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Anti-Hyperlipidemic Effect of Vitex Doniana Ethanol Extract in Poloxamer Induced Hyperlipidemia

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Abstract: *To determine the effect of Vitex doniana (leaves stem and root bark) ethanolic extracts on lipid profiles of Poloxamer 407 (P407) induced hyperlipidemic and normal rats. Fifty sfour mixed sex rats weighing 100-200g were divided into nine groups comprising six animals per group: group given feed and water only, group induced by an intra-peritoneal injection of P407 every 48 hours without treatment, groups induced and treated with atorvastatin, leaves, stem bark, root bark extracts and groups of normal rats treated with leaves, stem bark and root bark extracts without induction. In all the groups, P407, atorvastatin, leaves, stem bark and root bark extracts were administered at a dose of 1000mg/kg, 20mg/kg, 100mg/kg, 100mg/kg and 30mg/kg body weight respectively. At the end of the 21 day, the animals were sacrificed and blood sample were collected for determination of serum levels of: Total cholesterol (TC), Triacylglycerides (TAG), High-density lipoprotein cholesterol (HDL-c) and Low-density lipoprotein cholesterol (LDL-c). The studies showed that all induced treated groups significantly ($P<0.05$) lower serum levels of TC, TAG, LDL-c and significantly ($P<0.05$) increased HDL-c when compared to the P407 induced hyperlipidemic control. The normal treated groups showed no significant ($P>0.05$) difference in the serum levels of TC, TAG, LDL and HDL when compared to the normal control group. Calculation of atherogenic risk predictor indices of the induced treated groups showed that all the extracts significantly ($P<0.05$) lowered the LDL-c/HDL-c, log (TAG/HDL-c) and significantly ($P<0.05$) increased HDL-c/TC ratio when compared to the P407 induced hyperlipidemic control group. The atherogenic risk predictor indices of normal treated groups showed no significant difference ($P>0.05$) in LDL-c/HDL-c, Log (TAG/HDL-c) and HDL-c/TC ratio when compared to the normal control group. The study demonstrates the phytotherapeutic effect of Vitex doniana (leaves, stem and root bark) ethanolic extract in poloxamer 407 induced hyperlipidemia.*

Keywords: *Hyperlipidemia, Phytotherapeutic, Poloxamer 407, Polyphenol, Rats, Vitex doniana.*

1. INTRODUCTION

Hyperlipidemia is characterized by elevated serum total cholesterol, low density lipoprotein, very low density lipoprotein and decreased high density lipoprotein levels. It has been ranked as one of the greatest risk factors contributing to the prevalence and severity of coronary heart diseases (Grundy 1986). Coronary heart disease, stroke, atherosclerosis and hyperlipidemia are the primary cause of death (Davey 1993). Hyperlipidemia associated lipid disorders are considered to cause atherosclerotic cardiovascular disease (Saravanan *et. al.*, 2003). Among these hypercholesterolemia and hypertriglyceridemia are closely related to ischemic heart disease (Kaesancini and Krauss 1994). The main aim of treatment in patients with hyperlipidemia is to reduce the risk of developing ischemic heart disease or the occurrence of further cardiovascular disease or cerebrovascular disease (Davey and Pekkanen 1992). Currently available drugs have been associated with number of side effects (Brown 1996). The consumption of synthetic drugs leads to hyperuricemic, diarrhoea, nausea, myositis, gastric irritation, flushing, dry skin and abnormal liver function (Brown 1996).

Poloxamer 407 (P407), a non-ionic surfactant is a block copolymer comprising of polyoxyethylene and polyoxypropylene units. It is known for its bio compatibility and potential to deliver different drugs for a variety of disease states (Johnston *et. al.*, 1992) and as a barrier in preventing postsurgical adhesions (Steinleitner *et. al.*, 1991). It has an unusual thermoreversible properties, it is liquid at room temperature while it self-assembles into micelles then aggregate into a gel at body temperature. These

temperature-dependent micellization and gelation properties have led to the widespread use of P407 in personal care products such as mouthwashes, deodorants, and skin care products and also as an excipient in a variety of pharmaceutical preparations (Dumortier *et. al.,* 2006). Johnston *et al.* 1992showed that one intramuscular or intraperitoneal injection of Poloxamer 407 causes dose-dependent hyperlipidemia in rats, increasing plasma triacylglycerol (TAG) more than 60 fold and cholesterol 8 fold and since then has been a growing model in different hyperlipidemic studies.

Plants appear to be the major source of drugs for the majority of the world's population (Oluyemi *et. al.,* 2007), with substances derived from higher plants constituting about a quarter of all prescribed medicines (Kumar *et. al.,* 2011). Several herbal medicines have advanced to clinical use in modern times (Mahmood *et. al.,* 2010).A medicinal plant is a plant that one or more of its part or organ contains substances that may be used for therapeutic purposes or as precursor for the synthesis of useful drugs (WHO, 1998). One of such plant is *Vitex doniana*.

Vitex doniana is a widely used plant in Nigerian traditional medicine; the plant belongs to the dicotyledonous family of Verbenaceae. Its local names in Nigeriainclude; Black plum (English), dinya (Hausa and Igala), Ucha-koro (Igbo) and Orin-ola (Yoruba). The tree average 20-25 m in height and 1 m in diameter has a wide spreadingcrown and a short stout trunk. It is slow growing with an average life span of 60-200 years.Today, *Vitex* grows widely in most tropical and subtropical regions of the world, and iswell adapted to semi-arid tropical conditions and also grow well in many humid tropicalareas with seasonally high rainfall of 750-2000 mm. It is cultivated commercially in variety of soils of varying origins, usually alluvial soils and homestead gardens for its product (FAO 1983). The plant have been used asmedication for infertility, liver disease, anodyne, stiffness, leprosy, backache, hemiplegia, rash, measles, infertility, anemia, jaundice, dysentery, hypertension, gonorrhea, headaches, diabetes, chickenpox, rash, fever, cancer, as tonic galactagogue to aid milk production inlactating mothers, sedative, digestive regulator and treatment of eye troubles, kidney troubles and as supplement for lack of vitamin A and B (Sofowora 1993).Most of the biological activity of *Vitex doniana* has been attributed to the presence of a polyphenols (Quideau, 2011).

2. MATERIALS AND METHODS

2.1. Animals

A total of 54 apparently healthy Wistar albino rats of both sexes weighing between 100 -150 g were obtained from National Institute for Trypanosomiasis Research, Kaduna, Nigeria, and kept according to sexes in well aerated laboratory cages in the Animal house, Department of Pharmacology, Ahmadu Bello University, Zaria, Nigeria. The animals were allowed to acclimatize to the laboratory environment for a period of two weeks before the commencement of the experiment. They were fed with water and grower mash *ad libitum.*

2.2. Collection of Plant Material and Identification

The *Vitex doniana* plants were collected from its natural habitat at the Institute of Agricultural Research (IAR), Ahmadu Bello University (ABU), Zaria, Kaduna State in the month of April 2012, and authenticated at the Herbarium unit by Gallah U.J in the Department of Biological Sciences, Ahmadu Bello University, Zaria with a voucher number 1162.

2.3. Plant Preparation and Extraction

The collected plant sample was rinsed in clean water and dried at room temperature for two weeks. The dried plant sample will be grind into powder using a mortar and pestle, the powder obtained will then be used to prepare the extracts. 50 g of each of the grounded sample (leave, stem and root bark) was suspended in 500 ml of different extraction solvents for 48 hours at room temperature and filtered. The filtrate will then be concentrated by drying in a water bath maintained at a temperature of 45 degree Celsius until a brownish black residue are obtained and these will be kept in a sealed container and refrigerated at 2-4 degree Celsius until required.

2.4. Acute Toxicity Study (LD50)

The mean lethal dose (LD_{50}) of *Vitex doniana* (leaves, stem and root bark) ethanolic extracts were determined by a method described by Lorke (Lorke 1983).

2.5. Preparation of Standard Drug

Atorvastatin (Pfizer Ireland Pharmaceuticals, Ireland) was purchased in a tablet form at strength 20 mg. Tablets were crushed into powder, dissolved in distilled water and administered orally.

2.6. Induction of Hyperlipidemia

Poloxamer 407 (Lutrol F127; BASF, Ludwigshafen, Germany) was used as the inducing agent. Prior to the administration,Poloxamer 407 was dissolved in distilled water and refrigerated overnight to facilitate its dissolution. Needles and syringes to be used for administration were also cooled to prevent gelation within the syringe during injection (Megalli, 2005).

3. ANIMAL GROUPING

3.1. Animal Grouping and Treatment

A total of 54 rats were used. The rats were randomly divided into 9 groups of 6 rats each.

- **Group I:** were fed with normal chow and distilled water only for 21 days (NC).
- **Group II:** were induced without treatment (HC).
- **Group III:** were induced animals and treated with Atorvastatin (ATV) at 20mg/kg body weight/day for 21 days
- **Group IV:** were induced animals and treated with leaves extract (HLE) at 100mg/kg body weight/day for 21 days
- **Group V:** were induced animals and treated with stem bark extract extract (HSE) at 100mg/kg body weight/day for 21 days
- **Group VI:** were induced animals and treated with root bark extract extract (HRE) at 30mg/kg body weight/day for 21 days
- **Group VII:** were normal animals treated with leaves extract (NLE) at 100mg/kg body weight/day for 21 days
- **Group VIII:** were normal animals treated with stem bark extract (NSE) at 100mg/kg body weight/day for 21 days
- **Group IX:** were normal animals treated with root bark extract (NRE) at 30mg/kg body weight/day for 21 days

The dose regimens were administered once daily for the period of the study. The rats were monitored for clinical signs and death.

3.2. Collection And Preparation oF Sera Samples

At the end of the 21-day experimental period, the chloroform-inhalation anesthesiawas performed on all experimental animals. The anesthetized animals were bled by cardiac puncture. The blood samples were collected and centrifuged at a speed of 3000 r/m for 15 minutes and serum collected into plain sample bottles for lipid analysis.

3.3. Serum Lipid Analysis

Total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c) and Triacylglycerol(TAG) were determined by enzymatic method as described by Stein (1987), low-density lipoprotein cholesterol (LDL-c) was determined by the method of Friedewald *et al.*, (1972) and atherogenic risk factor was calculated using formula of Dobiasova and Froehlich (2001).

3.4. Data Analysis

Data are expressed as mean ± standard deviation (SD) and were analyzed by the analysis of variance (ANOVA). The difference between the various ethanolic extract and animal groups were compared using the Duncan Multiple Range Test. *P* value less than 0.05 was considered significant ($P<0.05$).

4. RESULTS

4.1. Changes in Lipid Profile

The effects of *Vitex doniana* (leaves, stem and root bark) ethanolic extracts on lipid profile is shown in Table 1 .The results shows that animals in the group induced without treatment shows a significant

($p<0.05$) increase in TC, TAG and LDL-c when compared with all other groups. All the animals in the groups treated with the extract without induction shows no significant ($P>0.05$) difference in TC, TAG, LDL-c and HDL-c when compared with animals in the normal control group. Animals induced and treated shows that the leaves extract significantly ($p<0.05$) decreased the TC, TAG and LDL-c when compared to other induced treated groups. The HDL-c level in induced without treatment shows a significant ($p<0.05$) decrease when compared with all other groups. Animals induced and treated with leaves, stem and standard drug shows a significant ($p<0.05$) increase in HDL-c when compared with animals in the root treated group.

Table1. *Effects of Vitex Doniana Ethanolic Extract on Lipid Profiles of P407 Induced Hyperlipidemic and Normal Rats.*

Group(n=6)	Serum TC (mg/dl)	Serum TAG (mg/dl)	Serum HDL –c(mg/dl)	Serum LDL-c(mg/dl)
NC	143.73 ±4.75^{a}	126.77 ±13.30^{a}	63.37 ±0.66^{d}	41.75±5.34^{a}
HC	269.60 ±3.40^{e}	437. 99±9.23^{e}	49.16 ±1.09^{a}	91.17±4.62^{d}
H+SD	194.66 ±2.196^{c}	170.06 ±9.48^{c}	61.65 ±1.32^{c}	72.31 ±2.93^{b}
H+LE	186.90 ±2.19^{b}	162.16 ±19.69^{b}	61.23 ±1.07^{c}	75.70 ±6.04^{b}
H+SE	195.88 ±1.45^{c}	199.15 ±7.87^{c}	61.39±0.61^{c}	77.43 ±2.25^{bc}
H+RE	207.76 ±1.50^{d}	224.88 ±13.18^{d}	59.72 ±0.33^{b}	82.51 ±3.76^{c}
N+LE	142.27± 5.01^{a}	123.56 ±15.46^{a}	63.48 ±0.35^{d}	41.04 ±6.36^{a}
N+SE	143.24 ±5.34^{a}	126.77 ±14.63^{a}	63.58 ± 0.33^{d}	41.48 ±6.44^{a}
N+RE	143.75 ±3.52^{a}	125.17±13.18^{a}	63.37 ±0.35^{d}	42.07 ±5.70^{a}

Values are mean ± SD. Values with different superscripts down the column are significantly different ($p<0.05$).

NC: Normal Control rat. HC: Lipid control rats. H+SD: Hyperlipidemic rats + 20mg/kg Atorvastatin. H+LE: Hyperlipidemic rats + 100mg/kg ethanolic leaf extract. H+SE: Hyperlipidemic rats + 100mg/kg ethanolic stem bark extract. H+RE: Hyperlipidemic rats + 30mg/kg ethanolic root bark extract. N+LE: Normal rats +100mg/kg ethanolic leave extract. N+SE: Normal rats + 100mg/kg ethanolic stem extract. N+RE: Normal rats + 30mg/kg ethanolic root bark extract.

TC: Total cholesterol. TAG: Triacylglycerol, HDL-c: High density lipoprotein. LDL-c: Low density lipoprotein.

4.2. Therogenic Risk Predictor Indices

Table 2 shows the effects of *Vitex doniana* (leaves stem and root bark) ethanolic extracts on serum atherogenic risk predictor indices of P407 induced hyperlipidemic and normal rats. The results shows that animals in group induced without treatment shows a significant ($P<0.05$) reduction in HDL-c/TC ratio, and increase in LDL-c/HDL-c ratio and LOG (TG/HDL-c) ratio when compared with all other groups. All the animals in the groups treated with the extract without induction shows no significant ($P>0.05$) difference HDL-c/TC, LDL-c/HDL-c and LOG (TG/HDL-c) ratio when compared with animals in the normal control group. Animals induced and treated shows that the leaves, stem bark and standard drug significantly ($P<0.05$) increased the HDL-c/TC ratio when compared to the root treated group. Similarly, animals induced and treated shows that the leaves significantly ($p<0.05$) decreased the LDL-c/HDL-c and LOG (TG/HDL-c) ratio when compared to other induced treated groups.

Table2. *Effects of Vitex Doniana Ethanolic Extracts on Atherogenic Predictor Indices of P407 Induced Hyperlipidemic and Normal Rats*

Group(n=6)	HDL-c /TC	LDL-c/HDL-c	LOG (TG /HDL-c)
NC	0.441 ±0.012^{d}	0.658±0.081^{a}	0.299 ± 0.044^{a}
HC	0.182 ±0.004^{a}	1.854 ±0.082^{d}	0.949 ± 0.014^{e}
H+SD	0.316±0.009^{c}	1.173±0.053^{b}	0.552 ±0.020^{C}
H+LE	0.327 ±0.003^{c}	1.235±0.086^{b}	0.420 ± 0.054^{b}
H+SE	0.313 ±0.002^{c}	1.261±0.034^{b}	0.510±0.015^{c}
H+RE	0.287 ±0.001^{b}	1.381±0.056^{c}	0.575 ±0.027^{d}
N+LE	0.446 ±0.01 7^{d}	0.646±0.100^{a}	0.286 ±0.053^{a}
N+SE	0.444 ±0.019^{d}	0.652±0.102^{a}	0.297 ± 0.049^{a}
N+RE	0.441 ±0.012^{d}	0.664±0.091^{a}	0.293 ± 0.044^{a}

Values are mean ± SD. Values with different superscripts down the column are significantly different ($p<0.05$).

NC: Normal Control rat. HC: Lipid control rats. H+SD: Hyperlipidemic rats + 20mg/kg Atorvastatin. H+LE: Hyperlipidemic rats + 100mg/kg ethanolic leaf extract. H+SE: Hyperlipidemic rats + 100mg/kg ethanolic stem bark extract. H+RE: Hyperlipidemic rats + 30mg/kg ethanolic root bark extract. N+LE: Normal rats +100mg/kg ethanolic leave extract. N+SE: Normal rats + 100mg/kg ethanolic stem extract. N+RE: Normal

rats + 30mg/kg ethanolic root bark extract. TC: Total cholesterol. TAG: Triacylglycerol, HDL-c: High density lipoprotein. LDL-c: Low density lipoprotein.

5. DISCUSSION

Poloxamer 407, a non-ionic surfactant is well known to induce dose dependent hyperlipidemia (Johnston 2004) by inhibiting capillary (heparin releasable) lipoprotein lipase (LPL), the major enzyme responsible for the hydrolysis of plasma lipoprotein triglycerides (TG) and indirectly stimulating the activity of 3-hydroxy-3-methylglutaryl CoA (HMG CoA) reductase, the rate limiting enzyme in cholesterol synthesis, thereby leading to hypertriglyceridemia and hypercholesterolemia respectively.Lipids are class of organic compounds that are fatty acids or their derivatives. They are insoluble in water but soluble in organic solvents. Lipids are known to perform a number of functions in the body which includes; chemical messengers, storage and provision of energy, maintenance of temperature and membrane lipid layer formation (Akoh 2005). However, abnormal elevations of lipids such as total cholesterol (TC), triglyceride (TG) and low density lipoprotein cholesterol (LDL-c) results in a condition known as "Hyperlipidemia".

Hyperlipidemia is responsible for the onset and progression of atherosclerosis (Poss *et. al.,* 20011), a major risk factor in the development of coronary heart diseases (CHDs) such as ischemic heart disease, myocardial infarction and stroke (Vaziri and Morris 2011).In clinical practice, effective and intensive lipid-lowering is important in order to reduce (Murphy *et. al.* 2007, Nissen *et. al.,* 2004) and prevent (Abdulazeez 2011) CHDs. *Vitex doniana* (leaves, stem and root bark) ethanolic extract significantly ($P<0.05$) reduced TC, TG and LDL-c concentrations. These reductions in TC, TG and LDL levels suggest the ameliorative potential of *Vitex doniana*extracts inhyperlipidemia**.**

The elevation of TC concentration in this study was achieved by the indirect stimulation of HMG CoA reductase following an intraperitoneal (i.p) injection of P407 (Johnston 2004). Hence the possible TC lowering effects of *Vitex doniana* (leaves, stem and root bark) extracts could be attributed to decreased activity of hepatic HMG CoA reductase and/or stimulation of cholesterol-7-alpha-hydroxylase, which converts cholesterol into bile acids. It could also be due to the presence of saponins, a phytochemical which forms insoluble complexes with cholesterol or their bile salt precursor, thus making them unavailable for absorption (Messina 1999). Besides, the standard drug (Atorvastatin) used in this study inhibits HMG CoA reductase, a rate limiting enzyme in the biosynthesis of cholesterol. The results obtained in this work conform to earlier report by (Beckmann *et. al.,* 2009) that polyphenols possesses antilipidemic activity.

Increase in TAG concentration following P407 i.p. injection results primarily from an inhibition of TAG degradation, P407 directly inhibits capillary lipoprotein lipase (LPL) responsible for plasma TG hydrolysis (Johnston 2004). Although the standard drug might not decrease TAG concentrations by activating lipoprotein lipase, the ethanolic extract from *Vitex doniana* could have reduced TAG levels by either activating endothelium bound lipoprotein lipase which hydrolyses the triglyceride into fatty acid hence decreasing triglyceride levels as seen in a report by Sikarwar and Patil (2011)or by inhibiting lipolysis so that fatty acids do not get converted to triglyceride.

LDL (low density lipoprotein) is responsible for transporting cholesterol to the body cells. It transports about 60-70% of total cholesterol. Therefore, an increase in TC level consequently increases LDL-c. The increased LDL-c which was not removed in the process of lipid metabolism is likely to flow into the sub-endothelial space, as well as to undergo oxidation. The oxidized LDL is phagocytized by the scavengers of macrophages and the fat-laden macrophage is left with the lipid core filled with cholesterol after necrocytosis and then arteriosclerosis is initiated (Beckmann *et. al.,* 2009).It was reported that some isoflavones (a type of flavonoid) increase resistance to LDL-c oxidation, like soybean isoflavones and genistein derivatives. This work also shows significant ($P<0.05$) reduction in LDL c levels by all *Vitex doniana* ethanolic extract (Tables 1). This result is in accordance with the work of Baum *et al,* (1998), who reported that phenolics may work by increasing LDL-c receptors densities in the liver binding to apolipoprotein B thereby making liver cells more efficient to remove LDL-C from blood.

HDL-c act as cholesterol scavengers, they pick up excess cholesterol and cholesterol esters from the blood and peripheral tissues to the liver where it is broken down to bile acids. It plays an important

role in reducing blood and peripheral cholesterol concentrations and inhibits formation of atherosclerotic plaque in the aorta (Kim *et. al.*, 2008, Karmarkar 2008) therefore known as the protective cholesterol. The present studies shows significant ($P<0.05$) increase in HDL-c by the standard drug, leaves and stem bark extracts. This could possibly be due to increasing activity of lecithin-cholesterol acyl transferase (LCAT), an enzyme responsible for incorporating free cholesterol into HDL-c as suggested by Geetha *et al.* (2011), there by promoting reverse cholesterol transport and competitively inhibiting the uptake of LDL-c by endothelial cells and preventing the generation of oxidized LDL-c (Yokozawa *et. al.*, 2006).

Atherogenic risk predictor indices (HDL-c/TC, LDL-c/HDL-c and log (TG/HDL-c) are mathematical relationships between TC, TG, LDL-c and HDL-c that have been successfully used as markers of assessing atherosclerosis development (Nicholls *et. al.*, 20076, Kastelein *et. al.*, 2008)and extent of CHDs. HDL-c/ TC ratio greater than 0.3 and LDL-c/HDL-c ratio less than 2.3 indicate a reduced risk of peripheral arterial disease (Ojiakor and Nwanjo 2005). However, log (TG/HDL-c) has been considered the most accurate in determining the extent of atherosclerosis and the risk of myocardial infarction (Dobiavosa *et. al.*, 2005). It has been suggested that log (TG/HDL-c) values of-0.3 to 0.1, 0.1 to 0.24 and above 0.24 are associated with low, medium and high cardiovascular risk disease (Dobiasova 2006).The study showed that theleaves,stem bark and root barkextract significantly ($P<0.05$) increased HDL-c/TC ratio, andlowered LDL-c/HDL-c and log (TG/HDL-c) ratio when compared with animals in the induced not treated group. The results suggest the anti-atherogenic potential of *Vitex doniana* (leaves, stem and root bark) ethanolic extracts and hence, reducing the development of coronary atherosclerosis as suggested by Dobiasova and Frohlich (Dobiasova and Frohlich 2001).

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