ACTA BIOSCIENTIA
Journal of Biomedical and Biological Sciences

Acta Bioscientia **2025**:1(3);123-133 **OPEN ACCESS**
https://doi.org/10.71181/actabioscientia12270

Powdered *Andrographis Paniculata* Leaves Ameliorates High-fat Diet-induced Dysmetabolism in Rats

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ABSTRACT

Andrographis paniculata (AP) is a well-known medicinal plant that has been shown to possess have ethnomedicinal value in treatment of diabetes mellitus, however there is a dearth of scientific information on its possible benefits in mitigating diet-induced dysmetabolism. This study examined the effects of powdered AP leaves on high-fat diet (HFD) induced changes in Wistar rats. Thirty-six rats were assigned into six groups of six animals each. Group A (control) were fed standard rodent chow, while group B (HFD-control) was fed high fat diet. Rats in groups C, D, and E were fed AP incorporated into HFD at 250, 500 and 1000 mg/kg of feed. Rats in group F (Metformin-control) were administered metformin by gavage at 25 mg/kg body weight, while rats in groups A-E were administered distilled water at 10 ml/kg body weight. Treatment was for a period of fifty-six days. At the end of this period animals were euthanised and blood taken for estimation of blood glucose levels, oxidative stress parameters, lipid profile and biochemical parameters of liver and kidney integrity. The liver, kidney and the pancreas were excised and processed for histological studies. Results showed diet-added AP reversed HFD-induced increase in body weight, oxidative stress, proinflammation, hyperglycaemia, hyperinsulinaemia, hyperlipidaemia and derangement of liver and renal function. Histomorphological assessment of the liver, kidneys and pancreas revealed variable degrees of preservation of the architecture of these organs in the AP treated groups. In conclusion, powdered *Andrographis paniculata* leaves showed nutraceutical potential in mitigating HFD-induced dysmetabolism in rats.

KEYWORDS: Acanthaceae, Adiponectin, Diet, Dysmetabolism, Nutraceuticals

1. Introduction

The global rise in obesity has become a major public health concern, significantly increasing morbidity and mortality rates worldwide [1]. Obesity is a complex and preventable condition often associated with chronic inflammation and oxidative stress, which contribute to comorbidities such as type 2 diabetes, cardiovascular disease, hypertension, chronic kidney disease (CKD), and non-alcoholic fatty liver disease (NAFLD) [2, 3]. Diets high in fat diets have been suggested as key contributors to dysmetabolism and the development of metabolic disorders, inducing glucolipotoxicity, oxidative stress, and inflammatory responses in various organs [4-7]. The consumption of food high in fats has been linked to oxidative stress and the production of reactive oxygen species (ROS) in pancreatic β-cells [8]. Similarly, there have been reports associating the consumption of diets high in fat with the development of low-grade proinflammatory states that exacerbates kidney disease

[9]. Additionally, NAFLD, one of the most common causes of chronic liver disease, is closely linked to obesity, insulin resistance, and hyperlipidaemia. In the liver, diets high in fat have been associated with the development of inflammation, and fibrosis, increasing the risk of cirrhosis and hepatocellular carcinoma [10].

The role of oxidative stress and pro-inflammatory cytokines, including IL-6 and TNF-α has also been demonstrated to be critical in the development of dysmetabolism and metabolic disorders. Excessive ROS production and reduced antioxidant defences have been shown to impair insulin signaling, promote fat deposition, and contribute to systemic inflammation [11]. Consequently, antioxidants derived from plants have gained attention for their ability to mitigate oxidative stress and inflammation.

While a lot has been done to improve our understanding of the pathophysiology of diabetes mellitus, and metabolic syndrome, the development of a cure remains elusive [12]. Current treatment options are directed towards managing blood glucose levels, preventing the development of complications. Also, research is beginning to demonstrated that the use of lifestyle changes and nutraceuticals could be beneficial in preventing the development of dysmetabolism and also delaying progression to diabetes mellitus and its complications [13-16]. The use of medicinal plants such as *Juglans regia* and *Andrographis panniculata* has also been shown to important in the management of dysmetabolism [14], including diabetes mellitus. These benefits have been attributed largely to the fact that a number of these plants are rich sources of bioactive compounds including alkaloids, flavonoids and tannins [14, 15]

Andrographis paniculata (Burm.f.) Nees, a medicinal plant widely used in Africa, America and Asia is renowned for its anti-inflammatory and antioxidant properties [17, 18]. Traditionally, it has been used to manage ailments such as diabetes mellitus, hypertension, bronchitis, and malaria. [19-21]. Its bioactive constituents, including andrographolide, have been shown to exhibit significant pharmacological effects, particularly in reducing oxidative stress and the production of inflammatory cytokines [22]. While there has been ample research on the beneficial effects of extracts of AP and andrographolide in the management of metabolic disorders, there is limited research on the plant's nutraceutical effects hence this study. The nutraceutical value of AP is examined in this study because it aligns with traditional practices in Nigeria and Africa, where the plant is consumed in its powdered form for various health conditions [23, 24]. Therefore, this study investigated the possible effects of powdered *AP leaves* on the liver, kidney, and pancreas in HFD-induced dysmetabolism in rats.

2. Methodology

2.1 Collection and Extraction of Plant Material

Andrographis paniculata leaves were sourced from a botanical farm in Osogbo, Osun State. The plant sample was verified for authenticity at the Department of Pure and Applied Biology, Ladoke Akintola University of Technology, and assigned the voucher number LHO 681. The leaves were dried under in doors to prevent photodegradation, and then grounded into a fine powder using a laboratory blender. The powdered leaves of *Andrographis paniculata* was kept in a cool and dry place until it was ready for use.

2.2 Diet

All animals were fed rodent chow from weaning. At the beginning of the experimental period, animals were either fed standard chow (29% protein, 11% fat, 58% carbohydrate) or high-fat diet (18% protein, 42% fat, 36% carbohydrate) which was compounded from palm olein and vegetable shortening (hydrogenated), as previously described [5]. Powdered *Andrographis panniculata* was incorporated into standard or high-fat diet at 250 mg/kg of feed), 500 mg/kg of feed) and 1000 mg/Kg of feed.

2.3 Animal Care

Healthy male Wistar rats used in this study were obtained from Empire Breeders, Osogbo, Osun State Nigeria. Rats were housed in wooden cages measuring 20 x 10 x 12 inches in temperature-controlled (22.5°C ±2.5°C) quarters with lights on at 7.00 am. Rats were allowed free access to food and water. All procedures were conducted in accordance with the approved protocols of the Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, abiding by the regulations for animal care and use outlined in European Council Directive (EU2010/63) on scientific procedures involving living animals.

2.4 Experimental Methods

Thirty-six rats were assigned into six groups of six animals each (Table 1). Group A (control) were fed standard rodent chow, while group B (HFD-control) was fed high fat diet. Rats in groups C, D, and E were fed AP incorporated into HFD at 250, 500 and 1000 mg/kg of feed. Rats in group F (Metformin-control) were administered metformin by gavage at 25 mg/kg body weight, while rats in groups A-E were administered distilled water at 10 ml/kg body weight. Treatment was for a period of fifty-six days. On day 57, animals were euthanised after an overnight fast and blood taken for estimation of blood glucose levels using the glucose oxidase method, lipid peroxidation measured as malondialdehyde levels, antioxidant

status was assessed using the Total antioxidant capacity (TAC). Also assayed were lipid profile, liver transaminase [aspartate (AST), and alanine (ALT)] levels, as well as levels of Urea, creatinine, inflammatory cytokines (Tumour necrosis factor-α and interleukin-10), adiponectin, leptin and insulin. The liver, kidney and the pancreas were excised and processed for general histological study using Hematoxylin/ & Eosin and Van Gieson stains.

2.5 Biochemical Tests

2.5.1 Estimation of blood glucose levels

Blood glucose levels were assayed using the glucose oxidase methods using a digital glucometer (Accu-chek Advantage, Roche Diagnoistics Germany).

2.5.2 Lipid Peroxidation

Serum lipid peroxidation levels were assayed using the malondialdehyde content which measures levels of thiobarbituric acid reactive substance within biological samples. Coloured complexes are formed when free malondialdehyde combines with thiobarbituric acid reactive substance. These coloured complexes are then measured spectrophotometrically and expressed as μmol as previously described [5].

2.5.3 Antioxidant Status

Antioxidant status in this study was measured using the Total antioxidant capacity that was determined using the Trolox Equivalent Antioxidant Capacity Assay method. This method examines the ability of antioxidants within a serum to react with oxidised products [25]**.**

2.5.4 Interleukin (IL) -10 and Tumour Necrosis Factor-α

Levels of inflammatory cytokines (Interleukin (IL)-10 and Tumour necrosis factor -α levels) were assessed using the enzyme-linked immunosorbent assay techniques with commercially available kits (Biovision Inc., Milpitas, CA, USA).

2.5.5 Lipid Profile

Total cholesterol, triglycerides, HDL-C and LDL-C in serum were assayed using commercially available kits and following the manufacturer instructions.

2.5.6 Liver function tests and renal function tests

Levels of alanine transaminase (ALT), aspartate transaminase (AST), urea and creatinine in serum were measured using the commercially available kits and following the instructions of the manufacturers of the kits.

2.5.7 Estimation of adiponectin, leptin and insulin levels

Levels of adiponectin, leptin and insulin were measured using commercially available kits.

2.6 Tissue Histology

Rat liver, kidney and pancreas were dissected, sectioned and fixed in neutral-buffered formol saline. The organs were then then processed for paraffin-embedding, cut at 5 μm and stained with haematoxylin and eosin and von Geison's stain for general histological study.

2.7 Photomicrography

Photomicrographs of the liver, kidneys and pancreas were taken using an Olympus binocular light microscope. Images were captured using a Canon PowerShot 2500 Digital camera.

2.8 Statistical Analysis

Data analysis was carried out using Chris Rorden's ANOVA for Windows (version 0.98). One-way analysis of variance (ANOVA) and a post-hoc test (Tukey HSD) used. Results were then expressed as mean ± S.E.M. and $p < 0.05$ was taken as the accepted level of significant difference from control.

3. Results

3.1 Effect of *Andrographis Paniculata* on Body Weight and Feed intake

Figure 1 shows the effects of *Andrographis paniculata* on body weight (upper panel) and feed intake (lower panel). Body weight increased significantly ($p < 0.05$) with HFD, HFD/AP25, HFD/AP50 and HFD/MET compared to control. Compare with HFD, body weight decreased with HFD/AP25, HFD/AP50, HFD/AP100 and HFD/MET. Compared to MET, body weight decreased significantly with AP50 and AP100.

Feed intake increased significantly with HFD, HFD/AP25 and HFD/MET compared to control. Compared with HFD, feed intake is decreased in HFD/AP25, HFD/AP50, HFD/AP100 and HFD/MET. Compared to MET, feed intake decreased significantly with AP50 and AP100.

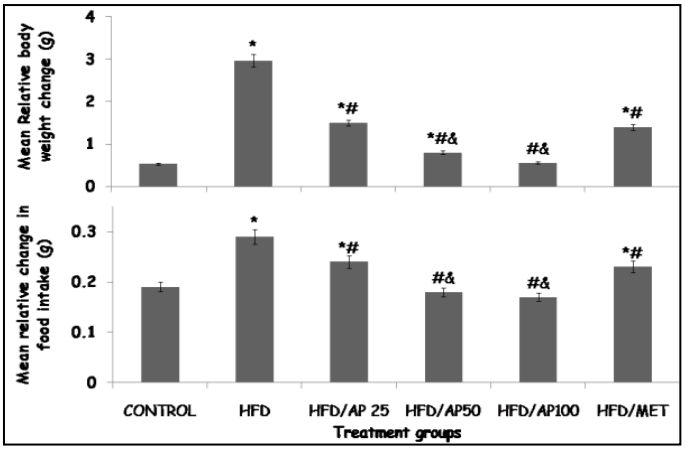

Figure 1: Effect of *Andrographis panniculata* (AP) on change in body weight (upper panel) and feed intake (lower panel). Each bar represents mean ±S.E.M, *p<0.05 vs. control, #p<0.05 significant difference from HFD, &p<0.05 significant difference from MET, number of rats per group =6, HFD: High Fat Diet, MET: Metformin.

3.2 Effect of *Andrographis Panniculata* on blood glucose and Insulin level

Figure 2 illustrates the effects of AP on blood glucose (upper panel) and insulin levels (lower panel). Blood glucose levels increased significantly (p<0.05) with HFD, HFD/AP50, HFD/AP100 and HFD/MET compared to control. Compared to HFD, blood glucose level decreased with HFD/AP25, HFD/AP50, HFD/AP100 and HFD/MET. Compared to MET, blood glucose level decreased with HFD/AP25 and increased with HFD/AP50, HFD/AP100.

Insulin levels increased significantly (p<0.05) with HFD, HFD/AP100 and HFD/MET compared to control. Compared to HFD, insulin levels decreased with HFD/AP25, HFD/AP50, HFD/AP100 and HFD/MET. Compared to MET, insulin levels increased with HFD/AP25, HFD/AP50, HFD/AP100.

3.3 Effect of *Andrographis Panniculata* on adiponectin and leptin levels

Figure 3 shows the effects of AP on adiponectin (upper panel) and leptin (lower panel) levels. Adiponectin levels decreased significantly with HFD, HFD/AP50 and HFD/AP100 while it increased with HFD/MET compared to control. Compared with HFD, adiponectin levels increased with HFD/AP25, HFD/AP50, HFD/AP100 and HFD/MET. Compared to MET, adiponectin levels decreased with HFD/AP25, HFD/AP50, HFD/AP100.

Leptin increased significantly (p< 0.05) with HFD, HFD/AP50, and decreased with HFD/MET compared to control. Compared with HFD, leptin decreased with HFD/AP25, HFD/AP50, HFD/AP100 and HFD/MET. Compared to MET, leptin levels increased with HFD/AP25, HFD/AP50, HFD/AP100.

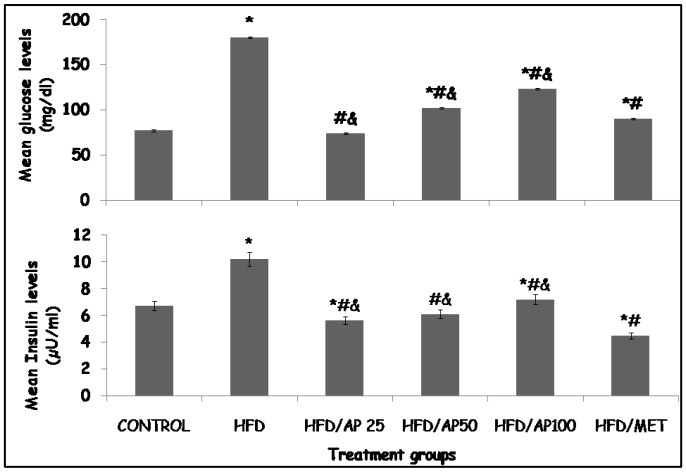

Figure 2: Effect of *Andrographis panniculata* (AP) on blood glucose (upper panel) and insulin (lower panel) levels. Each bar represents mean ±S.E.M, *p<0.05 vs. control, #p<0.05 significant difference from HFD, &p<0.05 significant difference from MET, number of rats per group =6, HFD: High Fat Diet, MET: Metformin.

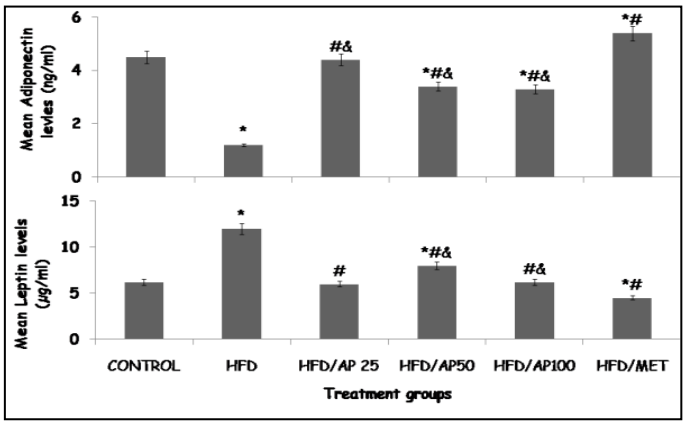

Figure 3: Effect of *Andrographis panniculata* (AP) on adiponectin (upper panel) and leptin (lower panel) levels. Each bar represents mean ±S.E.M, *p<0.05 vs. control, #p<0.05 significant difference from HFD, &p<0.05 significant difference from MET, number of rats per group =6, HFD: High Fat Diet, MET: Metformin.

3.4 Effect of *Andrographis Panniculata* on lipid parameters

Table 1 depicts the effects of AP on lipid levels including total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Levels of TC increased significantly with HFD, HFD/AP25, HFD/AP50, HFD/AP100 and HFD/MET compared to control. However, TC levels reduced in the HFD/AP25, HFD/AP 50, HFD/AP100, and HFD/MET groups compared to the untreated HFD group, with further reductions observed in the HFD/AP 25 and HFD/AP 50 groups compared to the HFD/MET.

Levels of TG were significantly higher in the HFD, HFD/AP 25, HFD/AP 50, HFD/AP 100, and HFD/MET groups compared to control. However, these levels were reduced in the HFD/AP25, HFD/AP50, HFD/AP100, and HFD/MET groups relative to the HFD group, with the HFD/AP25 and HFD/AP50

groups showing the most significant reductions compared to the HFD/MET group.

Levels of LDL were markedly increased in the HFD, HFD/AP25, HFD/AP50, HFD/AP100, and HFD/MET groups compared to control. In contrast, LDL levels were lower in the HFD/AP25, HFD/AP50, HFD/AP100, and HFD/MET groups compared to HFD. Also, the HFD/AP25 and HFD/AP50 groups exhibited lower LDL levels, whereas the HFD/AP 100 group had higher levels than HFD/MET.

High density lipoprotein levels were significantly reduced in the HFD, HFD/AP25, and HFD/MET groups compared to control. However, HDL levels were increased in the HFD/AP25, HFD/AP50, HFD/AP100, and HFD/MET groups relative to HFD. Notably, HDL levels were lower in the HFD/AP 25 group but higher with HFD/AP50 and HFD/AP100 compared to HFD/MET.

Table 1: Effect of Andrographis Panniculata on lipid parameters

Groups	TC (mmol/L)	TG (mmol/L)	LDL (mmol/L)	HDL (mmol/L)
Control	1.37±0.21	0.42±0.10	0.30 ±0.20	1.01±0.01
HFD	6.48±0.42*	2.94±0.17*	3.66±0.35*	0.44±0.05*
HFD/AP25	2.01±0.12$^{*\#\&}$	1.12±0.10$^{*\#}$	1.10±0.10$^{*\#\&}$	0.56±0.06$^{*\#\&}$
HFD/AP50	4.40±0.12$^{*\#}$	2.22±0.10$^{*\#\&}$	1.48±0.14$^{*\#}$	1.26±0.03$^{*\#\&}$
HFD/AP100	7.12±0.22$^{*\#\&}$	3.10±0.12$^{*\#\&}$	3.22±0.10$^{*\#\&}$	1.12±0.10$^{*\#\&}$
HFD/MET	5.10±0.16$^{*\#}$	1.72±0.10$^{*\#}$	1.60±0.10$^{*\#}$	0.88±0.02$^{*\#}$

Data presented as Mean ± S.E.M, *p<0.05 vs. control, #p<0.05 vs. HFD, $^{\&}$p<0.05 HFD/MET. Number of rats per treatment group =5. HFD: High fat diet, AP Andrographis panniculata, MET: Metformin TC: Total cholesterol, TG: Triglycerides, LDL: Low density lipoprotein, HDL: High density lipoprotein number of animals/group-5.

3.5 Effect of *Andrographis Paniculata* on Liver Transaminase, Urea and Creatinine Levels

Table 2 summarises the effects of AP on liver transaminases [aspartate transaminase (AST), alanine transaminase (ALT)] and markers of kidney function including urea, and creatinine levels. Levels of AST were significantly elevated in the HFD, HFD/AP25, HFD/AP50, HFD/AP100, and HFD/MET groups compared to control. However, compared to the untreated HFD group, AST levels were reduced in the HFD/AP25, HFD/AP50, HFD/AP100, and HFD/MET groups. Notably, AST was lower in the HFD/AP25 group but higher in the HFD/AP100 group relative to the HFD/MET group.

Levels of ALT were significantly increased in the HFD, HFD/AP25, HFD/AP50, HFD/AP100, and HFD/MET groups compared to control. Compared to HFD, ALT levels were reduced with HFD/AP25, HFD/AP50, and HFD/MET. However, ALT levels decreased with HFD/AP25 but increased with HFD/AP100 relative to the HFD/MET group.

Urea levels were significantly higher with HFD, HFD/AP50, HFD/AP100, and HFD/MET compared to control. Compared to HFD, urea levels were reduced with HFD/AP25, HFD/AP50, HFD/AP100, and HFD/MET. Also, HFD/AP25 exhibited lower urea levels, while the HFD/AP50 and HFD/AP100 showed higher levels relative to HFD/MET.

Creatinine levels were significantly elevated with HFD, HFD/AP 25, HFD/AP 50, HFD/AP 100, and HFD/MET groups compared to control. However, creatinine levels were reduced with HFD/AP25, HFD/AP50, HFD/AP100, and HFD/MET compared to HFD. Relative to the HFD/MET group, creatinine levels were higher with HFD/AP25, HFD/AP50, and HFD/AP100.

Table 2: Effect of *Andrographis panniculata* leaf on levels of transaminases, urea and creatinine

Groups	AST (mmol/L)	ALT (mmol/L)	Urea (mmol/L)	Creatinine (mmol/L)
Control	82.10±1.50	23.10±0.30	2.55±0.10	60.22±2.52
HFD	198.10±2.10*	55.30±1.24*	5.21±0.18 *	111.54±1.10$^{*\#}$
HFD/AP25	117.10±1.10$^{*\#\&}$	36.20±0.20$^{*\#\&}$	2.19±0.19$^{*\#\&}$	79.23±1.14$^{*\#\&}$
HFD/AP50	120.43±1.11$^{*\#\&}$	47.44±1.19$^{*\#\&}$	2.67±0.20$^{*\#\&}$	81.19±1.14$^{*\#\&}$
HFD/AP100	179.17±1.33$^{*\#\&}$	54.10±1.20$^{*\&}$	3.19±0.14$^{*\#\&}$	83.60±1.30$^{*\#\&}$
HFD/MET	123.10±1.10$^{*\#}$	46.20±0.10$^{*\#}$	2.40±0.20$^{*\#}$	60.22±1.10$^{*\#\&}$

Data presented as Mean ± S.E.M, *p<0.05 vs. control, #p<0.05 vs. HFD, $^{\&}$p<0.05 HFD/MET. Number of rats per treatment group =5. HFD: High fat diet, AP Andrographis panniculata, MET: Metformin TC: Total cholesterol, TG: Triglycerides, LDL: Low density lipoprotein, HDL: High density lipoprotein number of animals/group-5.

3.6 Effect of Andrographis panniculata on oxidative stress and inflammatory markers

Table 3 shows the effects of AP on malondialdehyde (MDA), total antioxidant capacity (TAC), tumor necrosis factor-α (TNF-α), and interleukin-10 (IL-10). Malondialdehyde level, an indicator of lipid peroxidation was significantly elevated with HFD, HFD/AP25, HFD/AP50, HFD/AP100, and HFD/MET compared to control. However, relative to HFD, MDA levels reduced with HFD/AP25, HFD/AP50, HFD/AP100 and HFD/MET. Also, MDA levels decreased with HFD/AP25 but increased with HFD/AP100 compared to HFD/MET. Total antioxidant capacity levels significantly decreased with HFD, HFD/AP25, HFD/AP50, HFD/AP100, and HFD/MET compared to control. When compared to HFD, TAC levels were lower with HFD/AP25, HFD/AP50, and HFD/MET. However, TAC levels were higher with HFD/AP25 and HFD/AP100 and increased further with HFD/AP50 compared to HFD/MET.

Tumour necrosis factor-α levels were significantly elevated with HFD, HFD/AP50, HFD/AP100, and HFD/MET compared to control. Compared to HFD, TNF-α levels decreased with HFD/AP25, HFD/AP50, HFD/AP100, and HFD/MET.

Nonetheless, TNF-α levels were higher with HFD/AP50 and HFD/AP100 compared to HFD/MET. Interleukin-10 levels were significantly lower with HFD, HFD/AP50, HFD/AP100, and HFD/MET compared to control. Compared to HFD, IL-10 levels were elevated with HFD/AP25, HFD/AP50, HFD/AP100, and HFD/MET. IL-10 levels increased with HFD/AP25 but decreased with HFD/AP100 compared to HFD/MET.

Table 3: Effect of Andrographis Panniculata on oxidative stress markers and inflammatory cytokines

Groups	MDA (µm)	TAC (mM TE)	TNF-α ng/L	IL-10 pg/ml
Control	6.20±1.06	15.20±1.02	88.23±1.10	30.22±0.14
HFD	24.01±1.18*	5.22±0.45*	122.11±2.14*	16.22±0.40*
HFD/AP 25	14.30±1.15$^{*\#\&}$	11.20±1.20$^{*\#\&}$	84.25±0.34$^{*\#}$	27.44±0.56$^{*\#\&}$
HFD/AP50	18.25±1.1o$^{*\#}$	7.30±0.20$^{*\#}$	90.22±1.18$^{*\#\&}$	23.55±0.21$^{*\#}$
HFD/AP100	20.20±1.20$^{*\#}$	9.76±0.20$^{*\#}$	97.23±1.44$^{*\#\&}$	19.34±0.24$^{*\#\&}$
HFD/MET	18.10±1.50$^{*\#}$	8.50±0.10$^{*\#}$	83.20±0.22$^{*\#}$	22.03±0.17$^{*\#}$

Data presented as Mean ± S.E.M, *p<0.05 vs. control, #p<0.05 vs. HFD, $^{\&}$p<0.05 HFD/MET. Number of rats per treatment group =5. HFD: High fat diet, AP Andrographis panniculata, MET: Metformin TC: Total cholesterol, TG: Triglycerides, LDL: Low density lipoprotein, HDL: High density lipoprotein number of animals/group-5.

3.7 Effect of *Andrographis panniculata* on Liver histomorphology

Figures 4(A-F) and 5(A-F) are representative photomicrographs of rat liver tissue sections stained with Haematoxylin & Eosin and von Gieson's stain respectively. Photomicrographs of rats in the control group (4A) displayed healthy liver tissue with normal hepatocyte arrangement and clear sinusoidal spaces. In contrast, the HFD (4B) group showed significant liver injury with disrupted liver architecture, loss of sinusoidal spaces, and shrunken, pale-staining hepatocytes. Liver sections of rats in HFD/AP25 (4C), HFD/AP50 (4D), and HFD/AP100 (4E) revealed varying degrees of preservation of liver architecture. Also, in the groups administered HFD/MET (4F) liver injury was observed. Von Gieson's staining revealed normal appearance of liver architecture, with minimal collagen staining in the control group(5A). Photomicrographs of HFD (5B) group revealed increased collagen staining, indicating liver fibrosis. In HFD/AP groups (Figures 5C, 5D, and 5E) there was graded reduction in collagen deposition, suggesting reduced liver fibrosis. In the and HFD/MET (5F), group increased collagen staining was observed.

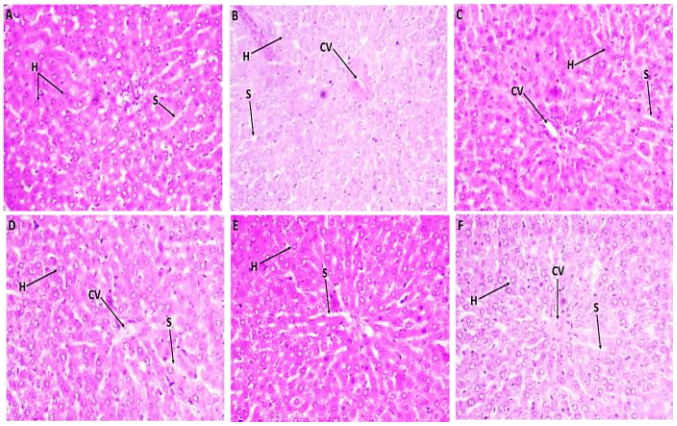

Figure 1: Photomicrograph of the Haematoxylin and Eosin-stained sections of the rat liver showing hepatocytes (H), central vein (CV), and sinusoids (S). Control-A, HFD=B, HFD/AP25=C, HFD/AP50=D, HFD/AP100 =E and HFD/MET= F, Magnification X160

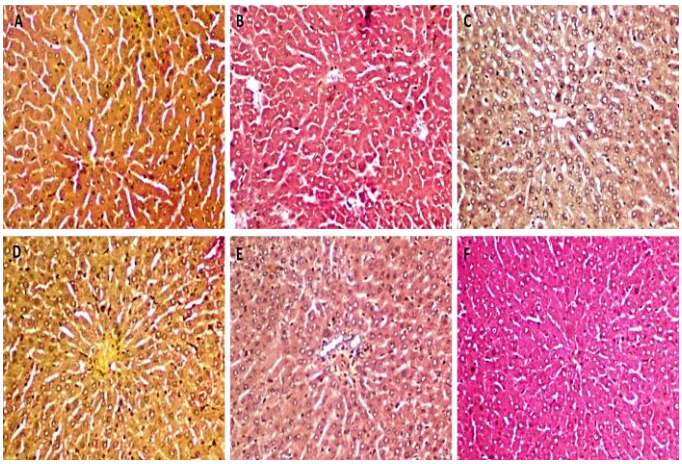

Figure 2: Photomicrograph of the von Gieson's-stained sections of the rat liver showing varying degrees of collagen staining. Control-A, HFD=B, HFD/AP25=C, HFD/AP50=D, HFD/AP100 =E and HFD/MET= F, Magnification X160.

3.8 Effect of *Andrographis panniculata* on kidney histomorphology

Figures 6(A-F) and 7(A-F) are representative photomicrographs of rat kidney tissue sections stained with Haematoxylin & Eosin and von Gieson's stain respectively. Photomicrographs of rats in the control group (5A) showed normal kidney architecture with well-defined cortex, medulla, healthy glomeruli and tubules. In contrast, HFD group (6B) showed significant changes including swollen glomeruli, loss of Bowman's space, and contracted renal tubules with pale-staining nuclei. Compared to HFD group, the HFD/AP 25(6C), HFD/AP50 (6D), HFD/AP100 (6E) and HFD/MET (6F) revealed varying degrees of amelioration of kidney injury. Von Gieson's staining revealed normal kidney architecture with moderate collagen fibre staining in the control (7A) group. In the HFD group (7B), there was increased collagen deposition, wider renal tubules, and degenerating glomeruli, while in the HFD/AP groups (7C, 7D, and 7E) or HFD/MET (7F) reduced collagen deposition and

partial recovery of kidney structure, with moderate distortions of tubules and glomeruli was observed.

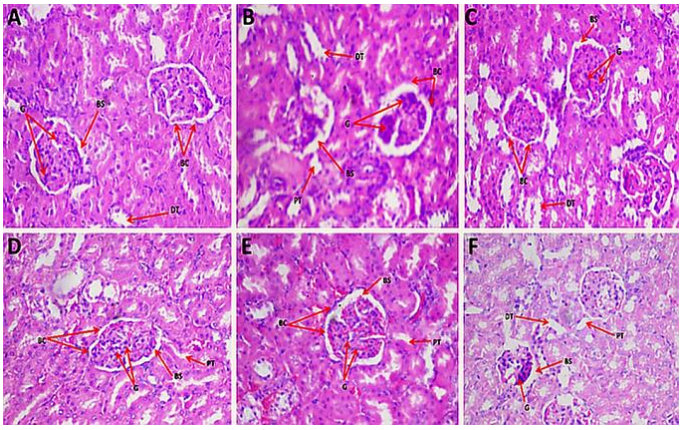

Figure 6: Photomicrograph of the Haematoxylin and Eosin-stained sections of the rat kidney showing the Glomerulus (G), Bowman's capsule (BC), Bowman's space (BS), Proximal tubule (PT), and Distal tubule (DT). Control-A, HFD=B, HFD/AP25=C, HFD/AP50=D, HFD/AP100 =E and HFD/MET= F, Magnification X160.

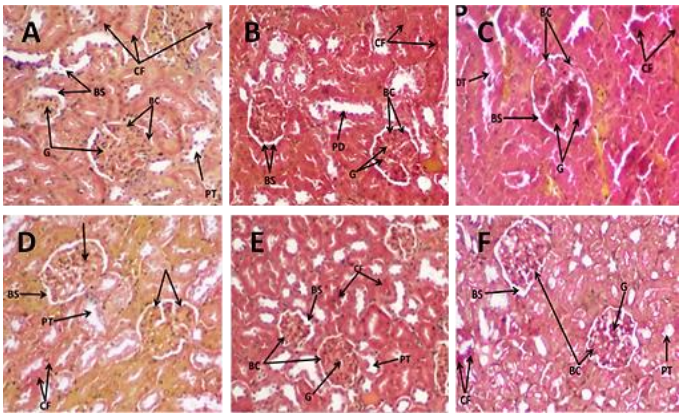

Figure 7: Photomicrograph of von Geison's stained sections of the rat kidney showing Collagen fibres (CF), Glomerulus (G), Bowman's capsule (BC), Bowman's space (BS), Proximal tubule (PT), and Distal tubule (DT), Control-A, HFD=B, HFD/AP25=C, HFD/AP50=D, HFD/AP100 =E and HFD/MET= F, Magnification X160.

3.9 Effect of *Andrographis panniculata* on pancreas histomorphology

Figures 8(A-F) and 9(A-F) are representative photomicrographs of rat pancreatic tissue sections stained with Haematoxylin & Eosin and von Gieson's stains respectively. Photomicrographs of rats in the control group (8A) revealed normal pancreatic islet cells and glandular tissue with deeply stained nuclei and well-defined blood vessels. In the HFD) group (8B), the pancreas appeared swollen with increased spaces between glands, engorged blood vessels, and smaller islets with lightly- stained nuclei, while in the HFD/AP groups (8C, 8D, and 8E) or HFD/MET (8F) showed varying levels of improvement with less swelling and fewer engorged vessels, though there was still some dilation of pancreatic ducts in the HFD/MET group.

Von Gieson's staining revealed normal pancreas architecture with moderate collagen fibre staining in the control (9A). The HFD group (9B) showed increased collagen deposition, suggesting fibrosis, while in the HFD/AP groups (9C, 9D, and 9E) or HFD/MET (9F) demonstrated a reduction in collagen staining, indicating a reversal of the fibrotic changes seen in the HFD group.

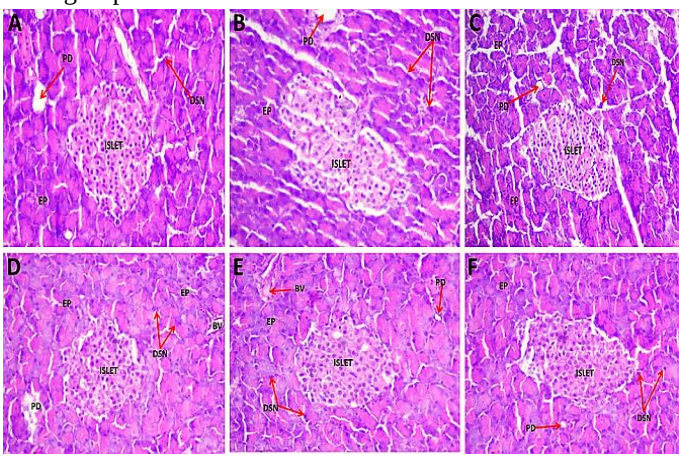

Figure 8: Photomicrograph of the Haematoxylin and Eosin-stained sections of the rat pancreas showing the Islet, deeply stained nuclei (DSN), Exocrine pancreas (EP), Blood vessels (BV) and the pancreatic duct (PD), Control-A, HFD=B, HFD/AP25=C, HFD/AP50=D, HFD/AP100 =E and HFD/MET=F Magnification X160.

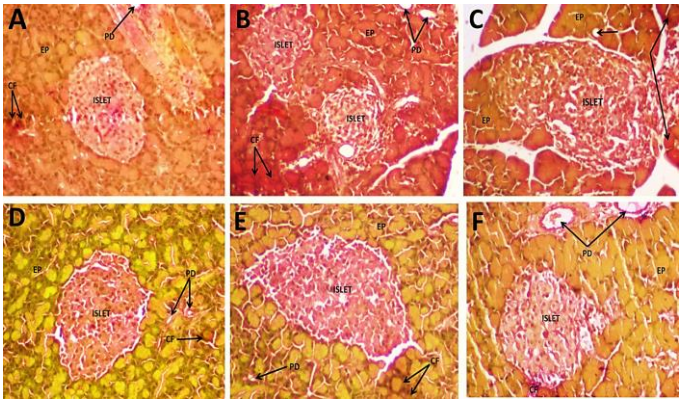

Figure 9: Photomicrograph of von Geison's stained sections of the rat pancreas showing collagen Fibre (CF), Islet, deeply stained nuclei (DSN), Exocrine pancreas (EP), and the pancreatic duct, Control-A, HFD=B, HFD/AP25=C, HFD/AP50=D, HFD/AP100 =E and HFD/MET= F (PD).X160

4. Discussion

Andrographis paniculata, a well-known plant from the *Acanthaceae* family, is renowned for its therapeutic properties. The primary phytochemicals in this plant include alkaloids, flavonoids, tannins, phenols, saponins, and glycosides [26]. Research has demonstrated the antimicrobial, antioxidant, and anticancer, antihyperglycaemic properties of extracts of AP leaves [27, 28]. While a studies have examined its antidiabetic properties of extracts of AP leaves in chemical models of diabetes mellitus [29, 30], there is however, a dearth of scientific evidence on its nutraceutical effect in diet induced dysmetabolism. This study examined the effect of powdered AP leaves on body weight, oxidative stress parameters, inflammatory cytokines and histomorphological changes in the liver, kidneys and pancreas of rats fed high-fat diet (HFD).

The consumption of foods high in fats has been associated increased feed intake, with this alteration in feed intake patterns contributing significantly to weight gain and

obesity. The increase in fat intake has also been linked to the disruption of homeostatic systems, also resulting in the dysregulation of satiety factors like satiety and energy expenditure. In this study, the consumption of HFD was associated with increased feed intake, increased body weight dysregulation of satiety factors (adiponectin and leptin levels), reduced glucose tolerance, increased total cholesterol, triglyceride levels and low-density lipoprotein levels. Its deleterious effects on organs were also evident by the derangement of liver transaminases, urea and creatinine levels. Also observed were an increase in oxidative stress and proinflammatory cytokines. These results corroborate previous research [4-7, 14, 31, 32] and validate the use of HFD as a rodent model of dysmetabolism. The ability of HFD to increase feed intake been attributed to increased palatability, this increased palatability results in the overconsumption of this feed [31, 33]. Studies have also shown that palatable foods also have the ability to activate the brain reward circuits driving the consumption of food above homeostatic requirements [34, 35]. The addition of Andrographis panniculata also known as the king of bitters to feed reduced feed intake, body weight reversed alteration in blood glucose, insulin levels, adiponectin and leptin. The reduction in palatability of the feed when AP which is bitter was supplemented with the HFD diet.

Also, in this study incorporation of AP into HFD was associated with the reversal of HFD induced hyperglycaemia, dyslipidaemia and insulin resistance. These findings align with previous research that have suggested that AP can mitigate diabetes mellitus [19,20] and insulin resistance through the inhibition of α-glycosidase and α-amylase enzymes, this effect could be attributed to its high flavonoid content [36]. Flavonoids, particularly andrographolides, have been shown to reverse insulin resistance through the downregulation of the NF-KB signaling pathway and suppression of the phosphorylation of IκBα and NF-κB p65 subunits in the presence of high glucose [37].

Dyslipidaemia which has been reported to significantly increased the risk of cardiovascular disease, and insulin resistance, is characterised by elevated triglycerides and LDL cholesterol and decreased HDL cholesterol which were observed in this study. This study found that AP administration for eight weeks significantly improved lipid profiles by reducing TG, TC, and LDL levels while increasing serum HDL levels. However, at the highest concentration a reversal of the beneficial effects was observed, suggesting that high doses of AP may not be effective for managing dyslipidaemia. Previous studies have demonstrated that AP extracts can reduce blood lipid and sugar levels in rats with alloxan and streptozotocin-induced diabetes mellitus [19, 20, 38].

The connection between oxidative stress and its impact on insulin resistance and cardiovascular health in obesity is well-documented [39]. Diets high in fat significantly increase oxidative stress [40]. In this study, AP notably lowered serum MDA levels and increased total antioxidant capacity, demonstrating its effective hydroxyl free-radical scavenging capability, which is attributable to the polyphenolic compounds present in the leaf powder [41, 42]. These findings support reports of AP's antioxidant properties, which include neutralising free radicals derived from oxygen and nitrogen, chelating metal ions, inhibiting oxidase activity, and enhancing the activity of antioxidant enzymes [43, 44]. Andrographolide, a key antioxidant further bolsters antioxidant defences by inhibiting enzymes that produce reactive oxygen species [43, 45, 46].

Leptin, a peptide hormone, plays a critical role in regulating appetite, body weight, immune responses, blood vessel formation, and fat metabolism [47]. In this study, leptin levels were significantly lower in rats treated with AP compared to those on HFD. The observed decrease in leptin was associated with improved insulin sensitivity, likely due to the suppression of factors contributing to leptin resistance. *Andrographis paniculata* has been shown to lower serum leptin levels, which may assist in weight management and reduce fat accumulation [48, 49]. Adiponectin also plays a significant role in enhancing insulin sensitivity, contrasting with leptin, where elevated levels can lead to metabolic disorders [50]. In HFD fed rats, a significant decrease in adiponectin level was observed. Decrease in adiponectin level is linked to metabolic disorder [51]. *Andrographis panniculata* incorporation into diet was associated with reversal of HFD-induced alteration in adiponectin levels, thereby improving it insulin sensitivity and anti-inflammatory response [52].

Interleutkin-10 is known for its anti-inflammatory properties and it plays a key role in regulating immune responses and protecting tissues [53]. Reduced IL-10 levels can indicate systemic inflammation associated with obesity. Interleutkin-10 also enhances the uptake of HDL and LDL by macrophages through actin filament rearrangement [54]. In this study, AP significantly increased IL-10 levels, while TNF-α levels, which are crucial in inflammation and immune cell recruitment, were notably reduced with AP treatment. This anti-inflammatory effect was supported by improved histopathological findings in treated groups.

Alanine transaminases and Aspartate transaminases are commonly used indicators of liver injury and hepatocyte necrosis [55]. Elevated ALT levels in rats on HFD or those receiving high doses of AP (1000 mg/kg) could suggest hepatocyte necrosis, which increases cell membrane permeability and leads to the release of aminotransferases into

the bloodstream. Conversely, lower ALT levels in rats receiving the two lower concentrations of AP could be due to the AP ability to reducing liver injury. Aspartate transaminases levels were significantly lower in both AP treatment groups compared to the HFD group, aligning with findings from Ogunlana et al [29] on AP's effects in diabetic rats.

Creatinine and urea levels, key indicators of kidney function, were also measured [56]. Elevated levels of these markers can suggest kidney injury, but can also arise from trauma or muscle injury [57]. The HFD group and the high-dose AP group (1000 mg/kg) showed elevated creatinine and urea levels, indicating possible kidney injury compared to the control. *Andrographis panniculata* treatments at 250 mg/kg and 500 mg/kg significantly reduced these levels, suggesting protective effects on kidney function. Previous studies have reported that andrographolide, a compound in AP, positively affects kidney function by lowering urea, BUN, and creatinine levels in diabetic rats [58].

In this study, Haematoxylin and Eosin staining revealed liver, kidney and pancreas injury in HFD fed rats, evidenced by wider bowman space in kidney, cell vacuolation in liver and swelling at the islet of Langerhans in the pancreas. *Andrographis panniculata* treated groups showed protection against HFD injury in cells morphology. These observations correlate with biochemical tests and liver function results. Von Gieson staining, which highlights collagen fibres and soft tissues, showed tissue injury in the liver, kidney, and pancreas of the HFD group; this is consistent with the biochemical findings. AP treatment reduced these tissue damages, likely due to its antioxidative properties.

Conclusion

This study underscores the significant benefits of Andrographis panniculata leaf powder in addressing diet induced dysmetabolism. The results also demonstrate the nutraceutical potential of powdered Andrographis panniculata leaves in rats. However, further research is needed to ascertain its benefits in humans.

Funding.
None received

Declaration of Ethics approval

Ethical approval for the research was granted by the Ethical Research Committee of the Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology.

Competing interests

None Declared

Received 11 February, 2025, Revised 9th March, 2025, Accepted 12th April, 2025, **Published online: 10/05/25**

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Cite as: Kolawole OE, Onaolapo OJ, Onaolapo AY Powdered *Andrographis Paniculata* Leaves Ameliorates High-fat Diet-induced Dysmetabolism in Rats. Acta Bioscientia 2025:1(3);122-133. https://doi.org/10.71181/actabioscientia12270