Journal of Complementary and Alternative Medical Research
1(2): 1-10, 2016, Article no.JOCAMR.26861

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Serum Lipid Profile of Adrenaline-induced Hypertensive Rats Administered with Aqueous Extract of *Arachis hypogeal* Testa

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Authors' contributions

This work was carried out in collaboration between all authors. Author AYK designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors BIM, MHG and FMM managed the literature searches and analyses of the result obtained. Authors MMN and AYK discussed the result citing relevant references. Author BIM also managed the experimental animals and process. Author YG identified the species of plant. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JOCAMR/2016/26861
Editor(s):
(1) Nawal Kishore Dubey, Centre for Advanced Studies in Botany, Banaras Hindu University, India.
Reviewers:
(1) Enyinnaya Anthony Ogbonnaya, University of Port Harcourt, Nigeria.
(2) Ntchapda Fidèle, University of Ngaoundéré, Cameroon.
Complete Peer review History: http://www.sciencedomain.org/review-history/16446

Original Research Article

Received 6th May 2016
Accepted 8th August 2016
Published 5th October 2016

ABSTRACT

Background: Hypertension is one of the leading causes of mortality and morbidity globally. Dyslipidemia is an index of hypertension that has also been identified as a risk factor in the development of coronary heart diseases.
Aim: This research set to investigate the potency; validate the traditional claim on the use *Arachi hypogeal* testa in the management of hypertension in experimental rats.

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Methodology: Thirty Albino Wister rats were grouped into six of five rats each. Hypertension was induced in Groups I to V animals by administering them with 0.1ml adrenaline intraperitoneally for six consecutive days. The rats in groups I to III were administered 400, 600 and 800 mg/kg body weight of *Arachis hypogea* testa extract respectively for seven days. Group IV was treated with a standard hypotensive drug – Propanolol, to serve as positive control, while rats in Group V were administered normal saline to serve as negative control and group VI rats were not induced with adrenaline but administered normal saline as placebo.
Results: The extract at a dose of 800 mg/kg body weight exhibited a significant effect on hypertensive rats compared to the standard drug-Propanolol in correcting the dyslipidemia caused by adrenaline - induced hypertension after seven days of treatment. There were significant increases in total cholesterol, HDL-Cholesterol, and Triglyceride levels in the group treated with 800 mg/kg body weight and the drug ($P = 0.05$), while the LDL-Cholesterol level for animals in the same groups were significantly lowered ($P= 0.05$) compared to the higher values obtained for the induced, untreated control group.
Conclusion: The results of this study demonstrated the ability of the aqueous extract of *A. hypogea* testa to significantly decrease LDL-cholesterol and increase HDL-cholesterol concomitantly in adrenaline-induced hypertensive rats, thus justifying its use in Nigerian traditional medical practice to manage hypertension.

Keywords: Hypertension; LDL-cholesterol; HDL-cholesterol; Arachis hypogeal; dyslipidemia.

1. INTRODUCTION

Hypertension is one of the most common health challenges in the modern times. The prevalence is on the rise, particularly in the urban areas. Recent studies have shown that the prevalence of hypertension in Nigeria is 33%, and there is great possibility that this rate will rise in the nearest future [1,2].

Lipid profile is an index for determining the susceptibility of individuals to hypertension. The profile is used to determine the risk of coronary heart diseases. The concentration and relative ratio of lipids to one another are among the best indicators of whether an individual is susceptible to heart attack or stroke resulting from atherosclerosis or blockage of the blood vessels [3,4,5].

Lipid profile assay checks the concentration of Total cholesterol, Triglycerides, Low-Density Lipoprotein-Cholesterol (LDL-C) and High-Density Lipoprotein –Cholesterol (HDL-C). The LDL-C is often referred to as bad cholesterol, while HDL-C is often referred to as good cholesterol. Sometimes the profile may include Very-Low density Lipoprotein-Cholesterol (VLDL-C) and non-HDL-C [6].

Abnormalities in lipid profile have also been identified as an independent risk factor in essential hypertension by many researchers from various parts of the world [7,8,9,10,11,12]. Abnormalities in lipid profile in hypertensive patients have been identified as a major risk factor in the development of Coronary Heart Diseases (CHD), Cerebro Vascular Accidents (CVA) and stroke [5]. It has been observed that various epidemiological studies and traditions suggest that there may be a connection between frequent nut consumption and a reduced incidence of Coronary heart disease [13].

In normal circumstances, circulating adrenaline plays an insignificant role in control of blood pressure in man and other animals such as rats. A small proportion of adrenaline secreted by the adrenal medulla is accumulated in sympathetic nerve endings and may be re-released by sympathetic nerve stimulation. Pharmacological studies recently conducted on animal models have revealed that adrenaline acts on a presynaptic beta-receptor on sympathetic nerve endings to facilitate noradrenaline release, and this observation led to the proposal that, adrenaline re-released from these nerve endings is therefore a functionally important "co-transmitter". Based on the afore-mentioned fact, it could be expected that Intermittently elevated secretion of adrenaline from the adrenal medulla could therefore lead indirectly to a sustained increase in neuronal release of noradrenaline and hence to hypertension [14].

Arachis hypogeal (pea nut) is nutritionally rich and has several medicinal uses. It has been used locally to manage several abnormalities like diabetes, hypertension, and hemophilia. It has

also been shown to reduce the risk of cancer, cardiovascular diseases and ageing [15,16]. These health benefits in peanuts have been attributed to their composition of mono- and polyunsaturated fatty acids, phytosterols (plant sterols) and phenols like resveratrol among others [17,18,19].

Phytosterols, due to their structural similarity with cholesterol, inhibit its intestinal absorption, thereby lowering total plasma cholesterol and LDL levels [20]. Peanut sterols that have been identified are β-sitosterol, campesterol, stigmasterol and brassicasterol [21].

Peanuts contain significant amount of resveratrol, a phenol belonging to the stilbene group of phenolic compounds. This antioxidant compound was studied for potential anti-aging effects and also associated with reduced cardiovascular disease and reduced cancer risk. This compound is among the major constituents of the pea nut testa [22,23]. It has recently been found that the average amount of resveratrol in one ounce of commonly eaten peanuts (15 whole peanut kernels) is 73 µg [24]. It also has several attributes that may provide protection from atherosclerosis, anti proliferative, and pro-apoptotic properties against breast, colon, prostatic, and leukemia cells [25,26].

Because of high incidence and morbidity associated with hypertension, various drugs and regimens have been suggested for its control in populations with high incidence rate. Many new drugs have been introduced which may demonstrate better efficacy but possess serious side effects. Current researches in the field of drug are focused towards herbal and mineral preparations which are traditionally used as potential therapeutic agents in the prevention and management of cardiovascular diseases [27].

2. MATERIALS AND METHODS

2.1 Collection of Seed Sample and Preparation of Extract

Arachis hypogea seeds were bought in Kure Market in Minna, North Central part of Nigeria in the month of November. The seeds were identified at the Biological Sciences Department of Federal University of Technology Minna.

The seeds were dried and the testa removed manually. It was then dried at room temperature, pulverized to powdered form, and then stored in polythene bag and sealed until required for the study. One hundred grams (100 g) of the powdered groundnut testa was extracted in 1500 ml of distilled water sequentially for 72 hours (the extract was filtered after every 24 hours and replaced with distilled water of the same volume). The extract was filtered using a Muslin sieve cloth and concentrated by removing the solvent using a rotary evaporator and further dried on a water bath. The semi-solid filtrate was then stored in the refrigerator at 4℃.

2.2 Animal Model

Albino Wistar rats of average weight 160 ± 15 g were purchased at the College of Health Sciences, Benue State University, Makurdi, Nigeria. The rats were transported to Federal University of Technology, Minna, and allowed to acclimatize in the departmental laboratory for two weeks. The rats were fed with poultry feed (chick mash) purchased from *Vital feed* (Nasko feeds Nig. Ltd, Jos, Nigeria) and water was given *ad libitum.* The study was conducted in compliance with the internationally accepted principles of laboratory animal use and care as contained in the Canadian Council on Animal Care [28] guidelines for Animal use.

2.3 Animal Grouping and Induction of Hypertension

Thirty Albino Wister rats were grouped into six of five rats each. Groups I to V were induced with hypertension by administering 0.1 ml adrenaline into each animal intraperitoneally using 1 ml disposable syringe for six consecutive days until they were confirmed hypertensive using the procedure described by Omale and Ebiloma [29]. Subsequently, the rats in groups I to III were administered 400, 600 and 800 mg/kg body weight of *Arachis hypogea* testa extract respectively for seven days. Group IV was treated with a reference hypotensive drug – Propanolol. Group V was administered normal saline (Control) and group VI (Not induced with hypertension) was also administered normal saline as placebo.

Group I: *Arachis hypogea* extract (400 mg/kg body weight)

Group II: *Arachis hypogea* extract (600 mg/kg body weight)

Group III: *Arachis hypogea* extract (800 mg/kg body weight)

Group IV: Positive control group treated with propanolol (80 mg/kg body weight)

Group V: Hypertensive rats (negative control) - administered normal saline

Group VI: Normal rats (not induced) - administered normal saline as placebo.

2.4 Dose Preparation of Hypotensive Drug (Propanolol)

The daily dose of Propanolol for human is 80 mg/70 kg body weight. The average body weight of hypertensive rats were determined and based on this, the daily dose was calculated. The drug was dissolved in normal saline and administered intraperitoneally using 1 ml syringe for six days.

2.5 Dose Preparation of the Plant Extract

A measured weight (1 g) of the extract was dissolved in a given volume of normal saline (10 ml) to obtain a concentration of 100 mg/ml stock solution. From this, dosages of 400, 600 and 800 mg/kg body weight/day were measured and administered by cannulation to groups I- III for seven days.

2.6 Analyses of the Biochemical Parameters

After seven days of treatment, the animals were sacrificed based on the method described by Omale and Ebiloma [29]. The blood was collected in a tube pre coated with Ethylinediaminetriacetate (EDTA) and centrifuged at 2000 g, the clear serum from the centrifuged blood was collected. Subsequently, blood glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides were determined using commercial reagent kits developed by DIALAB, Austria.

3. RESULTS

The result in Table 1 shows the effect of the extract on glucose level of rats administered different doses. The level of glucose after seven days of administration of extract was not significantly different in the groups administered 800 mg/Kg bodyweight/day and Propanolol, compared to normal rats thus indicating that the effect of the extract at the highest dose and the standard drug was same.

The results in Tables 2, 3, 4 and 5 show the effect of the extract on the lipid profiles of rats administered different doses. The aqueous extract demonstrated appreciable hypotensive potential in a dose-dependent pattern. The extract administered at 800 mg/kg bw demonstrated a significant hypolipidemic activity that was comparable to that exhibited by the reference drug – Propanolol. In both cases, the dyslipidemia caused by adrenaline - induced hypertension in the animals was reversed after seven days of treatment. There was significant increase in Total Cholesterol, HDL-Cholesterol, and Triglyceride values in the group treated with 800 mg/kg body weight/day and the standard drug ($P = 0.05$), while the LDL-Cholesterol level`was significantly lowered ($P = 0.05$). However, LDL - Cholesterol level was higher in the induced but untreated control group.

Table 1. Effect of the extract on the blood glucose levels of the animals

Group	Dosage of the extract (mg/Kg)	Glucose conc. (mg/dl)
1	400	116.40 ± 6.37^{c}
2	600	50.20 ± 10.46^{a}
3	800	105.0 ± 9.67^{bc}
4 Propanolol	80	103.00 ± 8.01^{bc}
5 Control	-	88.60 ± 3.32^{b}
6 Normal rats	-	105.60 ± 10.62^{bc}

The data are expressed as mean ± Standard Error of mean (SEM). Values carrying different superscripts differ significantly at P < 0.05

Table 2. Effect of the extract on the serum triglyceride levels of the animals

Group	Dosage of the extract (mg/Kg)	Triglyceride conc. (mg/dl)
1	400	31.81 ± 6.21^{a}
2	600	38.18 ± 5.01^{a}
3	800	105.76 ± 5.72^{b}
4 Propanolol	80	104.24 ± 7.42^{b}
5 Control	-	44.24 ± 7.43^{a}
6 Normal Rats	-	126.59 ± 15.05^{b}

The data are expressed as mean ± Standard Error of mean (SEM). Values carrying different superscripts differ significantly at P < 0.05

4. DISCUSSION

Peanuts contain high amounts of both mono- and polyunsaturated fats which have been generally shown to lower total cholesterol and the

incidence of heart diseases [30]. Hypertension and dyslipidaemia are well known to frequently co-exist. Cardiovascular disease (CVD) risk is synergistically enhanced when there is dyslipidaemia and for this reason, both conditions should be treated together [31,32,33].

Table 3. Effect of the extract on the serum cholesterol levels of the animals

Group	Dosage of the extract (mg/Kg)	Cholesterol conc. (mg/dl)
1	400	32.76 ± 5.57^{a}
2	600	81.64 ± 8.48^{d}
3	800	56.51 ± 5.70^{bc}
4 Propanolol	80	69.14 ± 9.52^{cd}
5 Control	-	41.54 ± 3.80^{ab}
6 Normal rats	-	78.00 ± 10.04^{cd}

The data are expressed as mean ± Standard Error of mean (SEM). Values carrying different superscripts differ significantly at P < 0.05

Table 4. Effect of the extract on the serum LDL-C levels of the animals

Group	Dosage of the extract (mg/Kg)	LDL conc. (mg/dl)
1	400	19.33 ± 0.78^{ab}
2	600	20.11 ± 0.59^{ab}
3	800	13.67 ± 1.16^{a}
4 Propanolol	80	23.00 ± 1.34^{b}
5 Control	-	30.45 ± 4.55^{c}
6 Normal Rats	-	24.84 ± 2.80^{bc}

The data are expressed as mean ± Standard Error of mean (SEM). Values carrying different superscripts differ significantly at P < 0.05

In this study, the glucose level of the group administered the highest dose of the extract (800 mg/kg bodyweight/day) was not significantly different from the normal (un-induced, un-treated group) and the standard drug treated group (Table 1). This is an indication that the extract and the standard drug may be acting in the same way in their effect on serum glucose. However, the serum glucose level in the group administered 600 mg/kg body weight of the extract was found to be significantly lower (50.20 ± 10.46 mg/ml) compared to other treated groups, implying that at this dose the extract hypoglycemic, thus reversing the effect of adrenaline (used to induce hypertension) which naturally raises the serum glucose level.

Table 5. Effect of the extract on the serum HDL levels of the animals

Group	Dosage of the extract (mg/Kg)	HDL conc. (mg/dl)
1	400	8.00 ± 5.11^{a}
2	600	53.89 ± 8.50^{c}
3	800	21.73 ± 5.51^{ab}
4 (Propanolol)	80	25.30 ± 7.57^{ab}
5 Control	-	4.27 ± 7.38^{a}
6 Normal rats	-	36.00 ± 8.14^{bc}

The data are expressed as mean ± Standard Error of mean (SEM). Columns carrying different superscripts differ significantly at P < 0.05

The effect of the extract on serum triglycerides was observed to be dose-dependent with the highest dose, 800 mg/kg bodyweight/day, producing a significantly high serum triglycerides level (*P = 0.05*) comparable to that of the standard drug – treated group and the normal group (un-induced, untreated) (Table 2), while lower doses of the extract produced significantly lower levels of serum triglycerides comparable to the induced but untreated group. The results obtained in this study regarding the effect of the extract on glucose and triglycerides does not agree with the results from previous studies [23,34,35,36]. They all reported that *A. hypogeal* extract elicited hypolipidemic and hypoglycemic effect in alloxan - induced diabetic rats. Mona et al. [37] and Ramesh et al. [38] also reported that dietary pea nut oil decreased serum glucose and triglyceride in streptozotocin - induced diabetic rats. Possible reasons for variations in the result obtained in this study could be attributed to the fact that since adrenaline facilitates the breakdown of glycogen to glucose, the adrenaline - induced rats became hyperglycemic and hyperlipidemic as a result of the increase in the activity of adrenaline on the system, and the extract did not reverse the trend.

Studies have shown that elevation in serum total cholesterol, LDL-C, and Triglycerides are among the salient anomalies that are observable in hypertensive humans. More so, high levels of LDL have been identified as the major factor in obesity, atherosclerosis and other related diseases [39,40,41,42,43,44].

The level of total cholesterol was not consistent in the extract-treated groups because the lowest dose used (400 mg/kg bodyweight) caused a decrease in total cholesterol level that was

significantly different from all other groups. The effect was therefore not dose-dependent.

This increase in the total cholesterol is attributable to the rise ($P < 0.05$) in the HDL-cholesterol in Table 5 because total cholesterol is the sum of HDL and LDL cholesterols. Similarly, Table 5 shows that the extract significantly lowers LDL-cholesterol at 800 mg/kg body weight much more than the reference drug. This is plausible because concomitant reduction of LDL-cholesterol and increase in HDL-cholesterol have been identified as good indicators in reducing cardiovascular diseases. Several researches in the past have shown that low level of HDL cholesterol is an important indicator of increased cardiovascular risk. There is also strong epidemiological evidence that low HDL-C is an independent risk factor for CVD with strong suggestions that interventions to increase HDL-cholesterol will yield clinically significant outcome benefits [45,46,47].

The Multiple Risk Factor Intervention Trial [48] showed that each decrease in HDL-cholesterol of 1 mg/dL (0.03 mmol/L) was associated with an increase in the risk of coronary heart disease of 2% in men and 3% in women. It has been shown that a 1% reduction in HDL-C is associated with a 2-3% increase in CHD risk. Clinical and experimental evidence show that HDL-Cs exert multiple anti-atherogenic and antithrombotic effects that together are consistent with a marked reduction in the risk of a morbid cardiovascular event, supporting an anti-atherogenic role for HDL-cholesterol [49,50].

The exact mechanisms by which a low HDL-C increases CVD risk has however not been fully elucidated, though experimental studies suggest a direct role for HDL-C in promoting cholesterol efflux (reverse cholesterol transport) from foam cells in the atherosclerotic plaque depots in blood vessels to the liver for excretion. HDL-C also exhibits potent anti-inflammatory and antioxidant effects that inhibit the atherogenic process [51,52,53].

5. CONCLUSION

Findings from this research clearly showed that aqueous extract of *A. hypogea* testa has significantly decreased and increased LDL-cholesterol and HDL-cholesterol respectively in adrenaline induced hypertensive rats, and therefore gives credence and scientific justification to the use of *A. hypogea* testa by trado-medical practitioners to treat hypertension. Since peanuts are among the common diet of humans all over the world, the above scientific appraisals further prove the nutraceutical significance Phytosterols are among the functional components of peanuts that are responsible for reduction of blood cholesterol, particularly LDL-cholesterol [54,55,56,57]. The mechanism of action for phytosterols is still unclear. One of the suggested mechanisms is that phytosterols, being more hydrophobic than cholesterol, have a higher affinity for micelles and may compete with cholesterol for incorporation into mixed micelles in the intestinal tract, thus resulting in reduced cholesterol absorption and higher fecal excretion of cholesterol. Another mechanism is that phytosterols increase cholesterol efflux out of the intestinal enterocytes back into the lumen; therefore, less cholesterol is incorporated into chylomicrons for entry into circulation. A lower level of intestinal-derived cholesterol prompts cells to restore cellular cholesterol homeostasis by other mechanisms. These alternative mechanisms include increasing the expression of total LDL receptors that in turn decreases LDL formation along the apolipoprotein B cascade and increase in cholesterol synthesis. The resulting effect of reduced serum LDL cholesterol has been suggested as a reason for the role of phytosterols in decreasing atherosclerosis through decreased plaque formation [58,59,60, 61,62] of *A. hypogea* seeds and it can also be packaged as phytomedicine against this dreaded disease of both developed and under developed countries.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Ethical approval was obtained from the research and ethical committee of the Federal University of Technology, Minna, Nigeria for the conduct of this work. The authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/16446