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Effects of Orally Administered Giant Snail (*Archachatina Marginata*) Chitin Extract in Oxidative Stress caused by Dexamethasone induced Hypertension in Wistar Albino Rat

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ABSTRACT

Background: *Oxidative stress is one of the most common disorders encountered in clinical practice. It has been noted as a major public health problem in many countries. It is a major risk factor for many chronic diseases. Giant snail chitin has been reported to contain thousands of bioactive ingredients which play a vital role in prevention and treatment of many diseases caused by oxidative damage.*

Aim: *This investigation aimed to study the effects of oral administration of extracts of giant snail chitin on the heart, kidney, spleen and plasma of dexamethazone- induced hypertensive rats.*

Study Design: *The study was designed and executed within a period of one year (10th April 2015- March 2016) using animal bioassay.*

Material and Methods: *Chitin was extracted from waste shells of giant snail (Archachatina marginata) obtained locally from Ado-Ekiti, Nigeria. The rats for the study were divided into four groups of five rats each with various treatments and administrations which lasted for three weeks. At the end the experimental period; total protein, marker enzymes [alkaline phosphatase (ALP), aspartate transaminase (AST) and alkaline transaminase (ALT)]; antioxidant enzymes[catalase and superoxide dismutase (SOD)];reduced glutathione (GSH), cholesterol (CHOL)and malondialdehyde (MDA) were evaluated.*

Results: *The results obtained revealed that dexamethasone actually caused oxidative stress as evidenced in increased malondialdehyde, reduced GSH concentrations and reduced catalase and SOD activities in the plasma and studied organs while the chitin extract produced a significant reduction to the elevated AST, ALT and MDA caused by dexamethazone and enhances the increase of the depleted catalase, GSH and SOD caused by dexamethazone which generally enhances conditions and functions of the studied organs.*

Conclusion: *The burden of the hypertension caused by drug and drug related chemicals as a result of other complications therapy can be assuaged using this giant snail chitin extract.*

Keywords: *oxidative stress; antioxidant enzymes; bioactive ingredients; marker enzymes; antihypertension.*

INTRODUCTION

The oxidative stress has been imposed due to the imbalance of biochemical processes that involves the generation of reactive oxygen and nitrogen species (ROS and RNS) and their neutralization by the inherent antioxidant (enzymatic or non-enzymatic) defense system of the cells. The exogenous agents including chemical carcinogens, UV and ionizing radiations and bacterial or viral infections are known to rectify the production of ROS and RNS. These reactive species interfere with the

physiological functions of cells either directly by damaging bio molecules including DNA, lipids, proteins and carbohydrates or indirectly by inducing mutations as a result of base modifications in DNA or cross linking it with other bio molecules[1].

Chitin resembles cellulose both in chemical structure and in biological function as a structural polymer. The crystalline structure of chitin has been shown to be similar to cellulose in the arrangements of inter- and intra-chain hydrogen bonding. The mucopolysaccharide, chitin is produced by the demineralization and deproteinisation of shrimp shell waste. It is considered as the second most abundant biopolymer in the world next to cellulose[2].

Giant snail Chitin occurs as odourless substance. It is an amorphous solid and off-white in colour. The main advantage of chitin for different biological applications is that it is nontoxic[3]in nature. When the cellular defense mechanisms are unable to deal with excessive generation of ROS, this oxidative stress has been reported to induce various pathogenic processes including aging, cancer, wrinkle formation, rheumatoid arthritis and inflammation[4,5,6,7,8]. Therefore, antioxidants including vitamin C and E play an important role in maintaining balance between the oxidative and reductive state inside the body. Among these antioxidants, chitins widely distributed among invertebrates and crustaceans as structural material in their exoskeletons and fungal cell walls have shown important biological antioxidant effect that has potentials for a wide variety of applications[9].Various scientific findings have reported chitin to possess antibacterial, haemostatic, fungistatic, antitumoral and anticholesteremic properties, which also has wide pharmaceutical applications. In view of wide spread biological uses of chitin and little information about oxidative stress caused by dexamethasone, hence, this study was undergone to determine and compare the effects of orally administered giant snail (*Archachatina marginata*) chitin extract in oxidative stress caused by dexamethasone induced hypertension in wista albino rat.

AIM OF THE STUDY

To study the effects of oral administration of extracts of giant snail chitin on the heart, kidney, spleen and plasma of dexamethazone-induced hypertensive rats.

MATERIALS AND METHODS

Collection of samples

Shells of snail were obtained from Ado-Ekiti local market and processed for chitin extraction as shown in the flow chart below.

Extraction of Chitin

DEPROTEINIZATION
(3.5% of NaOH solution) was used to dissolve the sample with continuous shaking in the ratio solid: solvent (1:10 w/v) for 2 hours at 65^0C
↓
WASHING
↓
DEMINERALIZATION (1M HCl)
Solid: solvent (1:15 w/v) for 30 minutes at room temperature
↓
WASHING
↓
DECOLORIZATION
Extract with acetones and bleached with 0.315% of NaOCl, Solid: solvent (1:10 w/v) for 5minutes at room temperature.
↓
WASHING AND DRYING
↓
CHITIN

Flow chart scheme for chitin production (modified from [10]).

Experimental Protocol

The study was performed on twenty wistar male albino rats housed in ventilated cages in the Animal House of College of Medicine, Ekiti State University, Ado-Ekiti, Nigeria. They were acclimatized for two weeks and divided into five groups of four rats each before administration of the dexamethasone and extracts accordingly. Group A served as the control and fed with water

and rat feed as normal feeding. Group B received giant snail chitin extract with normal feeding. GroupC rats were treated with dexamethasoneand normal feeding while Group D animals were administered with dexamethasone, giant snail chitin extract and normal feeding. The animals were kept at optimum temperature with a 12 h light/dark cycle for the period of administration that lasted for twenty one days.

Preparation of Organs homogenate

The animals were quickly dissected; the plasma and selected organs (heart, kidney, spleen) homogenates were obtained. 10% of each organ was prepared in 6.7mM potassium phosphate buffer, (pH 7.4) using the electrically driven homogenizer. The homogenate was centrifuged at 4,000rpm for 15 minutes at 4^0C to obtain a clear supernatant which was stored at 8^0C and used for measurement of biochemical contents while malondialdehyde was assayed immmediatly.

Biochemical Assay

Standard Randox kits purchased from United Kingdom were used to determine cholesterol (CHOL), total protein (TP), alkaline phosphatase (ALP), aspartate transaminase (AST) and alkaline transaminase (ALT).

Malondialdehyde which is the measure of lipid peroxidation was determined by measuring the formation of thiobarbituric acid reactive substances (TBARS) according to the method of Varshney and Kale[11]. The method ofJollow, et al.[12]was used to determine the level of reduced glutathione in the estimation of GSH.The determination of catalase activitywas carried out using the method described by[13]and superoxide dismutase was analyzed using the method described by[14].

Statistical Analysis

The experimental results of the analyses were obtained in triplicates with means and standard deviations. Various formulae were used to calculate the individual parameter and enzyme activities. The means and standard deviations of the triplicates results were determined using Microsoft Office Excel 2007.

RESULTS

Table 1 showed the effects of giant snail chitin extracts treatments on the malondialdehyde concentration of dexamethazone-induced hypertensive rats. The concentration of malondialdehyde in plasma, heart, spleen and kidney were shown to be significantly increased in dexamethazone induced rats when compared with the control.

Table 1.0: Concentration of malondialdehyde in selected tissues of dexamethazone- induced hypertension in rats treated with extract of giant snail (*Archachatina marginata*) chitin MDA concentration (unit/mg)

	MDA concentration (unit/mg)			
Groups	Heart	Kidney	Plasma	Spleen
A	$(2.40\pm0.30)\times10^{-3}$	$(1.20\pm0.10)\times10^{-3}$	$(4.90\pm0.40)\times10^{-3}$	$(2.00\pm0.30)\times10^{-3}$
B	$(1.70\pm0.10)\times10^{-3}$	$(2.10\pm0.20)\times10^{-3}$	$(4.20\pm0.30)\times10^{-3}$	$(1.20\pm0.20)\times10^{-3}$
C	$(3.10\pm0.20)\times10^{-3}$	$(3.20\pm0.20)\times10^{-3}$	$(9.80\pm0.50)\times10^{-3}$	$(10.00\pm1.20)\times10^{-3}$
D	$(2.20\pm0.20)\times10^{-3}$	$(1.10\pm0.20)\times10^{-3}$	$(2.70\pm0.30)\times10^{-3}$	$(3.40\pm0.50)\times10^{-3}$

Each value is a mean of 3 determinations ± SEM.

The effects of extracts of giant snail chitin treatments on the reduced glutathione (GSH) concentration of dexamethazone- induced hypertensive rat showed a significant reduction in the reduced glutathione levels of the hypertensive rats in group C when compared with the control group A as seen in Table 2.

Table 2.0: Concentration of reduced glutathione (GSH) in selected tissues of dexamethazone- induced hypertension inrats treated with extractof giant snail (*Archachatina marginata*) chitin

	GSH concentration (mg/dL)			
Groups	Heart	Kidney	Plasma	Spleen
A	0.769±0.005	0.114±0.005	0.641±0.008	0.097±0.003
B	0.369±0.006	0.915±0.006	0.575±0.007	0.676±0.005
C	0.080±0.006	0.252±0.004	0.427±0.005	0.464 ±0.005
D	0.823±0.008	0.308±0.007	0.440±0.004	0.077 ±0.002

Each value is a mean of 3 determinations ± SEM.

Table 3 revealed the effects of extracts of giant snail chitin treatments on the catalase activity of dexamethazone-induced hypertensive rat. The reduction in catalase activity after injection of dexamethazone is another significant finding in this study. The decreased concentration of plasma, heart, kidney and spleen catalase is attributable in part to the reduced synthesis of this antioxidant enzyme (which functions in the detoxification of hydrogen peroxide) whose concentrations would have fallen with the dexamethazone that was injected into the animals.

Table 3.0: Specific activity of catalase in selected tissues of dexamethazone- induced hypertension in rats treated with extract of giant snail (*Archachatina marginata*) chitin

	Catalase activity (unit/mg)			
Groups	Heart	Kidney	Plasma	Spleen
A	0.018±0.002	0.056±0.008	0.011±0.002	0.015±0.002
B	0.520±0.030	0.055±0.006	0.009 ±0.001	0.019±0.003
C	0.006±0.001	0.016±0.002	0.004±0.001	0.007±0.001
D	0.012±0.002	0.027±0.003	0.007± 0.001	0.010±0.001

Each value is a mean of 3 determinations ± SEM.

There was appreciable increase in the plasma, kidney and spleen of AST activities of hypertension-induced rats as compared to control rats except in the heart which did not show any increase in the enzyme activity as a result of the drug in rats as evidenced in Table 4.0

Table 4.0: Specific activity of aspartate transaminase (AST)in selected tissues of dexamethazone- induced hypertension in rats treated with extract of giant snail (*Archachatina marginata*) chitin

	AST activity (U/L)			
Groups	Heart	Kidney	Plasma	Spleen
A	163.00±4.15	82.50±1.40	29.50±1.10	65.50±2.10
B	148.50±3.25	97.55±2.00	32.09±1.20	88.50±3.54
C	161.00±5.45	215.50±4.00	123.00±6.50	127.00±7.00
D	119.00±2.22	168.50±6.50	67.00±2.00	98.10±7.00

Each value is a mean of 3 determinations ± SEM.

The plasma and organs ALT activities were observed to be highly reduced when the hypertension-induced rats were treated with giant snail chitin extract in the plasma and the organs when compared with group C rats as seen in Table 5

Table 5.0: Specific activity of alanine aminotransaminase (ALT)in selected tissues of dexamethazone-induced hypertension in rats treated with extract of giant snail (*Archachatina marginata*) chitin

	ALT activity (U/L)			
Groups	Heart	Kidney	Plasma	Spleen
A	5.40±0.25	13.56±1.50	23.00±2.00	9.05±2.00
B	8.20±0.35	12.85±1.50	22.20 ±1.03	6.40±1.80
C	68.20±2.15	17.86±1.02	67.10±3.80	22.10±1.00
D	19.20±0.65	14.80±0.80	17.40±1.50	7.40± 0.76

Each value is a mean of 3 determinations ± SEM.

Table 6.0 presents the alkaline phosphatase (ALP) activity in selected tissues of dexamethazone-induced hypertension in rats treated with extract of giant snail (*Archachatina marginata*) chitin extract. The results of ALP activities in the plasma and organs studied did not follow a particular trend as the activities increased in plasma and spleen but reduced in heart and kidney on administration of dexamethazone, though reduction was observed in plasma, heart and kidney but an increase in spleen ALP activities on the treatment with giant snail chitin extract.

Table 6.0: Specific activity of alkaline phosphatase (ALP) in selected tissues of dexamethazone- induced hypertension in rats treated with extract of giant snail (*Archachatina marginata*) chitin

	ALP activity (U/L)			
Groups	Heart	Kidney	Plasma	Spleen
A	571.32±4.50	549.24±3.50	35.88±1.25	140.76±4.50
B	576.84±5.00	281.52±2.50	34.56±1.50	121.44±2.52
C	505.08±4.50	389.16±3.50	91.28±2.50	480.24±5.50
D	295.32±2.50	516.12±4.50	55.75±2.50	540.96±6.50

Each value is a mean of 3 determinations ± SEM

It can be noticed in Table 7.0 that the administration of dexamethazone reduced the activities of the superoxide dismutase in all the organs and plasma, this observation showed that the drug might be a producer of free radicals as a result of its interaction on the organs and plasma.

Table 7.0: Specific activity of superoxide dismutase (SOD) in selected tissues of dexamethazone- induced hypertension in rats treated with extract of giant snail (*Archachatina marginata*) chitin

	SOD activity (% Inhibition)			
Groups	Heart	Kidney	Plasma	Spleen
A	14.00±1.50	8.15±0.50	48.20±1.20	4.55±0.40
B	16.00±2.50	7.22±0.45	50.35±1.50	4.25±0.52
C	4.00±0.50	4.15±0.50	14.25±2.50	2.42±0.45
D	32.00±2.50	16.20±4.50	28.10±2.50	6.10±0.50

Each value is a mean of 3 determinations ± SEM

The results obtained for the concentrations of cholesterol in the organs and plasma showed that dexamethazone increased the level of cholesterol in the plasma and organs studied, though the administration of the chitin extract reduced the cholesterol concentration in both cases as obtained in Table 8.0.

Table 8.0: Cholesterol concentration (CHOL) in selected tissues of dexamethazone- induced hypertension in rats treated with extract of giant snail (*Archachatina marginata*) chitin

	Concentration of cholesterol (mg/dL)			
Groups	Heart	Kidney	Plasma	Spleen
A	21.4±4.50	11.97±3.50	60.40±1.25	25.83±4.50
B	18.61±5.00	10.32±2.50	56.50±1.50	13.22±2.52
C	77.49±4.50	16.38±3.50	101.43±2.50	46.61±5.50
D	10.71±2.50	12.79±4.50	70.45±2.50	28.92±6.50

Each value is a mean of 3 determinations ± SEM

DISCUSSION

The increase in malondialdehyde concentration which is an index of peroxidation of membrane lipids from Table 1.0 could be due to presence some metabolites or toxic compounds that can change the redox potential of cell that favour lipogenesis and in turn promote NADPH dependent thiobarbituric acid reactive substances (TBARS) in the presence of cytochrome P_{450}. This increased level of malondialdehyde was grossly reduced on treatments with the extracts; this observation was similar to what was reported by [15], who observed increased MDA concentration in oxidative damaged tissues of rats which was subsided when treated with their experimental extract. On the other hand, the level of malondialdehyde in the plasma was quit higher than in all the studied organs, this same trend was also observed in the spleen followed by kidney and the heart in the dexamethazone induced group. The extract also produced a pronounced effect in the plasma in reversing this negative trend followed by kidney, heart and the spleen. It has also been reported by [16] that hypertensive patients show an increased plasma malondialdehyde levels. However, rats placed on giant snail chitin extracts had a remarkable decrease in their plasma malondialdehyde levels when compared with the control, indicating the free radical scavenging ability of giant snail chitin extracts on oxidative stress in hypertensive rats.

As observed from Table 3.0, depletion in blood glutathione is attributable primarily to the dexamethazone injected in the rats which can act as xenobiotic that can aid hypertension. Both xenobiotics and normal metabolism are known to deplete antioxidants as they are consumed in the course of scavenging reactive species generated. The reduction in glutathione to the level that was observed, could lead to a devastating decrease in the total antioxidant status of the animals because glutathione helps in recycling cellular antioxidants, inhibits free radical damage and plays a key role in the detoxification of harmful compounds [17]. This agrees with earlier works carried out by [18], who reported reduced total plasma antioxidant capacity in uncontrolled hypertension. However, giant snail chitin extracts intake by the hypertensive rats increased their glutathione status to near the control level and this is remarkable as this implies that giant snail chitin could have an effect on the altered antioxidant status of a hypertensive rats.

The result of the study in Table 3.0 show a resemblance in catalase activity with earlier reports by [19,20] who reported a decreased catalase activity in alloxan-induced diabetic rats when treated with watermelon juice. The treatment with giant snail chitinextracts however caused slight increase in catalase activity in the various groups, even the ingestion of the giant snail chitin in group B revealed a major increase in the heart and slightly in the spleen as there was no much increase in kidney and plasma. The similar observation was reported by [21] in effects of aqueous extract of nutmeg in Potassium bromate induced renal toxicity in Wistar albino rats where catalase was grossly reduced in bromate fed rat but on treatment with nutmeg extract, a two fold increase in the catalase concentration was obtained.

The present finding was similar to what was obtained by [22] in lipid profile and cardio-protective effects of aqueous extract of *Moringa*

oleifera leaf extract on bromate induced cardiotoxicity on Wistar albino rats where the extract brought a reduction close to control in AST concentration from increase obtained as a result of the bromate treatment. The observations in this study was also in agreement with what was obtained by [23] who worked with hepatotoxic drugs and found out that such drugs are known to cause marked elevation in serum level of enzymes, such as ALT, AST, ALP, and bilirubin, indicating significant hepatocellular injury like hypertension state significantly stimulate AST activity mostly in the plasma as seen in Table 4. Moreover, plasma AST activity highly decreased in hypertension-induced rat treated with giant snail chitin when compared with hypertensive induced rat.

There was observed increase in alanine transaminase (ALT) in the plasma, kidney, heart and spleen as a result of the treatment with dexamethazone in group C rats as seen in Table 5.0.The sharp rise in the ALT levels in plasma and organs as a result of the drug could probably be due to sudden physiological changes following acute drug tissue interaction and possibly pathological. It has been reported that some drugs are known to cause marked elevation in serum level of enzymes, such as ALT, AST, ALP. When there is hepatopathy, these enzymes leak into the blood stream in conformity with the extent of liver injury [24,25]. However, the giant snail chitin extract reversed the enzyme activities in both plasma and the organs under study.

It was also observed that administration of chitin extract to the animals caused almost 50% reduction in ALP activity in the kidney, almost constant in heart and plasma but slightly reduced in the spleen as evidenced in Table 6.0.These observations for these enzymes in this study are somehow similar to the enzyme activities reported by [26] on the effect of alkaloids extract of *Gnetum africanum* repeated treatment, daily for 3 and 30 days on activities of aspirate aminotransaminase (AST), alanine aminotransaminase (ALT), and alkaline phosphotase (ALP) in albino rats.

As seen from Table 7.0, treatment with the chitin extract produced an upward reversal in the activities of the SOD antioxidant enzyme in the studied organs and plasma. This observation was in conformity with what was obtained in the work of [27,28] on the effect of lindane and curcumin on LPO, GSH and antioxidant enzyme estimations in different groups in liver of Wistar rats.

Table 8.0 revealed the cholesterol concentration in selected tissues of dexamethazone- induced hypertension in rats treated with extract of giant snail (*Archachatina marginata*) chitin. It has been reported that cholesterol concentration is increased in smokers and patients with coronary heart disease as coronary heart disease is caused by long-term deposition of lipids in coronary arteries, which lead to atherosclerosis and necrosis of the heart tissue [29].

CONCLUSION AND RECOMMENDATION

Dexamethazoneis a potent hypertensive agent. Direct administration of dexamethazone or any foods that contain dexamethazone may result to hypertension and other cardiovascular diseases and as such should be avoided. This preliminary study has been able to determine and compare the effect of orally administered giant snail (*Archachatinamarginata*) chitin extract in oxidative stress caused by dexamethasone induced hypertensive rat. It further shows the benefits of giant snailchitin extract as it significantly reduced the extent of antioxidant loss and risk of hypertension caused by dexamethasone in this study. These results however, suggest that giant snailchitin extract has beneficial effects on oxidative stress and hypertension. Further investigations should be conducted to establish and possibly identify these bioactive compounds present in of giant snailchitin extract.

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