A STUDY OF *Adansonia digitata* ON LIPID PROFILE AND NFkb-p65 IN DIET AND STREPTOZOTOCIN-INDUCED METABOLIC SYNDROME IN MALE WISTAR RATS

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ABSTRACT

Background: Hypercholesterolaemia is increasing in Nigeria. *Adansonia digitata* (AD) is used traditionally for managing disorders including hypercholesterolaemia. The present study aims to evaluate lipid-lowering effect of AD, and gene expression of NFkb-p65 on diet and streptozotocin-induced dyslipidaemia in Wistar rats.

Methodology: Forty-two male Wistar rats were divided into 7 groups (n=7) A to G; given food and water *ad libitum*. Group A was fed standard animal diet. B to F were fed high-fructose high-fat diet (HFHFD) for 6 weeks, and all groups except A, were then injected with 40mg/kg streptozotocin. Just before treatment began, an animal each from C to F was sacrificed (CC), to confirm hypercholesterolaemia. The remaining animals in C to F were administered AD (400mg/kg, 800mg/kg and 1600mg/kg) and standard drugs Metformin plus atovastatin respectively for another 6 weeks. Group G was concomitantly fed HFHFD and AD 1600mg/kg from the beginning, then terminated at 6 weeks. At the end of the study (12 weeks), the remaining animals were sacrificed by cervical dislocation, serum samples were analysed for lipid profile; adipose tissue homogenates were analysed for NFkb-p65 using ELISA kits.

Results: Groups C, F and G had higher total cholesterol; Triglyceride level was significantly higher in all except group F (treated with metformin plus atovastatin). HDL was significantly highest in C; group A had lower LDL. Lowest level of NFkb-p65 was insignificantly recorded in group G.

Conclusion: Aqueous AD supplementation (400mg/kg) improved HDL level in male Wistar rats subjected to HFHFD, but no significant effect on NFkb-p65 expression.

Keywords: *Adansonia digitata* Metabolic syndrome Lipid profile Nuclear-factor kappa-B-p65

INTRODUCTION

Metabolic syndrome (MetS) is a cluster of conditions including high blood pressure, dyslipidaemia, hyperglycaemia (Chan *et al.*, 2021) which occur together to increase the risk for, or complicate existing metabolic disorders particularly type 2 diabetes mellitus (T2DM) and cardiovascular disease (Cho *et al.*, 2021). The prevalence rate is increasing globally ranging from 10% up to about 84% (Cicolari *et al.*, 2020), and as high as 60% in Nigeria as reported in 2012. It has therefore become a global epidemic (Liu *et al.*, 2023).

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Management of metabolic syndrome is challenging, considering the constellation of metabolic dysregulations involved. Nonetheless, prevention may be achieved by modifying lifestyle to maintain normal weight, increasing physical activities and healthy diet comprising lots of vegetables, whole-grains and fruits (Cicolari *et al.*, 2020). However, in some cases the modalities of lifestyle changes and diet may be inadequate to abate MetS, in which event pharmacological therapy containing statins (aimed to lower hyperlipidaemia), and or metformin (targeted at reducing hyperglycaemia) may be used. But these medications can cause serious side-effects that could reduce patient compliance which may subsequently lead to therapeutic failure. In addition, a considerable number of individuals in Nigeria cannot afford the high cost of treatment/management of MetS with conventional medication. It has therefore become necessary to explore alternative means such as nutritional intervention to manage MetS by targeting dyslipidaemia, one of its major manifestations.

The most important risk indicator for type-2 diabetes mellitus and related complications is dyslipidaemia (Belete Biadgo *et al.*, 2017). The overall prevalence of dyslipidaemia in Nigeria ranged between 60% among apparently healthy Nigerians, to 89% among diabetic Nigerians, showing a pattern with low HDL and high LDL (Oguejiofor, 2012). These rates are alarmingly high and is a cause for concern to medical practitioners and affected individuals.

Adansonia digitata (AD) is the scientific name for Baobab tree, all parts of which are rich in nutrients (Azadniya *et al.*, 2023) including dietary fibre (Coe *et al.*, 2013), antioxidants (Ayele *et al.*, 2013), healthy mono- and polyunsaturated fats. It is an endemic African plant (Cicolari *et al.*, 2020) that is abundantly found in North-eastern Nigeria, and is rich in health-promoting compounds (Baky *et al.*, 2021). Proximate analyses and phytochemical studies on AD revealed the presence of flavonoids, polyphenols (Ghoneim *et al.*, 2016), antioxidants (Babatunde *et al.*, 2021) and other micronutrients (Silva *et al.*, 2023). Antioxidants present in the fruit may play some roles in prevention against oxidative damage to cells (Ahmed *et al.*, 2022), which is the hallmark linking dyslipidaemia, inflammation and MetS.

Previous studies have reported the use of AD in lowering blood lipids (Abdelgadir et al., 2019). Individuals who consume AD juice had significantly lower levels of TC, TGs and LDL when compared with individuals who do not consume AD (Ahmed *et al.*, 2022). LDL oxidation was also found to be inhibited, with subsequent reduction of formation of malondialdehyde (MDA) by AD essential oil (Ahmed *et al.*, 2022). Oxidation of LDL signifies a process where free radicals could cause damage to tissues, leading to several deleterious effects including inflammation and increased risk of cardiovascular disease. Furthermore, reduction in formation of MDA, a reactive compound formed in the process of lipid peroxidation, is established to ameliorate oxidative damage to LDL (Dare *et al.*, 2021).

Nuclear factor kappa B (NF-kB) is a transcription factor complex that plays a crucial role in controlling immune responses (O'Hara *et al.*, 2024), inflammation and cell survival (Mantione *et al.*, 2024). It is closely associated with various biological processes including those that are linked to immunity and inflammation (Zhang *et al.*, 2024b). NF-kB-p65 is a subunit of NF-kB that plays fundamental role in regulation of genes more related with body systems, metabolism and inflammation (Zhang *et al.*, 2024a).

In adipose tissues, NF-kB substantially affect adipocyte function and inflammation (Tomasello *et al.*, 2023). When NF-kB expression is inhibited in adipose tissues, several outcomes may arise. One important facet of this is a possible decrease in inflammatory signalling which could be favourable in obesity-related inflammation, insulin resistance (Xu *et al.*, 2021) and metabolic disorders.

For instance, it could lower chronic inflammation that could be seen in obesity and metabolic syndrome. Likewise, it could also subside pain and discomfort which accompany inflammation.

Moreover, NF-kB inhibition may also diminish adipose tissue inflammation, and inflammation in adipose tissue have been found to closely associate with insulin resistance and T2DM (Zhu *et al.*, 2024). Decrease in NF-kB expression may therefore potentially improve insulin sensitivity. Similarly, lipid profile could be improved by inhibition of NF-kB expression, specifically the p-65 subunit, by decreasing inflammation and changing metabolic mechanisms. Inhibition of NF-kB-p65 may therefore greatly minimize the risk of developing metabolic syndrome and cardiovascular disorders (Wu *et al.*, 2023).

Nonetheless, inhibition of NF-kB expression may be hazardous in certain respects. Cell survival and immune responses entail a good function of NF-kB signalling (Wang *et al.*, 2024). Consequently, suppression of NF-kB expression may possibly diminish immune response, and this could make the tissue more prone to infections as well as hinder repair of the damaged tissues. In any case, normal cell survival may also be affected by impacting on apoptosis of adipocytes that could lead to changes in adipose tissue function and structure. These changes could trigger effects detrimental to metabolism, which mainly result due to factors that influence deformation and differentiation of new adipocytes.

There is paucity of literature concerning effect of AD on genes that are related to lipid metabolism and inflammation, particularly NF-kB and the transcription factor sub-unit NF-kB-p65. The present study aims to evaluate lipid-lowering effect of AD, and gene expression of NF-kB-p65 on diet-induced dyslipidaemia in male Wistar rats.

MATERIALS AND METHODS

Collection and Preparation of plant

Dried AD fruit pulp was sourced from the local market in Potiskum, Yobe State, Nigeria during the month of March, and transported to Kaduna. It was authenticated in Kaduna State University, Kaduna, Nigeria, Faculty of Pharmaceutical Science Herbarium by botanist (Mr. Usman Hamzah) with voucher number of KASU/HERB/101. Then 100g of the pure fruit powder was soaked in 500ml distilled water, a solution was obtained. It was passed through a Buchner funnel with filter paper the residue was removed and obtained the fine aqueous solution. It was then poured inside petri-dishes placed in a water-bath at 45◦C, allowed to dry completely. The resulting aqueous extract was homogenized by ceramic mortar and pestle, and stored in desiccator. The fine, dried extract was used for the study.

Diet Preparation:High-fructose high-fat diet

Fructose in Drinking water

HFHFD was constituted by dissolving 10g of fructose in 100mL distilled water to form a stock solution of 10% fructose. Each day about 10mL of the stock solution was added to the drinking water of the study animals. Fresh sample was prepared and given to the animals daily. The remaining water gets discarded on the next morning.

High fat diet

High fat diet was prepared by mixing 2.5g of margarine to every 10g of regular animal feed. These were mixed thoroughly and formed into large chunks that were fed to the animals daily.

Standard drugs

Metformin tablets were obtained from a standard Pharmaceutical centre in Kaduna, and crushed inside a homogenizer. The appropriate concentration (500mg/kg) was weighed and dissolved in distilled water daily before administration to the relevant study animals (group F) through gastric gavage.

Atovastatin was also obtained from a standard Pharmaceutical centre in Kaduna, crushed inside a homogenizer and dissolved in distilled water daily before administration of 10mg/kg to each relevant study animal (group F).

Experimental design

A total of 42 male Wistar rats weighing between 120 to 130 kg (aged six-eight weeks) were sourced from Agricultural Research Institute at Mando, Kaduna, kept in the animal house unit in the Department of Human Physiology, Kaduna State University, and allowed to acclimatize for 2 weeks before commencement of the experiment. The study protocol was approved by the Institutional Animal Ethic Committee of Kaduna State University (Approval number KASU/AEC/2023/003). They were divided into 7 groups (n=6) A to G, and subjected to high-fructose-high fat diet for 6 weeks (except group A which served as the negative control group), and then injected with 40mg/kg Streptozotocin intraperitoneally at the end of the 6 weeks, before commencement of treatment.

The study animals were given the following treatment (Table 1).

At the end of 6 weeks; animals in group G and randomly selected animals from groups C, D, E and F (labelled as group CC) were administered low-dose (40mg/kg) streptozotocin intraperitoneally and sacrificed on the next day. Group CC were to confirm successful induction of dyslipidaemia.

Blood samples were aseptically collected by cardiac puncture using a 5 mL syringe, and stored inside pre-labelled plain tubes and serum was extracted.

Table I: Experimental design

Groups	Diet	Treatment
	0 – 6 Weeks	**6-12 Weeks**
A	Standard animal-diet (sd)	sd
B	High-fructose high-fat diet (HFHFD)	sd
C	HFHFD	sd +AD 400mg/kg/day
D	HFHFD	sd +AD 800mg/kg/day
E	HFHFD	sd +AD 1600/kg/day
F	HFHFD	sd +Metformin + Atovastatin
G	HFHFD + AD 1600mg/kg	Terminated at week 6

Key: sd-standard animal diet; HFHFD=high fructose high-fat diet; AD=*Adansonia digitata*

Adipose tissue (1g) for each sample was taken from abdominal fat and immediately placed inside pre-labelled plain tubes containing 5mL PBS buffer, and frozen until needed for NF-kB-p65 gene expression.

The remaining groups of study animals (except group A), were then administered low-dose (40mg/kg) streptozotocin intraperitoneally. They were removed from HFHFD and switched to standard animal diet plus AD supplementation (Table I) and water *ad libitum*. These were maintained for an additional 6 weeks. The entire experiment lasted 12 weeks.

At the end of a total of 12 weeks from commencement of the study, the animals were fasted overnight, and sacrificed by cervical dislocation. Blood samples were drawn by cardiac puncture and serum was obtained for biochemical analyses. Adipose tissues were correspondingly harvested, 1g from each sample was placed into plain tubes containing 5mL PBS buffer, and frozen until needed for NF-kB-p65 gene expression analyses.

Biochemical Investigation

Lipid profiling: Lipid profile was assessed by colorimetric method.

Adipose tissue NF-kB-p65 gene expression: Gene expression of NF-kB-p65 in adipose tissue was quantified by commercially available ELISA kit, using adipose tissue homogenate.

Statistical analyses

Statistical analysis was conducted by using SPSS version 25. ANOVA was used to determine differences between the groups, and Tukey post-hoc test was used to show positions of such differences. Results are expressed in charts. Value of $p \leq 0.05$ were considered significant.

RESULTS

In the present study, lipid profile revealed some statistically significant differences between the groups. Group A was the negative control group which was given tap water and standard laboratory diet. Group B was the positive control group which was given tap water and HFHFD only. Groups C, D and E were the experimental groups supplemented with graded doses of AD (400mg/kg, 800mg/kg and 1600mg/kg respectively). Group F was the group treated with standard drugs (atovastatin 10mg/kg and metformin 500mg/kg, while group G were concurrently fed HFHFD and supplemented with AD. On the other hand, group CC (randomly selected from groups B, C, D and F to confirm successful induction of dyslipidaemia) were terminated from the experiment at 6 weeks.

The level of total cholesterol was found to be significantly ($p<0.05$) lower in group A (negative control group) when compared with groups B (group fed with HFHFD without AD); group C; group D; group E group G and group CC (Figure I).

Also, group E were observed to have significantly higher total cholesterol when compared with groups A, and F. Higher value of total cholesterol was also observed in groups G and CC when compared to groups A, B and F. In addition, group CC had the highest total cholesterol (Figure I).

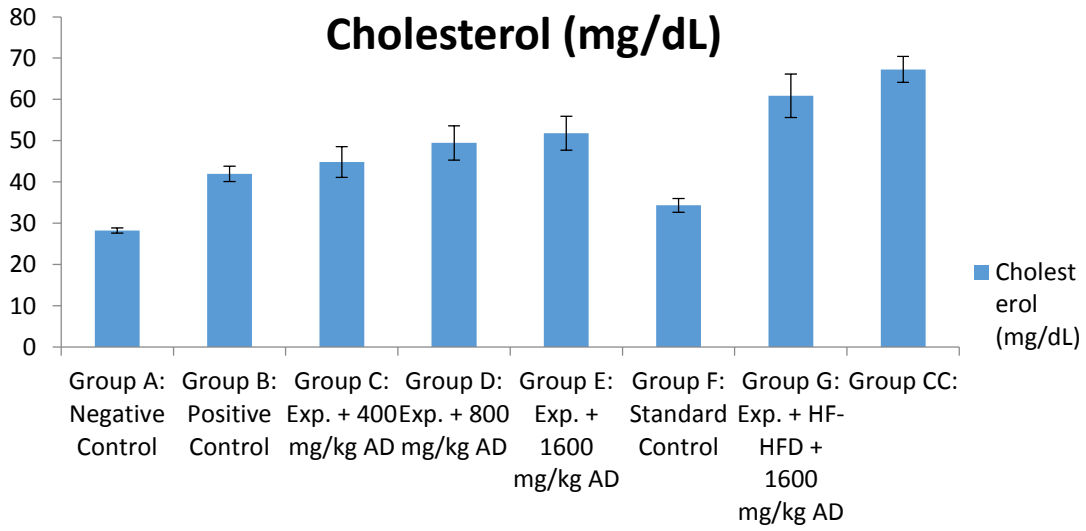

Figure I: Total cholesterol level (mg/dL) in all the study groups

Group C recorded the highest value for HDL, which was significantly higher than groups A, B and F. But it was not significantly different in the other groups (Figure II).

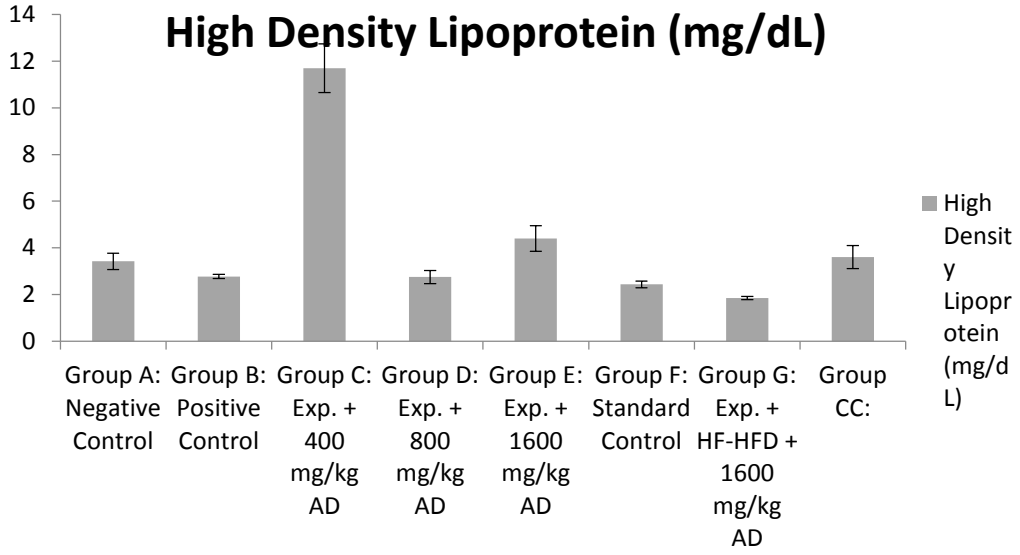

Figure II: High density lipoprotein (HDL) level (mg/dL).

For triglycerides, the lowest value was seen in group F, which was also significantly lower than the negative control group A, positive control group B, experimental groups C, D, and E. Highest value for triglycerides was recorded in the experimental group G which were concurrently fed HFHFD as well as 1600mg/kg AD (Figure III).

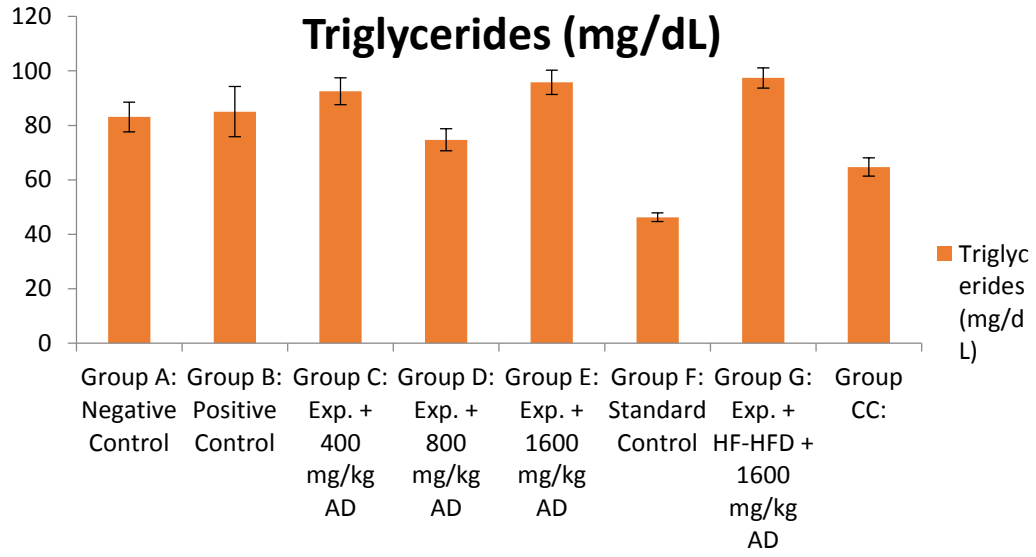

Figure III: Triglycerides level (mg/dL) in all the study groups.

LDL level was also significantly different between the groups. Group A had a significantly lower value for LDL when compared with groups B, D, E, G and CC.
Group B had a significantly lower value of LDL than groups E, G and CC Group CC recorded the highest value of LDL. The standard control group (Group F) also exhibited lower level of LDL (Figure IV).

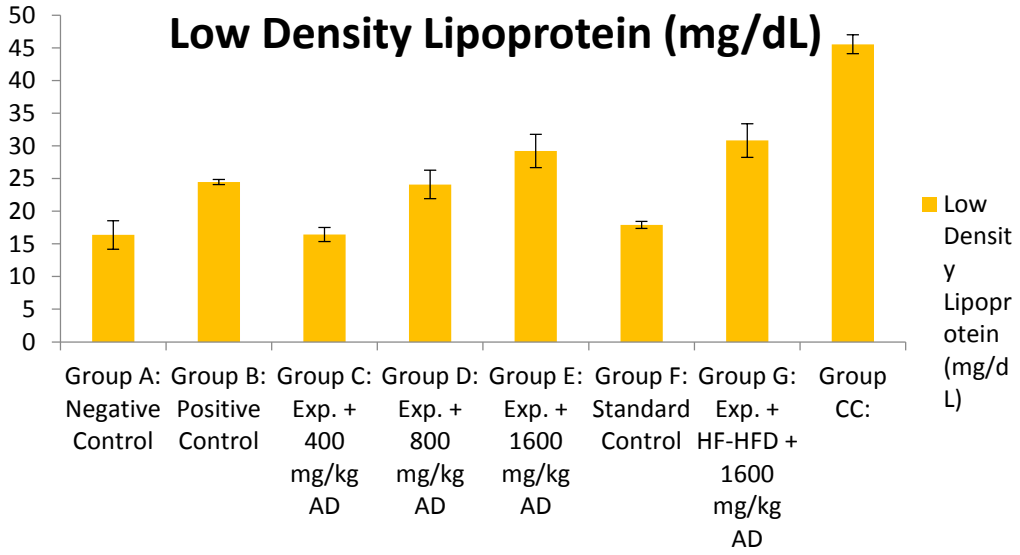

Figure IV: Low-density lipoprotein (LDL) level (mg/dL) in study groups

NF-kB-p65 level was not statistically significantly different between the groups. Notwithstanding, lowest value for NF-kB-p65 gene expression was insignificantly observed in group G In addition, Groups A and B had higher values of NF-kB-p65 (Figure V).

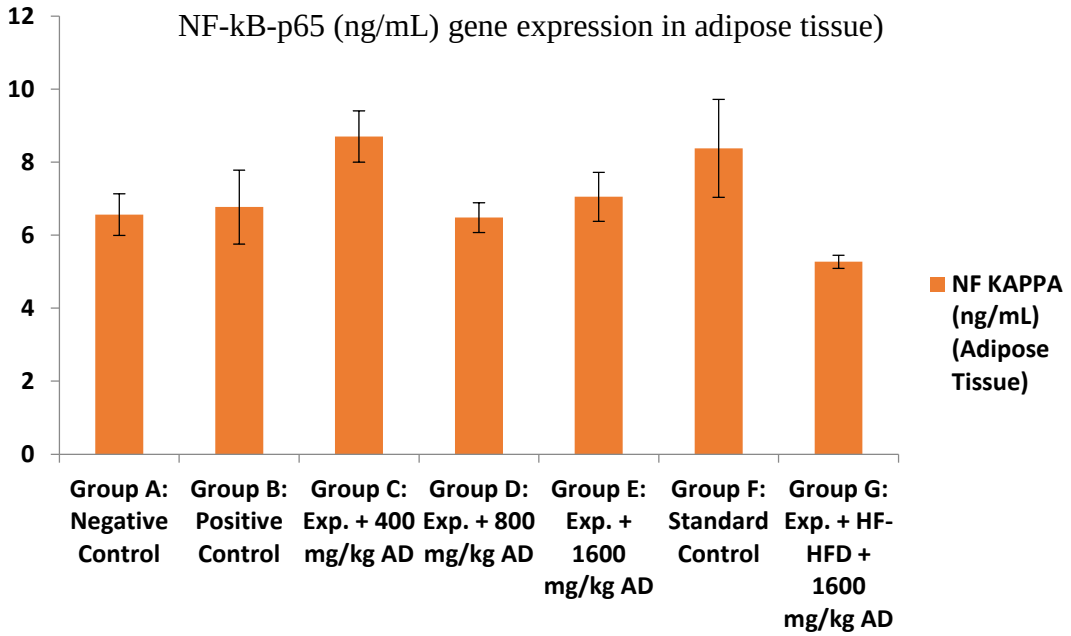

Figure V: Nuclear factor kappa B-p65 level in adipose tissue of all the study animals

DISCUSSION

Hypercholesterolaemia was successfully induced in the present study, as was observed in group CC (Figure I) which was designed to confirm dyslipidaemia. Feeding with HFHFD was expected to cause dyslipidaemia, particularly a rise in TC level (Apryatin *et al.*, 2016).

The negative control group that was maintained on regular animal diet and water did not receive the HFHFD, and had a significantly lower TC level. Higher TC observed in groups G and CC (Figure I) could be explained thus: the two groups received HFHFD but no treatment and were terminated at 6 weeks, hence there was no chance for the body to try and resolve the dyslipidaemia by natural physiological mechanisms. Although group G received concurrent AD supplementation and HFHFD, it was terminated at 6weeks. Still, group CC had higher TC which could suggest a possible cholesterol-lowering effect of AD since the group was not administered the AD supplement, neither was it given time for natural resolution of hypercholesterolaemia. AD was reported to have hypolipidemic effect (Ahmed *et al.*, 2022) and (Mohammed *et al.*, 2021). Furthermore, AD has been shown to have even higher lipid-lowering activity than the conventional simvastatin (which is another form of atorvastatin) by affecting pancreatic lipase enzyme (Alameen *et al.*, 2023), thereby modulating the breakdown of triglycerides.

Dosage of 400mg/kg aqueous AD extract was observed to cause the highest HDL concentration (Figure II), possibly suggesting a better dose that may improve HDL cholesterol level.

Lowest value for TGs recorded in the group treated with conventional standard drug combination of atorvastatin and metformin may signify the likelihood that TG cholesterol-lowering activity may be more impactful with the conventional combination, or AD aqueous extract may not be an effective alternative at reducing TG level in the current study. This inference may be substantiated by similar observation still in the present study; group concurrently treated with AD extract dose of 1600mg/kg plus HFHFD (Figure III) showing the highest value for TGs. This conforms to the study of Benkhaled *et al* who also observed development of dyslipidaemia when animals were fed fructose in drinking water (Benkhaled *et al.*, 2022). Supplementation with AD aqueous extract 1600mg/kg may therefore not be effective in preventing development of hypertriglyceridemia in male Wistar rats fed with HFHFD. Nonetheless, these findings contrast that of Abdelgadir *et al*., (2019) who reported significant reduction in TGs and LDL cholesterol by AD supplementation at 200mg/kg and 400mg/kg; Ahmed *et al*., (2022) also noted decreased levels of TGs, TC and LDL in individuals who frequently drink AD juice.

LDL transports cholesterol from liver to other tissues in the body. High levels have been found to increase the risk of developing cardiovascular diseases, or complicate existing conditions (Gomez-Barrado *et al.*, 2024). Therefore, one crucial target treatment and management of dyslipidaemia is to abate increased LDL level.

Feeding with HFHFD elevated the level of LDL above all the other groups , further verifying successful induction hyperlipidaemia in the study.

Besides, the observed higher LDL level in group G may signify that concurrent supplementation with aqueous AD extract of 1600mg/kg while still feeding on HFHFD may not necessarily prevent an increase in LDL concentration in male wistar rats. In fact, the best dose which effectively lowered LDL level in the present study is aqueous AD extract of 400mg/kg. More studies are recommended to validate the present findings, and also to investigate if ingesting AD at other doses could actually prevent the development of hypercholesterolaemia while on HFHFD.

NF-kB-p65 is a sub-unit of NF-kB, which is a transcription factor that plays important role in maintaining immune response, inflammation in response to overnutrition and metabolic stress. In adipose tissues, NF-kB notably affect adipocyte function and inflammation. Inhibition of NF-kB expression in adipose tissue may have several outcomes including decrease in inflammatory signalling that could subsequently be beneficial in obesity-related inflammation and metabolic disorders.

Although there were no significant statistical differences between all the groups in the present study, when NF-kB gene expression was assayed, it does not really mean there were no biological effects (Wakabayashi *et al.*, 2012). Therefore, the lowest value observed for NF-kB-p65 expression may possibly point towards inhibition of NF-kB-p65 expression at molecular level by AD supplementation in HFHFD. In any case, further research is recommended to clarify the effect.

CONCLUSION

Administration of aqueous extract of AD fruit pulp reduced HFHFD-induced hypercholesterolaemia, and improved HDL in male Wistar rats in a dose-dependent manner. Cholesterol-lowering activity was best observed at 400mg/kg, also enhancement of HDL cholesterol. However, NF-kB-p65 expression in adipose tissue was not significantly affected by aqueous AD extract in the present study.

Study Limitations

The protective group had no subgroupings hence other doses were not evaluated to assess for protective effect against the development of dyslipidaemia.

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Conflict of interest

All authors declare no conflict of interest.

Author Contribution

CFL conceptualised idea, designed the study, collected data, conducted laboratory analyses, interpreted results, drafted manuscript; SMN designed the study, collected data, conducted laboratory analyses, interpreted results, edited manuscript; GADT designed the study, collected data, conducted laboratory analyses, analysed data, edited manuscript; OOT designed the study, collected data, conducted laboratory analyses, interpreted results, edited manuscript; JFY designed the study, collected data, conducted laboratory analyses, interpreted results, edited manuscript; AA designed the study, collected data, conducted laboratory analyses, analysed data, interpreted results, edited manuscript; AOM designed the study, collected data, conducted laboratory analyses, interpreted results, edited manuscript; AI designed the study, collected data, conducted laboratory analyses, interpreted results, edited manuscript.

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