnight, and anaesthetized using chloroform anaesthesia. Blood samples were collected from the animals through cardiac puncture, into clean, dry plain containers. The rats were later sacrificed through lumbar dislocation. The blood collected was allowed to clot and then centrifuged at 5000 rpm for 10 minutes. The serum was separated and kept frozen at-4℃ until required for analysis [10].

2.4.3 Body weight

The rats in all the groups were weighed using a sensitive balance, once before commencement of dosing, twice weekly during the period of dosing and once on the day of sacrifice. Doses of the extract administered were adjusted accordingly.

2.4.4 Biochemical analysis

2.4.4.1 Estimation of thyroid hormones

Total Triiodothyronine (tT3) was determined using Competitive Enzyme Immunoassay ELISA micro wells [14], total thyroxin (tT4) Accu Bind ELISA micro wells [15] and thyrotropin (TSH) using Accu Bind ELISA micro wells [16].

2.4.4.2 Estimation of MDA

Level of lipid peroxidation was determined by measuring the formation of thiobarbituric acid reactive substances (TBARS) using the method of Varshney and Kale [17]. The principle is based on the fact that malondiadehyde (MDA) produced from the peroxidation of membrane fatty acid, reacts with the chromogenic reagent; 2-thiobarbituric acid (TBA) under acidic conditions to yield a pink–coloured complex measured spectrophotometrically at 532 nm. 1, 1, 3, 3-tetramethoxylpropane was used as standard.

2.4.4.3 Estimation of TAS

TAS was determined using the ferric reducing / antioxidant power (FRAP) assay. 1.5 ml of working pre-wormed 37℃ FRAP reagent (300 mM acetate buffer - pH 3.6, 10 mM 2,4,6-tripyridyl-s-triazine in 40 mM HCl and 20 mM $FeCl_3$ at ratio 10:1:1) was vortex mixed with 50 µl of test sample and standards. Absorbance was read at 593 nm against a reagent blank. The result was reported as µmol Trolox equiv. / L [18].

3. RESULTS

The data obtained from this work were analysed using the Sigma plot version 11.0.

3.1 Acute Toxicity

Table 1 shows the result of oral acute toxicity in the Wistar rats. The result of oral acute toxicity showed that no death was recorded in the rats after 24 hours and up to 14 days post oral treatment.

Table 1. Acute oral toxicity (LD_{50}) study of *Vitellaria paradoxa* stem bark extract in Wistar rats

Groups	No. of animals	Dosage/Kg body weight	Volume of extract (ml)	Observation period	Behavioural changes	Mortality
1	5	1 ml D/H_2O	3	Up to 48 hours	None	None
2	5	5 mg/kg	3	Up to 48 hours	None	None
3	5	50 mg/kg	3	Up to 48 hours	None	None
4	5	300 mg/kg	3	Up to 48 hours	None	None
5	5	2000 mg/kg	3	Up to 48 hours	None	None
6	5	5000 mg/kg	3	Up to 48 hours	None	None

Table 2. Mean ± S.D. of T_3, T_4 and TSH in Wistar rats exposed to *Vitellaria paradoxa* stem bark

Parameters	Group 1 control	Group 2 50 mg/kg	Group 3 100 mg/kg	Group 4 200 mg/kg	Group 5 300 mg/kg	Group 6 400 mg/ kg
T_3 (ng/ml)	1.18±0.25	1.04±0.19	0.86±0.09	0.85±0.09	0.80±0.07	0.67±0.03
T_4 (µg/dl)	6.74±1.23	6.51±1.37	6.53±1.43	4.52±0.23	4.65±0.72	4.76±0.42
TSH (µ/Ulml)	0.31±0.67	0.25±0.87	0.26±0.04	0.26±0.03	0.20±0.12	0.10±0.09

Table 3. Oxidative stress biomarkers in Wistar rats exposed to *Vitellaria paradoxa* stem bark

	Group 1 control	Group 2 50 mg/kg	Group 3 100 mg/kg	Group 4 200 mg/kg	Group 5 300 mg/kg	Group 6 400 mg/kg
MDA	8.94±1.05	7.56±1.53	7.63±1.65	6.30±0.87	3.55±2.78	4.42±0.59
TAS	388.00±82.88	424.00±77.65	335.00±80.21	333.33±46.19	280.00±97.98	442.50±86.17

4. DISCUSSION

Herbal products, due to their natural origin, were used to be considered as safe for human consumption but however, the potential risks involved with the use of such plants have been reported [19]. EL-Mahmoud and his co-workers [20] established the presence of some active phytochemical compounds in *Vitellaria paradoxa* such as carbohydrates, alkaloids, tannins, saponins, and cardiac glycosides.

From this study, it was found that single dose of oral administration of *Vitellaria paradoxa* to Wistar albino rats at 5000 mg/kg body weight did not cause any behavioural changes or mortality. Therefore, the oral acute toxicity (LD_{50}) was higher than 5000 mg/kg. This finding is in agreement with the work of Clarke and Clarke [21], who reported that any compound or drug with oral LD_{50} higher than 1000 mg/kg body weight could be considered to be of low toxicity and safe. However, Zbinden and Roversi [22] reported that variables such as animal species, strain, age, gender, diet, bedding, ambient temperature, caging conditions, and time of the day can all affect the LD_{50} values obtained and as such there are considerable uncertainties in extrapolating the LD_{50} obtained for one specie to other species.

Orisakwe et al. [23] and Nwinyi et al. [24] reported that LD_{50} not necessarily guarantee the safety of the tested agent not withstanding its value. According to the report, rinbacin with a higher LD_{50} value induced toxic effects to the rat's testes. Despite these limitation however, acute toxicity furnishes some useful information. For instance, it helps in the selection of dose range that could be used for subsequent studies. The possible clinical signs induced by the substance of investigation could manifest at this level of study. It is also applied in the establishment of therapeutic index (LD_{50}/ED_{50}) of drugs and xenobiotics [25].

From this study, there was significant reduction ($p<0.05$) in T_3 values in the study groups when compared with control group. However, T_3 values in all the groups were within the reference range. Also the values obtained for T_4 for group 4, 5, and 6 were significantly lower ($p<0.05$) than that of control group but the T_4 values of group 2 and 3 were not statistically different ($p>0.05$) from that of control group. Considering the numerous role of T_3 and T_4 in metabolic processes, growth and development among others, consumption of *Vitellaria paradoxa* may have harmful effect in the long term user. Hence T_3 and T_4 level should be monitored in *Vitellaria paradoxa* consumers so as to prevent induction of hypothyroidism. However it may still be of clinical benefit in the treatment of hyperthyroidism. The TSH values for group 2, 3, 4, and 5 were not significantly different ($p>0.05$) from the values obtained for control group but TSH value for group 6 was significantly lower ($p<0.05$) than that of control group. Free radicals are highly reactive molecules generated by biochemical redox reactions which occur as a part of normal cell metabolism and in the course of free radical mediated diseases such as cancer, diabetes mellitus, cardiovascular and renal diseases [26]. Oxidative stress results from imbalance between the production and manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage. Free radicals may cause lipid peroxidation, the level of lipid peroxidation expressed as malondialdehyde, that damage all components of the cell, including proteins, lipids, and DNA. Malondiadehyde is a metabolic product of peroxidative reactions (auto-oxidative) of lipids exposed to oxygen [27].

It serves as a reliable marker of lipid peroxidation [28]. Free radicals are eliminated from the body by their interaction with non-enzymatic antioxidants such as uric acid, albumin, bilirubin, vitamin A, C, E, glutathione, peroxidase, superoxide dismutase and catalase [25,29]. MDA values were significantly lower in treated animals than the control group but there was no significant difference in the values of TAS, an indication that it did not induce lipid peroxidation, hence may not induce oxidative stress diseases.

5. CONCLUSION

In conclusion, the present study has provided some information on the safety of V*itellaria paradoxa* stem bark extract. T3 and T4 should be monitored in *Vitellaria paradoxa* consumers so as to prevent induction of hypothyroidism. However, it may still be of clinical benefit in the treatment of hyperthyroidism. From our findings, consumers may not develop oxidative stress induced diseases. Further toxicity studies including hepatotoxic, nephrotoxic and haematotoxic potential is on-going in our laboratory. However the present LD_{50} studies have shown relative safety of the extract in 24 hours oral acute toxicity study while the sub-chronic studies of 30 days duration shown toxicity related dose on thyroid hormones.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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