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Effect of *Phragmanthera incana* Leaves Extracts on Lipid Profile in Wistar Rats Fed High-Fat Diet

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Abstract

Use of herbal medicines assumes significance in the prevention of lipid disorders associated with intake of high fat diets. The search for new drugs capable of reducing and regulating serum cholesterol and triglyceride levels has gained momentum over the years. Herein, antihyperlipidemic potential of *Phragmanthera incana* extract on Wistar rats fed with high fat diet was evaluated. Forty-eight rats were divided into eight groups of six animals each. Group I (normal) received distilled water only, Group II (control) received high-fat diet only, Group III, IV, V, VI and VII received high fat diet and 400 mg/kg dose of hexane, ethyl acetate, aqueous, butanol, dichloromethane fractions of *P. incana* orally and daily for 9 weeks respectively. Group VIII (Standard) received high fat diet and 1.8 mg/kg Simvastatin. Serum lipids profile was estimated using standard procedures. The administration of *P. incana* extracts and standard drug resulted to a significant reduction (P<0.05) in the total cholesterol, triglycerides (TG), low density lipoproteins (LDL) and increase (P<0.05) in high density lipoproteins (HDL) as compared the control. The present work indicates that fractions of *P. incana* significantly suppressed the lipid profile parameters in high fats diet treated animals, suggesting the antihyperlipidemic potential of *P. incana*.

Keywords: Phragmanthera incan; High-fat diet; Lipid profile; Antihyperlipidemia.

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1. Introduction

Hyperlipidemia and related complications such as Obesity, is a global public clinical condition resulting from an imbalance between food consumption and energy expenditure which leads to abnormal or excessive fat accumulation in white adipose tissue, thereby causing adipocyte enlargement, increased adipose cell number and fat pad weight consequences [1-3]. It increases the risk and contribute strongly to several chronic non-communicable diseases (NCD), including metabolic syndrome, type2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), cancer, hypertension, obesity, stroke, osteoarthritis and infertility [4-11].

Numerous therapies and drugs have been introduced in an attempt to curtail the rampage of hyperlipidemia and its complication, some of these drugs includes Orlistat, Lorcaserine and Phentermine which have been approved for use by the United States Food and Drug Administration (FDA) [12], to enhance weight loss. Several findings have linked these drugs to gastrointestinal and cardiovascular risk factors [2]. However, more recently, scientists have searched for measures that will tip the scales in mankind favor such as phytotherapy. This has led to an upsurge in the use of medicinal plants to support the traditional claims of the various biological activities attributed to them. Some of these plants have been reported to have a significant effect on adipogenesis and lipogenesis that contributes to the development of obesity [13-17]. Due to the increasing number in hyperlipidemia in both developed and developing countries, there is still a need to search for more locally available plants that can help reduce these disorders associated with higher chances of premature death, especially in children (WHO, 2018).

Plants such as *Phragmenthera incana* is highly regarded because of its abundant phytochemicals and several biological activities, hence its use in this study. *Phragmanthera incana* (mistletoe) generally called Afomo in Yoruba language of the South-western Nigeria, is a woody parasitic shrub belonging to the family of Loranthaceae [18, 19] and usually grows on *Theobroma cacao* (cocoa) and *Kola nitida (kola nut)*. The ethnobotanical survey reported that it is native to Europe, America and Africa and have been widely used in Nigeria folk medicine to treat several human and animal diseases including hypertension, diabetes, inflammation, insomnia, hepatitis, stroke, cancer and nervous disorders[20]. There is yet limited information on its effect on lipid profile in high-fat diet induced obesity. Hence, the objective of this study is to investigate the effect of the fractionated extracts of *Phragmanthera incana* on high-fat diet induced obese rats.

2. Materials and methods

2.1 Collection and Preparation of Plant Extracts

Matured fresh *Phragmanthera incana* leaves were bought from a local market in Ikorodu division of Lagos State, Nigeria and were authenticated at the Botany Department, Lagos State University. The leaves were rinsed under a running tap water, air dried and later grounded to powdery form using blender. 200g of the powder leaves was weighed and soaked in 2000ml of methanol for 72 hours and the residue was separated from the filtrate using Whatmann grade 1 paper. The filtrate was concentrated to a slurry form using a heating mantle and was further dried on water bath at very low temperature of 40˚C to eliminate all solvents. Five fractions

including aqueous, hexane, butanol, dichloromethane and ethylacetate fractions were obtained from the resulting concentrated extract by dissolving a known weight of the plant concentrate in 120ml of distilled water. 100ml of the concentrate solution was then poured into a separating funnel together with 100ml of hexane, butanol, dichloromethane and ethylacetate each. The separating funnel was shaken properly to allow proper mixture and then allowed to stand for 15mins. Each fraction were then collected, labeled and concentrated in a hot air oven and then refrigerated until use.

2.2 Toxicity studies

Acute toxicity study was carried out according to OECD Guideline 423 in assessing the acute oral toxicity [21]. LD50 was calculated and 400 mg/kg dose chosen for the present study.

2.3 Animals

Forty-eight female wistar rats weighing an average of 180g were purchased and kept in the Biochemistry Department Animal house, Faculty of Science, Lagos state University, and were used for this study. They were kept in a well-ventilated rat cages and exposed to 12 hours light and 12 hours darkness. The rats were placed on growers pellet produced by Caps Feed Mill Nigeria Limited with access to sufficient water ad libitum and were allowed to acclimatize for fourteen (14) days prior to the experiment. The experiment was carried out for a period of 5 weeks. Animals' cares under ethical and experimental protocol duly approved by institutional ethic committee were considered. Rats were divided into eight groups of six rats each. Mistotle extracts (*Phragmanthera incana*) were administered to the rats at a dose of 400mg/kg each as gotten from the acute toxicity test.

2.4 Preparation of High Fat Diet

High fats diet was prepared by mixing cholesterol 2%, sodium cholate 1%, yellow corn 15%, milk powder 15%, coconut oil 11% and 11% butter and one multivitamin capsule with powdered standard animal food [22].

2.5 Induction

Hyperlipidemia was induced in the rats by single daily oral dose of 10mg/kg body weight of high fats diet mixture prepared.

2.6 Preparation of Simvastatin Suspension

The stock solution was prepared by dissolving 20 mg of simvastatin in 70 ml of normal saline and used as a standard drug (1.8 mg/kg) for the individual group. Using the description of Gosh, (2005), the daily dose of simvastatin for rats was calculated by extrapolation from the human dose (20 mg/day) [23, 24].

2.7 Experimental Design

A total of forty-eight (48) Wistar albino rats were randomly divided into eight groups of six rats each to examine

the anti-obesity effect of *Phragmanthera incana*. Group I: rats fed with normal diet (normal). Group II: rats fed with high-fats diet only (control). Group III: rats fed with high fat diet + 400 mg/kg hexane fraction. Group IV: rats fed with high fat diet + 400 mg/kg ethylacetate fraction. Group V: rats fed with high fat diet + 400 mg/kg aqueous fraction. Group VI: rats fed with high fat diet + 400 mg/kg butanol fraction. Group VII: rats fed with high fat diet + 400 mg/kg dichloromethane fraction. Group VIII: rats fed with high fat diet + 1.8 mg/kg Simvastatin (Standard).

2.8 Determination of Lipid profile

Lipid profile of all the rat groups was determined after separation of serum from blood collected from the tail vein of overnight fasted rats, and the lipid profile parameters estimated includes Total Cholesterol (TC), Triglycerides, (TG), Low Density Lipoprotein Cholesterol (LDL) and High Density Lipoprotein Cholesterol (HDL). Serum LDL was estimated by calculation using: LDL mg/dl = Total cholesterol – HDL - TG/5 [25].

2.9 Statistical analysis

Results were expressed as Mean ± SEM. The statistical significance between control and treated groups were performed using analysis of variance ANOVA. For multiple comparisons among the groups Bonferroni test was performed using Graph-Prism. A probability level of $*p < 0.05$ was accepted as statistically significant.

3. Results

From the table 1 below, the result showed that there was a significant increase in the total cholesterol (TC) in the dichloromethane fraction and aqueous fraction groups compared to the normal at the 0^{th} week. After the 3^{rd} week of treatment, the control and hexane fraction group TC increased significantly compared to the standard. However, at the 6^{th} and 9^{th} week of treatment hexane, dichloromethane, ethyl acetate and butanol fractions group TC reduced significantly compared to the 0 week of administration.

Table 1: Serum Total Cholesterol levels in high fat diet fed rats

TEST FRACTIONS	0 WEEK	3 WEEKS	6 WEEKS	9 WEEKS
NORMAL	157.74 ± 15.96^{a}	159.68 ± 21.47^{a}	161.39 ± 18.32^{a}	158.23 ± 10.18^{a}
CONTROL	266.15 ± 15.70^{ab}	377.23 ± 50.56^{b}	304.72 ± 30.29^{a}	258.97 ± 20.94^{a}
HEXANE FRACTION (400mg/kg body weight)	294.67 ± 32.99^{ab}	$379.39\pm94.95^{b\$}$	255.39 ± 35.93^{a}	$167.67\pm40.63^{a\#}$
ETHYLACETATE FRACTION (400mg/kg body weight)	$302.77\pm5.54^{ab\$}$	$278.16\pm2.16^{ab\$}$	227.69 ± 45.53^{a}	$146.31\pm17.54^{a}*^{\#}$
AQUEOUS FRACTION (400mg/kg body weight)	$393.23\pm27.10^{b\delta\$}$	$293.54\pm42.92^{ab\$}$	$239.18\pm15.63^{a}*$	$155.82\pm16.52^{a}*^{\#}$
BUTANOL FRACTION (400mg/kg body weight)	$301.74\pm38.48^{ab\$}$	256.82 ± 11.55^{ab}	204.77 ± 25.70^{a}	$152.08\pm31.19^{a}*$
DICHLOROMETHANE FRACTION (400mg/kg body weight)	$346.87\pm26.07^{b\$}$	258.00 ± 27.69^{ab}	228.62 ± 47.58^{a}	$179.08\pm7.26^{a}*$
STANDARD(1.8mg/kg body weight)	243.07 ± 12.11^{ab}	252.51 ± 33.18^{ab}	176.41 ± 18.26^{a}	130.21 ± 16.65^{a}

Values in the same column with different alphabets are significantly (P<0.05) different.

*#δ$indicates a significant (P<0.05) difference in Total cholesterol levels in comparison with week 0, 1, 2 3 respectively.

From the table 2 below revealed that at the 0th week and 3rd week, the control and hexane fraction group TAG concentration increased significantly compared to the normal. Whereas the Dichloromethane and standard group reduced TAG concentration significantly compared to the hexane fraction group. At the 3rd week of treatment, the control and the butanol increased and reduced the TAG concentration compared to the normal and control respectively. However, the standard reduced the TAG concentration significantly compared to the control.

Table 2: Serum Triglyceride levels in HFD fed rats

TEST FRACTIONS	0 WEEK	3 WEEKS	6 WEEKS	9 WEEKS
NORMAL	66.67±17.65^{a}	65.78±32.19^{a}	67.40±23.08^{a}	66.56±13.43^{a}
CONTROL	285.95±18.02^{b}	263.14±12.73^{bc}	294.77±14.65^{b}	266.01±32.99^{b}
HEXANE FRACTION (400mg/kg body weight)	265.78±7.11^{b}	279.41±2.68^{c}	200.33±1.37^{ab}	151.31±10.60^{ab}
ETHYLACETATE FRACTION (400mg/kg body weight)	220.39±5.88^{ab}	201.31±5.41^{abc}	192.16±95.46^{ab}	122.88±9.27^{ab}
AQUEOUS FRACTION (400mg/kg body weight)	234.64±30.16^{b}	202.94±48.40^{abc}	212.26±2.46^{ab}	157.52±2.55^{ab}
BUTANOL FRACTION (400mg/kg body weight)	217.97±25.80^{ab}	169.12±21.08^{abc}	124.67±3.83^{a}	114.38±11.86^{ab}
DICHLOROMETHANE FRACTION (400mg/kg body weight)	245.10±28.23^{b}	212.68±85.70^{ab}	174.51±12.75^{ab}	148.70±7.20^{ab}
STANDARD (1.8mg/kg body weight)	168.04±27.15^{ab}	120.26±68.39^{ab}	109.80±8.83^{a}	106.87±43.14^{a}

Values in the same column with different letters are significantly different at P<0.05.

*#δ$indicates a significant (P<0.05) difference in Triglyceride levels among values in the same row.

From table 3 below the result showed that at the 3rd week of treatment, the hexane fraction increased the HDL-CHOL concentration significantly compared to the normal. Also the at the 3rd week treatment, the butanol and Dichloromethane fraction group reduced the HDL-CHOL concentration significantly compared to the control. The ethylacetate, butanol, aqueous and dichloromethane fractions tend to increase the HDL-CHL level significantly compared to the negative control which had a lowered HDL-CHL level.

Table 3: HDL-Cholesterol levels of *P. incana* in HFD fed rats

TEST FRACTIONS	0 WEEK	2 WEEKS	6 WEEKS	9 WEEKS
NORMAL	85.67 ± 17.65^{a}	83.37 ± 19.16^{ab}	84.77 ± 20.18^{a}	86.28 ± 38.27^{a}
CONTROL	$51.77\pm19.02^{a\#}$	$151.36\pm17.64^{bc*\delta\$}$	$61.14\pm31.13^{a\#}$	$61.74\pm3.46^{a\#}$
HEXANE FRACTION (400mg/kg body weight)	$81.52\pm4.61^{a\#}$	$171.74\pm29.59^{c*\delta\$}$	$80.89\pm0.19^{a\#}$	$86.47\pm24.21^{a\#}$
ETHYLACETATE FRACTION (400mg/kg body weight)	102.72 ± 21.91^{a}	114.05 ± 4.80^{abc}	92.94 ± 8.05^{a}	92.20 ± 1.72^{a}
AQUEOUS FRACTION (400mg/kg body weight)	64.10 ± 0.84^{a}	76.99 ± 20.48^{ab}	88.04 ± 50.73^{a}	83.56 ± 1.73^{a}
BUTANOL FRACTION (400mg/kg body weight)	99.84 ± 2.63^{a}	62.77 ± 9.22^{a}	82.75 ± 0.55^{a}	97.37 ± 4.73^{a}
DICHLOROMETHANE FRACTION (400mg/kg body weight)	65.33 ± 3.84^{a}	68.10 ± 5.51^{a}	78.24 ± 2.88^{a}	73.05 ± 0.23^{a}
STANDARD (1.8mg/kg body weight)	117.80 ± 6.32^{a}	118.07 ± 2.89^{abc}	101.90 ± 1.13^{a}	104.27 ± 0.57^{a}

Values in the same column with different letters are significantly different at $P<0.05$.

$*^{\#\delta\$}$indicates a significant ($P<0.05$) difference in HDL-Cholesterol levels among values in the same row.

From the table 4 below, the result revealed at the 0th, 3rd and the 6th week of treatment the control LDL concentration increased significantly compared to the normal. Hence, at the 3rd week treatment, the aqueous, butanol and dichloromethane fraction group increased the LDL concentration compared to the normal. However, at the 6th and 9th week of treatment the ethyl acetate, butanol, dichloromethane and standard significantly reduced the LDL concentration compared to the control.

Table 4: LDL-Cholesterol levels of *P. incana* in HFD fed rats

TEST FRACTIONS	0 WEEK	3 WEEKS	6 WEEKS	9 WEEKS
NORMAL	47.90 ± 22.38^{a}	47.59 ± 25.85^{a}	48.86 ± 11.67^{a}	49.01 ± 4.27^{ab}
CONTROL	166.13 ± 20.70^{bc}	116.16 ± 39.72^{ab}	180.72 ± 5.79^{b}	129.61 ± 7.36^{b}
HEXANE FRACTION (400mg/kg body weight)	$143.67\pm15.37^{bc\$}$	97.52 ± 18.43^{ab}	113.99 ± 1.61^{ab}	$65.53\pm1.45^{ab*}$
ETHYLACETATE FRACTION (400mg/kg body weight)	$157.66\pm14.54^{bc\delta\$}$	$124.02\pm13.39^{ab\$}$	$71.87\pm8.88^{a*}$	$31.07\pm2.13^{a*\#}$
AQUEOUS FRACTION (400mg/kg body weight)	$274.76\pm23.63^{d\#\delta\$}$	$162.94\pm38.75^{b*\$}$	$113.45\pm31.93^{ab*}$	$47.35\pm6.79^{ab*\#}$
BUTANOL FRACTION(400mg/kg body weight)	$138.99\pm13.68^{bc\$}$	$157.21\pm1.75^{b\delta\$}$	$80.02\pm38.33^{a\#}$	$24.65\pm2.96^{a*\#}$
DICHLOROMETHANE FRACTION (400mg/kg body weight)	$220.89\pm0.67^{cd\#\delta\$}$	$136.20\pm5.06^{b*}$	$89.68\pm5.30^{a*}$	$73.89\pm0.97^{ab*}$
STANDARD (1.8mg/kg body weight)	88.46 ± 3.45^{ab}	$97.50\pm23.57^{ab\$}$	63.79 ± 2.14^{a}	$25.67\pm4.60^{a\#}$

Values in the same column with different letters are significantly different at $P<0.05$.

*#δ$indicates a significant (P<0.05) difference in LDL-Cholesterol levels among values in the same row.

4. Discussion

The main contributing factors to a thrombotic disease are the disturbances occurring in lipid metabolism. Despite the presence of various hypolipidaemic pills available in the market, their healing software is typically related to intense aspect effects [26]. However, efforts are being made to find safer, cheaper and more efficient anti-hyperlipidaemic drugs. Hence, medicinal plants have been considered as promising resources for the discovery of new drugs. In this present study, the anti-hyperlipidaemic activity of *P. incana* extract was evaluated among the high-fat diet rats.

In this current study, dyslipidaemic changes like elevated Total cholesterol (TC), Triglycerides (TAGs), Low density Lipoproteins (LDL), and serum level of High density Lipoproteins (HDL) were observed. The results of total cholesterol clearly show much higher levels in the negative control rats as compared to normal rats. [27] reported that the high cholesterol level in high fat diet untreated group can be attributed to the hyperlipidaemic condition which normally lowers high density lipoprotein (HDL) referred to as the good cholesterol and increases the harmful cholesterols; triglycerides (TG) and low density lipoprotein (LDL), thereby elevating the overall cholesterol level that may result in serious hyperlipidaemic complications. [28] have shown similar results in obese individuals. Increased cholesterol level may contribute its role towards atherosclerosis indirectly having relationship with coronary heart disease[29]. A previous toxicological evaluation of the *P. incana* reported by [30], showed that regardless of its host plant, it possesses a good lipid lowering property via significant reduction of lowering low density lipoprotein (LDL), and also in addition decreases blood glucose and alleviate some diabetes complication such as liver and kidney injury. It can be obtained from this research that the ethyl acetate, dichloromethane and hexane treated animals' poses to reduce the total cholesterol level after 9weeks of treatment. The fractions of the hemiparasitic plant extracts showed better hypolipidemic control compared to simvastatin in lowering total blood cholesterol levels, which is the desired effect of an oral hypolipidemic agent. Our results showed that treatment was effective from the 6^{th} week to the 9^{th} week using the aforementioned fractions above which was compared to the standard drug Simvastatin, which also had similar effect.

Higher levels of triglycerides are found in individuals on high fat diets which can due to the dietary cholesterol that appears to decrease the unsaturated fat oxidation, which resulted in long-lasting levels of plasma and hepatic TAG and also the extreme accumulation of TAG in the lipid stores [31]. From the result obtained the Dichloromethane treated rats had a low TAG concentration when compared to the negative control group which had an increased TAG level. This pronounced decrease can be correlated with that of the group treated with the standard drug.

Reduced levels of high-density lipoproteins (HDL) in individuals on high fat diets are associated with increased risk for the development of coronary artery disease [32]. Therefore, it is important to ascertain the process accountable for decreased HDL in overweight states and, conversely, to study treatments geared toward growing HDL concentration in those individuals. High HDL is cooperative in transporting redundant LDL cholesterol to

the liver for emanation in the bile [33]. From the results obtained, most of the fractions (aqueous, butanol, ethyl acetate and dichloromethane) increased the HDL-cholesterol level which tends to be in line with the work of [34]. The established standard drugs also increased the HDL in high fat diet treated rats. These results are in conformity with those of [32].

LDL (low-density lipoprotein), sometimes called "bad" cholesterol, makes up most of the body's cholesterol [35] and its high concentration raises the risk for heart disease and stroke. LDL levels were also increased statistically in obese persons as compared to the normal after the 9^{th}week; these results are amply supported by [36, 37]. Administration of the butanol and ethyl acetate fraction lowered the LDL-C levels significantly which was similar to the lowering activity if the standard drug.

5. Conclusion

In conclusion, our data clearly indicate the anti-hyperlipidaemic effects of some fractions of *P. incana* in animals fed with high fat diet.

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