# Aqueous Leaf Extract of *Petiveria alliaceae* Attenuates Hyperglycaemia and Obesity in High-Fructose Induced Metabolic Syndrome in Rats

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**Abstract**

The growing preference for consumption of sugar-rich and fatty products has led to a surge in metabolic disorders which often result in mortality. The present study aims to assess the therapeutic efficacy of aqueous leaf extract of *Petiveria alliaceae* in male Wistar rats exhibiting high fructose-induced metabolic syndrome manifested as hyperglycaemia and obesity. Various doses of aqueous leaf extract of *Petiveria alliaceae* extract and metformin (control drug) were administered for 3 weeks, starting from week 7 of high fructose diet treatment. Several biochemical parameters were assessed including blood glucose, abdominal circumference, insulin, insulin resistance, body mass index, HMG CoA reductase, tumour necrosis factor-α, adiponectin, leptin, interleukin-6 and interleukin-8. The most effective dose of the aqueous leaf extract was found to be 400 mg/kg BW as it significantly ($p < 0.05$) reversed the alterations induced by the high fructose diet (HFD) by restoring normalcy in the blood glucose levels, body weight, body mass index, insulin levels, insulin resistance, and other anthropometric parameters of experimental rats. Findings from this study suggest that *Petiveria alliaceae* leaf extract contains phytochemicals responsible for its therapeutic potential in managing hyperglycaemia and obesity in metabolic syndrome. Therefore, the plant could serve as a basis for the development of drugs aimed at managing these conditions.

**Keywords:** *Petiveria alliaceae*, high fructose, hyperglycaemia, obesity, metabolic syndrome

## 1. Introduction

Metabolic Syndrome (MS) is a combination of medical disorders that increases the risk of developing cardiovascular disease and diabetes [1]. It is also known as metabolic syndrome X, cardiometabolic syndrome, syndrome X, insulin resistance syndrome, Reaven's syndrome (named for Gerald Reaven), and coronary artery disease, hypertension, atherosclerosis, obesity and stroke (CHAOS in Australia) [2]. It is also described as a cluster of some physiological and metabolic abnormalities characterized by overall or central obesity, impaired glucose tolerance, dyslipidemia and hypertension [3]. MS is a clinical condition composed of anthropometric, physiologic and biochemical abnormalities predisposing affected individuals to type 2 diabetes and cardiovascular disease (CVD). Rather than total adiposity, the core clinical component of the syndrome is visceral [4] and/or ectopic fat [5] whereas the principal metabolic abnormality is insulin resistance [6].

The inclusion of MS by all expert groups underscores its importance with the International Diabetes Federation (IDF) dubbing it as "central obesity syndrome" [7]. Identifying individuals at risk is crucial for pre-empting cardiovascular disease and type 2 diabetes [8]. MS can therefore be defined as a cluster of metabolic disorders including hyperglycaemia, insulin resistance, obesity, hypertension and oxidative stress [9] that increases the risk of diabetes mellitus, coronary heart diseases (CHD) and cardiovascular diseases (CVD). An individual considered to have MS must present a condition of hyperglycaemia, insulin resistance and obesity or hypertension with oxidative stress [10]. This disorder has been dominant in western countries, but it is becoming prevalent in African countries owing to sedentary lifestyle, westernization of diets [11], heavy alcohol consumption, age and genetic predisposition [12].

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Sugars are naturally occurring sweeteners, the most common in nutrition being sucrose, glucose and fructose. Notably, fructose has emerged as a significant dietary component implicated in the pathogenesis of MS [13]. Once scarce in historical diets, fructose now features prominently in modern western diets due to its sweetness advantage over glucose or sucrose [14]. Diet plays a pivotal role in the development of MS as certain dietary choices can either elevate or mitigate the risk of developing specific diseases by influencing metabolism and other factors like hormones and lipids [15], which serve as markers for disease risk. Hyperglycaemia, a key component of MS, refers to elevated blood glucose levels, frequently observed in diabetes mellitus [16]. Insulin resistance often underpins hyperglycaemia, occurring when the body either lacks sufficient insulin or cannot effectively use insulin to convert glucose into energy. Obesity, another major component that characterizes MS is the accumulation of excess body fat, which manifests as increased weight or waist circumference. It is commonly associated with insulin resistance. A functional link between hyperglycaemia and obesity is proposed, both being associated with insulin resistance.

While current management strategies for MS target its individual components [17], their efficacy is often limited by associated side effects, fuelling growing interest in medicinal plants. In many countries, medicinal plants are gaining prominence as primary healthcare therapies and are increasingly recognized as valuable sources of bioactive compounds for drug discovery and development of innovative treatments for various human diseases [18]. *Petiveria alliaceae*, commonly referred to as 'garlic guinea weed,' is a multifaceted flowering plant from the *Phytolaccaceae* family, renowned for its medicinal properties [19]. This perennial shrub, characterized by its robust, straight stem, is known by various names across different cultures in Nigeria including *Awogba* in Yoruba, *Anwushi* in Igbo, *Owewe* in Edo, and *Oze* in Ijaw. In traditional folk medicine, the plant's roots, leaves, and stems are employed in diverse preparations, including decoctions, powders, and infusions to address a broad spectrum of disorders [20].

Recent research has spotlighted *Petiveria alliaceae* leaf for its therapeutic potential in managing MS-related conditions, notably hyperglycaemia and obesity. The plant's bioactive compounds exhibit promising properties in regulating blood glucose levels, enhancing insulin sensitivity, and mitigating obesity, positioning it as a compelling candidate for the development of innovative therapeutic interventions and alternative healthcare approaches [20]. Biochemically, *Petiveria alliaceae* is rich in secondary metabolites, encompassing alkaloids, flavonoids, terpenes, and polyphenols. These bioactive compounds not only contribute to the plant's medicinal attributes but also play pivotal roles in its defense mechanisms. The intricate interactions between these compounds and cellular pathways offer valuable insights into their potential mechanisms of action and therapeutic efficacy [21]. In addition, the combined pharmacological and biochemical significance of *Petiveria alliaceae* accentuates its importance as a valuable natural resource for drug discovery, alternative medicine, and scientific exploration aimed at elucidating and addressing MS and associated health conditions.

Existing therapies to challenge various components of MS are restricted by several factors. Firstly, the existence of only a handful of medications that have been shown to have a convincing effect on long-term outcomes makes the choice of therapy challenging. Secondly, the chronic nature of the components of MS warrants prolonged and often indefinite use of various medications such as statins, leading to an increased burden of drug-related adverse effects and patient non-compliance. In this context, the development of nutraceuticals that are readily available and with minimal side effects may represent an area of promise in the development of novel therapies. Thus, this study is aimed at investigating the potential of *Petiveria alliaceae* leaf extract in the management of high fructose-induced MS manifested as hyperglycaemia and obesity in Wistar rats.

## 2. Materials and Methods

### *2.1 Chemicals*

Assay kits for insulin, adiponectin, leptin, tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8), HMG-CoA reductase and other diagnostic kits were products of Randox Chemical Company. All other chemicals were products of Sigma-Aldrich Co. Mo. USA. Metformin was a product of Santa Cruz Biotechnology, Inc, USA.

*2.2 Animals*

Male Wistar rats (n=125), weighing 116 ± 7.90 g were obtained from the Animal Holding Unit, Department of Biochemistry, University of Ilorin, Ilorin, Nigeria. They were kept in well-ventilated room with free access to feed and water under optimum conditions (temperature: 23±1℃, Photoperiod: 12h natural light and 12h dark, relative humidity; 45-50%). The rats were used according to all the Guidelines of National Research Council Guide for the Care and Use of Laboratory Animals [22].

*2.3 Collection of Petiveria alliaceae and preparation of aqueous leaf extract*

Fresh leaves of *Petiveria alliaceae* were obtained from Ile Oluji in Ondo State, Nigeria. The plant was identified and authenticated at the Herbarium Unit of the Department of Plant Biology, University of Ilorin (Voucher No: UILH/001/1224). A specimen sample of the plant was prepared and deposited at the Herbarium. The leaves were washed with distilled water to remove dirt and dust before air-drying to a constant weight. The dried leaves were crushed, and 500 g of the crushed sample was extracted in 1.5 mL of distilled water for 48 hours. The mixture was filtered using Whatman No. 1 filter paper and concentrated using steam from water bath. The concentrate recovered from the aqueous leaf extract of *P. alliaceae* (76.92 g) was stored in an air-tight container and kept inside a refrigerator until required for use.

*2.4 Induction of MS and animal grouping*

MS was induced in experimental rats by feeding them for 6 weeks with a high fructose diet as formulated in Table 1 [23]. A total of 45 Wistar rats were randomized into 7 groups and maintained as follows.

**Group 1** (Control): 10 rats fed with control diets and distilled water *ad libitum* for 9 weeks
**Group 2:** 10 rats fed with high fructose diet and distilled water *ad libitum* for 9 weeks
**Group 3 (Control):** 5 rats fed with control diets and 400 mg/kg body weight of extract at 24 h interval *ad libitum* for 9 weeks
**Group 4:** 5 rats fed with high fructose diet *ad libitum* for 9 weeks and daily administered 100 mg/kg body weight of the extract 24 h interval orally starting from week 7.
**Group 5:** 5 rats fed with high fructose diet *ad libitum* for 9 weeks and daily administered 200 mg/kg body weight of the extract orally 24 h interval starting from week 7.
**Group 6:** 5 rats fed with high fructose diet *ad libitum* for 9 weeks and daily administered 400 mg/kg body weight of the extract 24 h interval orally starting from week 7.
**Group 7:** 5 rats fed with high fructose diet *ad libitum* for 9 weeks and daily administered 100 mg/kg body weight of metformin orally at 24 h interval starting from week 7.

*2.5 Determination of body weight, body mass index and abdominal circumference*

Rats were weighed weekly during the 9-week experimental period and weight gain was expressed as a percentage of initial body weight to eliminate variability between animals. The weight and length of rats was used in calculating the body mass index (BMI) [24] using the following expression.

$$Body\ mass\ index\ (BMI) = \frac{Weight\ of\ rats\ (g)}{Length\ of\ rats^2\ (cm^2)}$$

The Abdominal circumference was measured using the measuring tape around the anterior abdomen in centimetre [25].

**Table 1: Feed composition and formulation**

| Feed components | Control diet (g/kg) | High fructose diet (g/kg) |
|---|---|---|
| Corn starch | 506 | - |
| Fructose | - | 600 |
| *Casilan 90 | 250 | 250 |
| +Soybean oil | 40 | 40 |
| Sucrose | 100 | 6 |
| Corn shaft | 40 | 40 |
| DL-Methionine | 4 | 4 |
| Lysine | 10 | 10 |
| **Vitamin mix | 10 | 10 |
| **Mineral mix | 40 | 40 |
| **Total** | **1000** | **1000** |

*Casilan 90 (g/100g), energy (1572 kg/100g), protein (90 g), carbohydrate (0.3 g), fat (1.0 g), fibre (trace), sodium (0.03 mg), calcium (1400 mg).
**Vitamin mix (per kg of diet): Thiamine hydrochloride (6 mg), pyridoxine hydrochloride (7 mg), nicotine acid (30 mg), calcium pantothenate (16 mg), folic acid (2 mg), biotin (0.2 mg), cyanocobalamin (0.01 mg), retinol palmitate (4,000 IU), cholecalciferol (100 IU), a - tocopherol acetate (50 IU), menadine (0.05 mg), choline chloride (2g).
***Mineral mix (g/kg): $CoCl_2.6H_2O$ (0.001), $CuSO_4.5H_2O$ (0.079), $MnSO_4.7H_2$ (0.178), KI (0.033), NaCl (3.573), $ZnCO_3$ (1.60), $CaSO_4$ (11.61), $MgSO_4.7H_2O$ (2.292), $K_2HPO_4$ (10.559). $FeSO_4.7H_2O$ (1.075).
+Soybean oil: Polyunsaturated Fatty acids (58%), monounsaturated fatty acids (29%) saturated fatty acids (13%)

*2.6 Determination of blood glucose level, insulin and insulin resistance*

Blood glucose level was determined using fine test strips and blood glucometer, insulin concentration was estimated using enzyme linked immunoassay assay kit (Sigma) and insulin resistance was estimated using HOMA-IR (Homeostasis model assessment for insulin resistance) based on an index from the product of fasting plasma glucose concentrations and plasma insulin. These were monitored weekly throughout the 9-week experimental period using blood sample carefully collected from the tail vein of the animals.

$$\text{Insulin resistance} = \frac{\text{Fasting plasma glucose concentrations (mmol/L) x plasma insulin (µU/mL)}}{22.5}$$

Where 1 µU/mL = 6.945 pmol/L

*2.7 Animal sacrifice, collection of blood and preparation of serum*

Five (5) rats were sacrificed from Groups 1 and 2 after week six (6) to confirm induction of MS while animals in other groups were sacrificed after the 9-week experimental period. Under ether anaesthesia, the neck area of the animals was quickly cleared of fur and skin to expose the jugular veins. The veins were sharply cut with a sterile scalpel blade, and blood was collected into EDTA heparinized bottles and allowed to clot for 30 minutes. This was then centrifuged at 33.5 × *g* for 15 min using a laboratory centrifuge [26]. Serum was aspirated using Pasteur pipettes into clean, dry, sample bottles for the enzyme assay.

*2.8 Statistical analysis*

The data generated were subjected to one-way analysis of variance (ANOVA) followed by Tukey-Kramer test for differences between means using StatPlus, 2011 (AnalystSoft Inc., Alexandria, VA, USA). Results were expressed as mean ± Standard Error of Mean (SEM) of five determinations and are considered statistically significant at $p < 0.05$.

## 3. Results

*3.1 Biomarkers of obesity*

The body weight, BMI and abdominal circumference of rats fed with high-fructose diet alone increased significantly all through the 9-weeks experimental period (6 weeks of induction with MS and 3 weeks administration of aqueous leaf extract of *Petiveria alliaceae*). Administration of aqueous leaf extract of *Petiveria alliaceae* from week 7 of the experimental period significantly ($p < 0.05$) reduced all parameters of rats in a dose dependent manner and significantly ($p < 0.05$) compared with the reference drug, metformin (Figures 1,2 and 3). The highest dose of extract evaluated (400 mg/kg body weight) reversed this increase in body weight by 60% and compared significantly with the reference drug, metformin. Following the oral administration of the aqueous leaf extract from week 7, the highest dose of extract evaluated (400 mg/kg body weight) also reversed the observed increase in the BMI and the abdominal circumference of the rats.

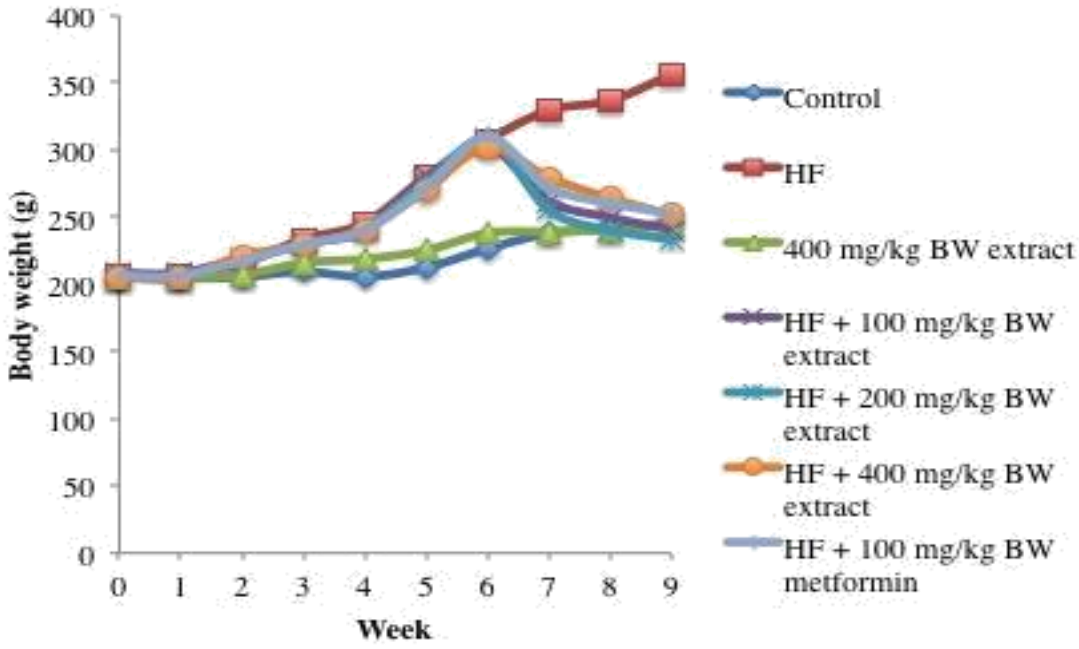


**Figure 1: Body weight indices of high-fructose diet-fed rats following oral administration of aqueous leaf extract of *Petiveria alliaceae* and metformin. Values are mean ± SEM of five determinations. HF: High-fructose; BW: body weight**

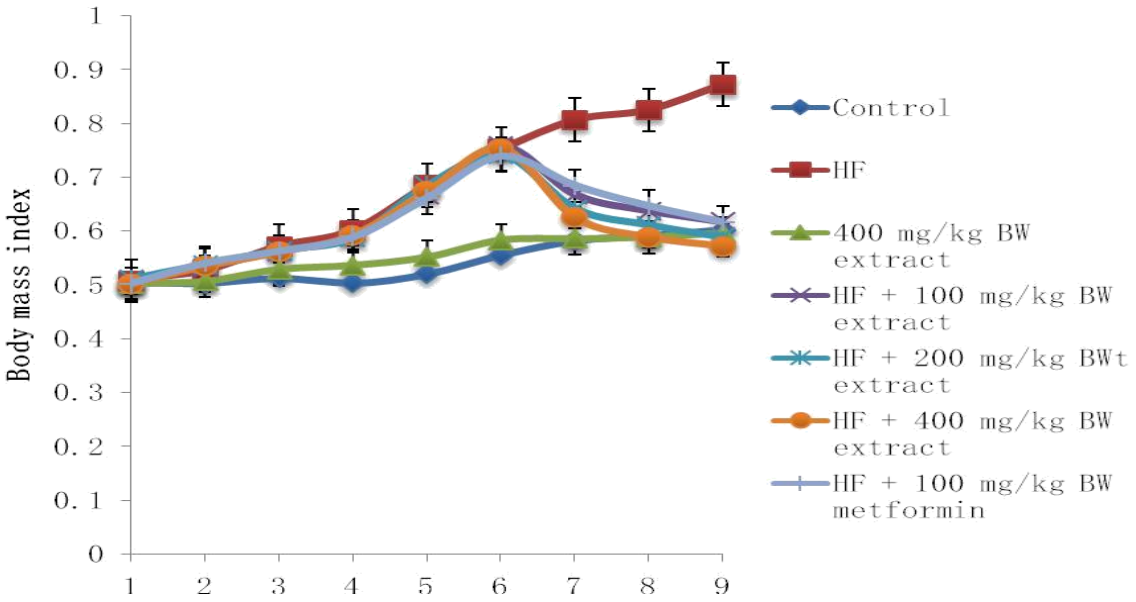


**Figure 2: Body mass index of high-fructose diet-fed rats following oral administration of aqueous leaf extract of *Petiveria alliaceae* and metformin. Values are mean ± SEM of five determinations. HF: High-fructose; BW: body weight**

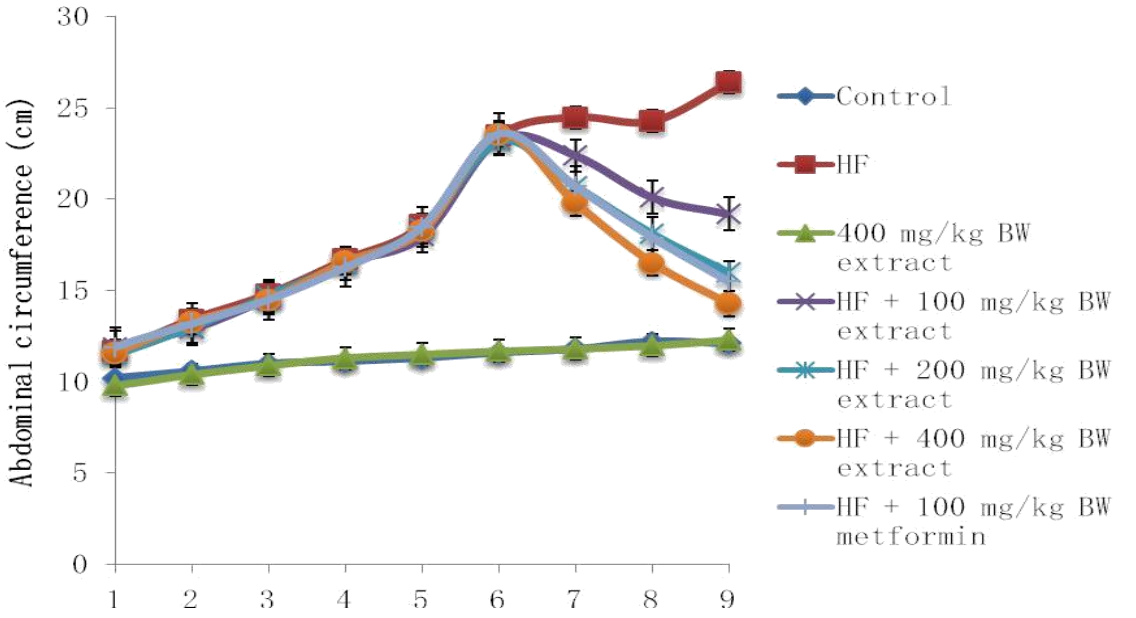


**Figure 3: Abdominal circumference of high-fructose diet-fed rats following oral administration of aqueous leaf extracts of *Petiveria alliaceae* and metformin. Values are mean ± SEM of five determinations. HF: High-fructose; BW: body weight**

The HMG CoA reductase level of high-fructose diet fed rats increased significantly after 9 weeks when compared to control rats (Figure 4). Furthermore, the aqueous leaf extract of *P. Alliaceae* dose dependently reversed high-fructose diet-mediated increase in HMG CoA reductase level. Specifically, the aqueous extract of the plant (400 mg/kg BW) fed rats showed the highest reduction when compared with control rats and those administered with the control drug (Figure 4).

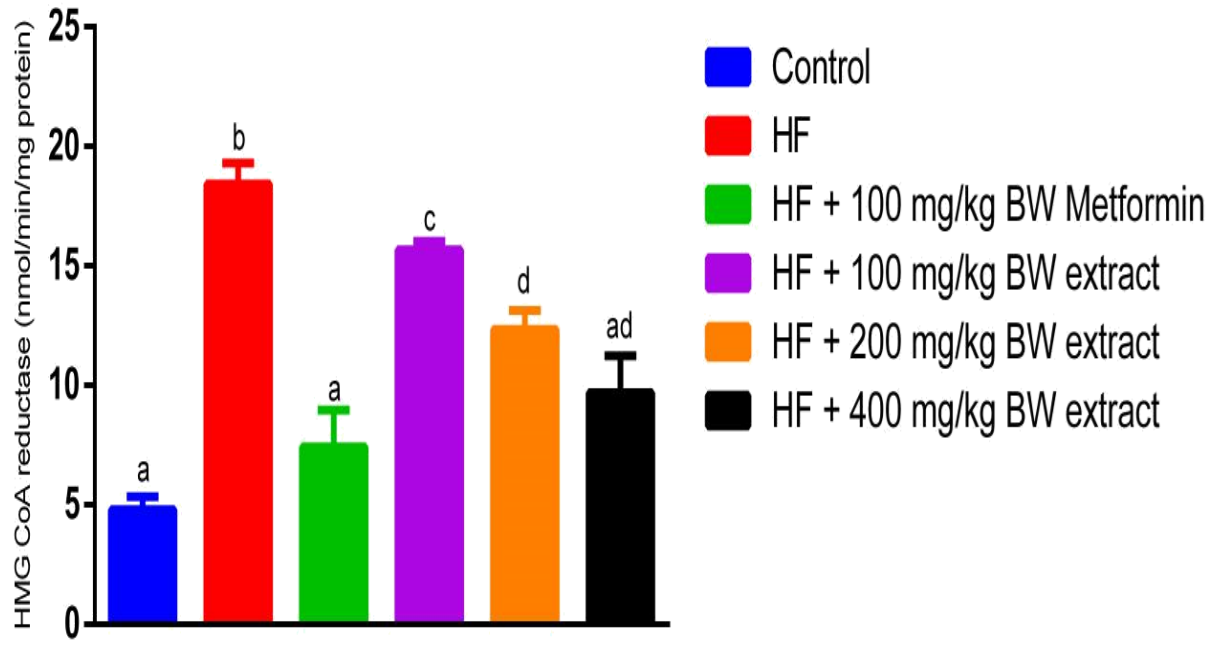


**Figure 4: HMG CoA reductase activity in high-fructose diet-fed rats following oral administration of aqueous leaf extract of *Petiveria alliaceae* and metformin. Values are mean ± SEM of five determinations. Bars with different letters are significantly different. HF: High-fructose; BW: body weight**

*3.2 Biomarkers of hyperglycaemia*

Feeding of rats with high-fructose diet for 9 weeks increased the blood glucose, insulin, insulin resistance, leptin, TNF-α, IL-6 and IL-8, while adiponectin decreased steadily all through the experimental period when compared to the control rats. Following the administration of aqueous leaf extract from week 7 of the experiment period, the highest dose investigated (400 mg/kg BW) significantly ($P<0.05$) reversed high-fructose diet mediated increase in the level of blood glucose (Figure 5), insulin (Figure 6), seven-folds increase in insulin resistance (Figure 7) and the 2-fold decrease in adiponectin and compared significantly ($P<0.05$) with the reference drug, metformin (Figure 8). The extract dose dependently lowered high fructose diet-mediated 117% increase in the level of leptin with the highest dose (400 mg/kg BW) comparing significantly ($p < 0.05$) with the reference drug, metformin and control group (Figure 9). The aqueous leaf extract reversed the high-fructose diet-mediated increase in the level of TNF-α, IL-6 and IL-8 (Table 2) when compared to rats fed with only high-fructose diet. This reversal compared significantly ($p < 0.05$) with the metformin treated rats with the 400 mg B/W dosage of the extract having the highest percentage beneficial effect.

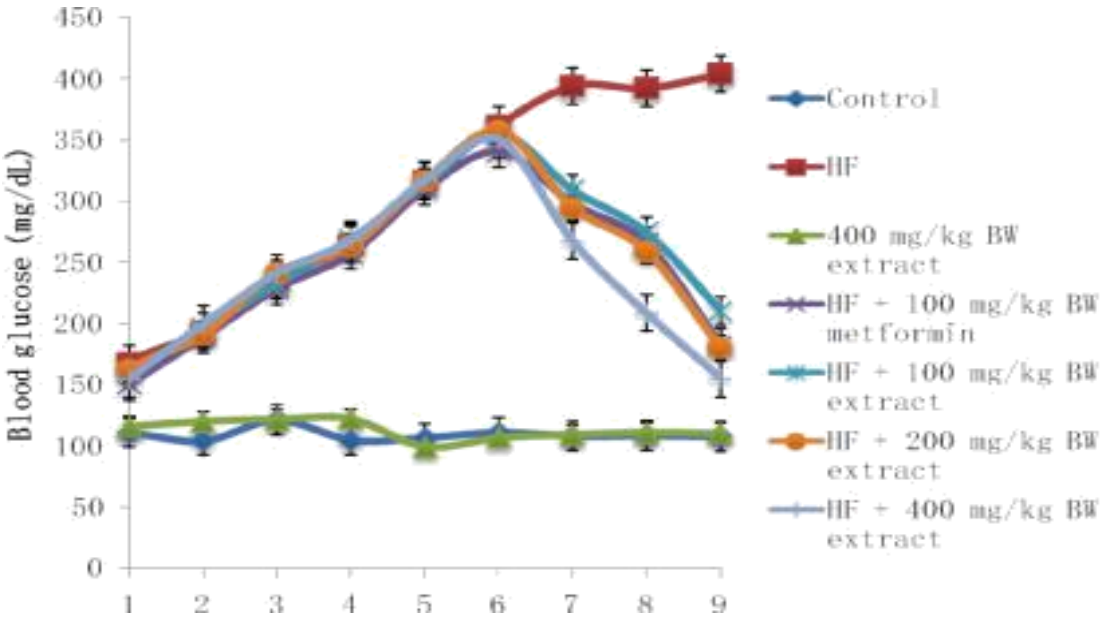


**Figure 5: Blood glucose of high-fructose diet-fed rats following oral administration of aqueous leaf extract of *Petiveria alliaceae* and metformin. Values are mean ± SEM of five determinations**

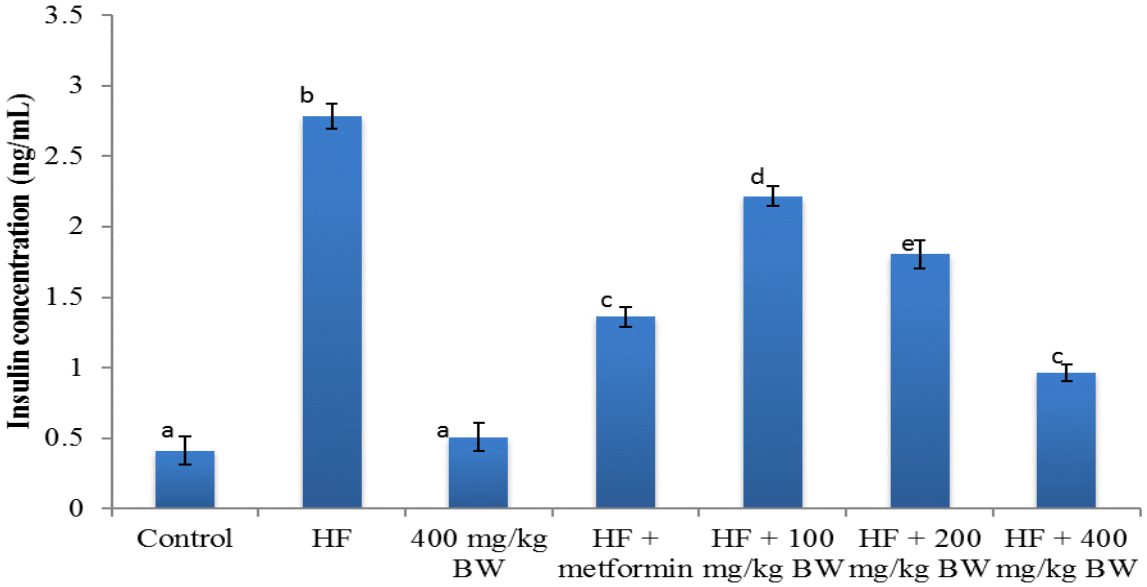


**Figure 6: Insulin concentration in the serum of high-fructose diet-fed rats following oral administration of aqueous leaf extract of *Petiveria alliaceae* and metformin. Values are mean ± SEM of five determinations. Bars with different letters are significantly different. HF: High-fructose; BW: body weight.**

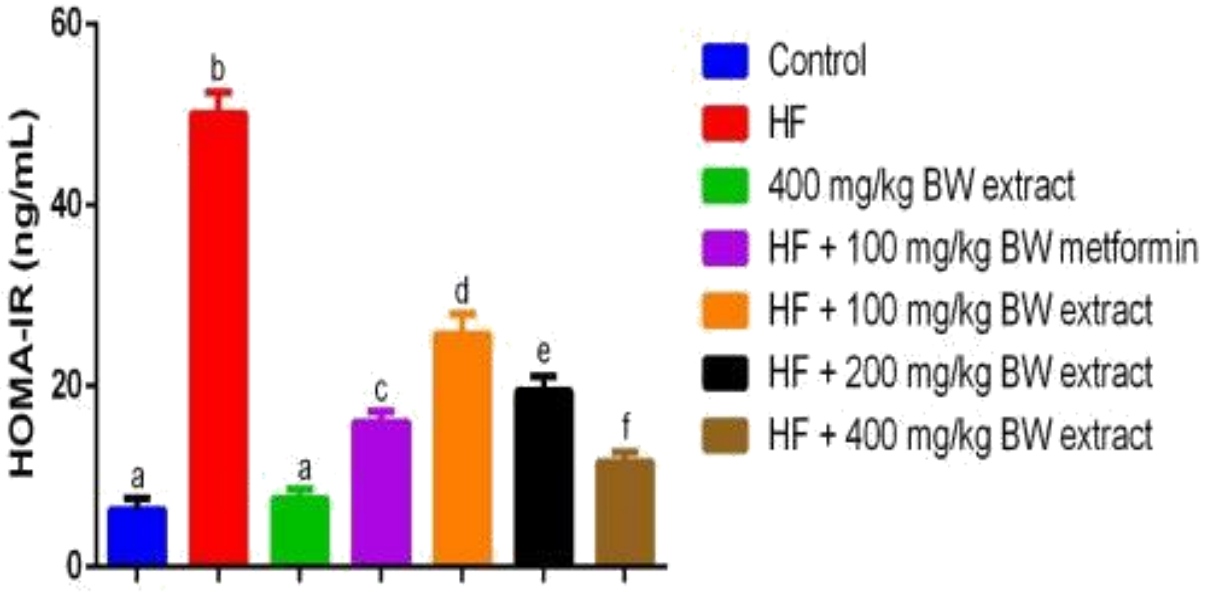


**Figure 7: Basal insulin resistance in high fructose diet-fed rats following oral administration of aqueous leaf extract of *Petiveria alliaceae* and metformin. Values are mean ± SEM of five determinations. Bars with different letters are significantly different. HF: High-fructose; BW: body weight.**

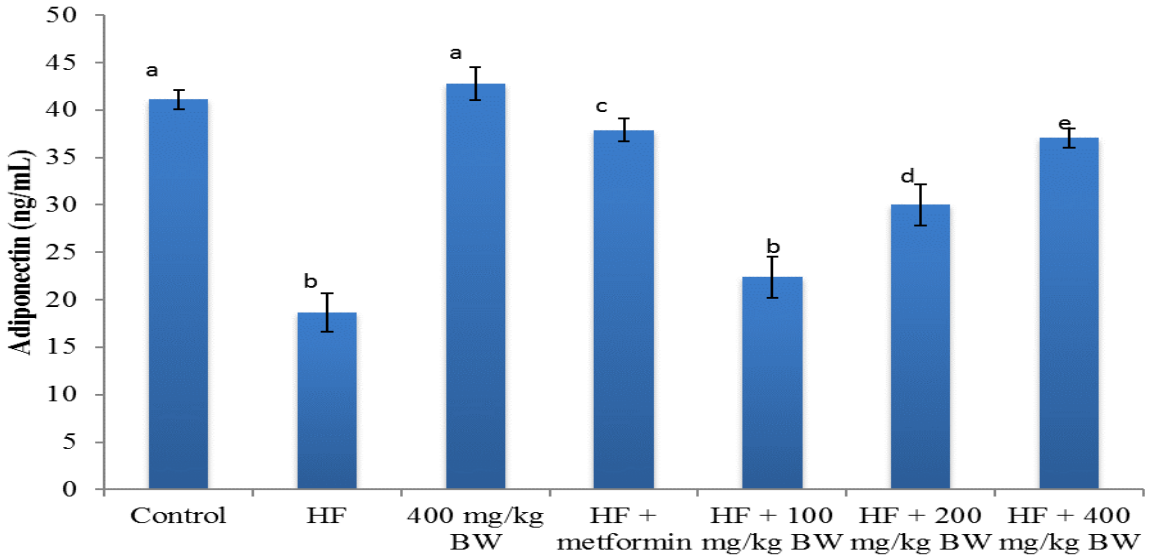


**Figure 8: Adiponectin concentration in the serum of high-fructose diet-fed rats following oral administration of aqueous leaf extract of *Petiveria alliaceae* and metformin. Values are mean ± SEM of five determinations. Bars with different letters are significantly different. HF: High-fructose; BW: body weight.**

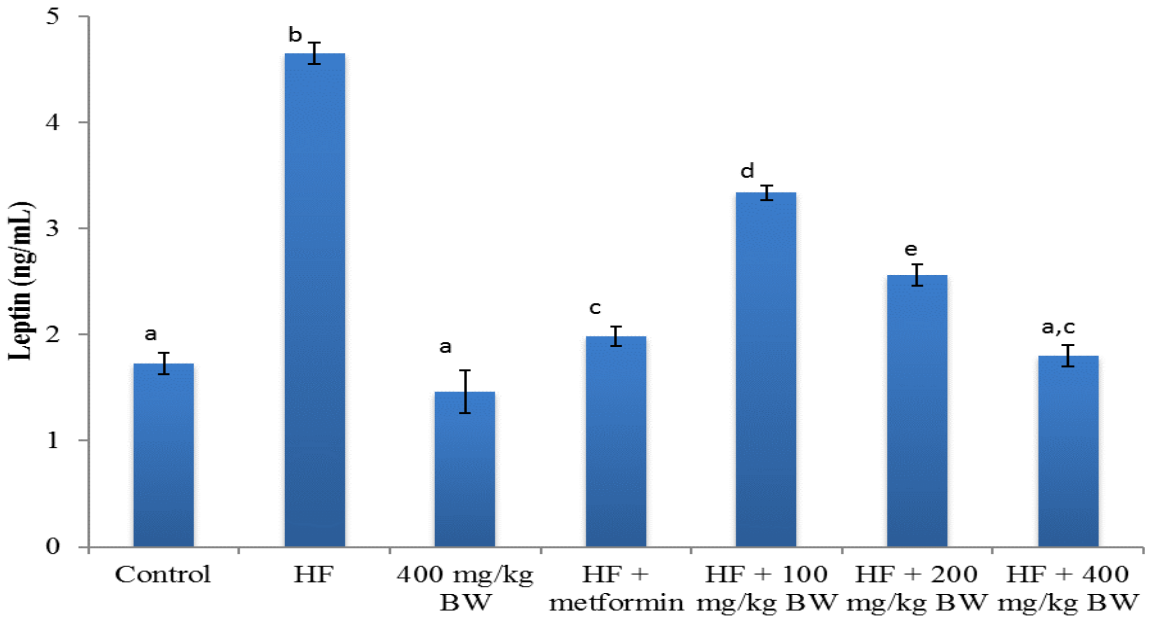


**Figure 9: Leptin concentration in the serum of high-fructose diet-fed rats following oral administration of aqueous leaf extract of *Petiveria alliaceae* and metformin. Values are mean ± SEM of five determinations. Bars with different letters are significantly different. HF: High-fructose; BW: body weight.**

**Table 2: Level of proinflammatory factors in the serum of high-fructose diet-fed rats following oral administration of aqueous leaf extract of *Petiveria alliaceae* and metformin (control drug)**

| | TNF-a (ng/mL) | IL-6 (ng/mL) | IL-8 (ng/mL) |
|---|---|---|---|
| Control | $6.65 \pm 0.02^{a}$ | $3.37 \pm 0.09^{a}$ | $2.99 \pm 0.07^{a}$ |
| HF | $36.26 \pm 1.12^{b}$ | $10.01 \pm 0.13^{b}$ | $23.33 \pm 0.17^{b}$ |
| 400 mg/kg BW extract | $5.45 \pm 1.13^{a}$ | $3.13 \pm 0.11^{a}$ | $3.32 \pm 0.19^{a}$ |
| HF + 100 mg/kg BW metformin | $18.32 \pm 1.21^{c}$ | $1.78 \pm 0.24^{a}$ | $11.61 \pm 0.26^{c}$ |
| HF + 100 mg/kg BW extract | $32.91 \pm 0.12^{c}$ | $7.38 \pm 0.11^{a}$ | $16.25 \pm 0.31^{d}$ |
| HF + 200 mg/kg BW extract | $23.81 \pm 0.26^{d}$ | $5.27 \pm 0.21^{d}$ | $10.79 \pm 0.37^{d}$ |
| HF + 400 mg/kg BW extract | $15.23 \pm 0.18^{c}$ | $3.83 \pm 0.11^{a}$ | $4.51 \pm 0.07^{a}$ |

Values are presented as mean ± SM (n = 5) Test values carrying superscripts different from the control for each parameter are significantly different ($p < 0.05$).

## 4. Discussion

Medicinal plants play a crucial role in promoting human health and well-being by offering pharmacological benefits through their bioactive compounds. Among these compounds, secondary metabolites like alkaloids, anthraquinones, polyphenols, flavonoids, saponins, tannins, and terpenes are particularly significant [27]. These compounds are reportedly responsible for the biological and pharmacological activities of medicinal plants in the treatment of diabetes, inflammation, cancer, diarrhoea, and MS among others [28]. In Nigeria, *Petiveria alliaceae* is a medicinal plant with numerous ethnomedicinal usage, which include diabetes, cystitis, inflammation, pain, paralysis, headache, rheumatic pains, neuralgia and malaria. Indeed, numerous secondary metabolites have been isolated from the plant with the major ones being sulphur compounds, flavonoids, lipids and triterpenes [29].

Obesity is a component of MS induced via feeding of high-fructose diet [30]. The disorder is assessed using anthropometric parameters such as weight gain, BMI and abdominal circumference [31]. Research indicates that extracts of *Petiveria alliaceae* leaves can regulate body weight by counteracting obesity, reducing weight gain, BMI and abdominal circumference linked to high-fructose diet. This aligns with prior studies highlighting the body weight-regulating properties of flavanones [32]. Furthermore, the impact of the extract on HMG-CoA reductase activity, a key enzyme in cholesterol synthesis, suggests an anti-obesity potential. Reduced HMG-CoA reductase activity could decrease liver cholesterol synthesis, leading to increased LDL receptor expression and enhanced cholesterol degradation. This multifaceted mechanism underscores the potential of the plant extract in combating obesity and related metabolic disorders [33].

Hyperglycaemia is also a pivotal aspect of MS [34]. In this study, the elevation of blood glucose levels in the experimental rats following a 9-week high-fructose diet may be attributed to increased forkhead box protein O1 (FOXO1) synthesis, leading to enhanced gluconeogenesis. Furthermore, elevated level of fructose prevents phosphorylation of FOXO1 allowing its translocation into the nucleus and transcription of enzymes that promote gluconeogenesis [35]. Flavonoids have been reported to suppress gluconeogenesis leading to decrease hepatic glucose production [36]. Hence, the improvement in blood glucose after oral administration of the aqueous extract could have resulted from inhibition of gluconeogenesis or it could have also targeted glycerol 3-phosphate dehydrogenase similar to the action of metformin [37]. Thus, the observed reduction in blood glucose levels suggests the hypoglycaemic potential of the aqueous leaf extract of *P. alliaceae*. This could have been achieved through flavonoid-mediated inhibition of gluconeogenesis or enhanced glucose uptake in peripheral tissues possibly through stimulation of glucose transporter proteins (GLUT) [38].

Insulin resistance is one of the first indicators of MS and it is manifested by decreased biological response to normal level of circulating plasma insulin [39]. Insulin resistance is characterized by impaired glucose tolerance, hyperglycaemia and elevated plasma insulin [39]. The significant increase ($p < 0.05$) in insulin concentration with concomitant increase in HOMA-IR after 9 weeks of high-fructose diet feeding suggests insulin resistance. This could have resulted from the upregulation of mitogen activation protein kinase-8 and protein kinase C by fructose 1-phosphate, leading to serine phosphorylation and inactivation of insulin receptor substrate-1 [40]. Studies have reported improved insulin sensitivity in high-fructose diet-induced MS following treatment with medicinal plants [41]. The reversal of MS following oral administration aqueous leaf extract from week 7 is consistent with previous studies and indicates enhanced insulin sensitivity. This may be responsible for the improved blood glucose, since the hyperglycaemia in high-fructose diet induced MS in rats is linked to reduced insulin sensitivity. The enhanced insulin sensitivity observed following the administration of aqueous leaf extract of *P. alliaceae* could be due to the different secondary metabolites contained in the plant. Indeed, the plant is rich in flavonoids and sulphur containing compounds which may be responsible for the activity.

Fructose contributes to increased food consumption and obesity. Direct effects of fructose on the central nervous system include stimulation of appetite and reward hormones [42]. Fructose also causes reduction of hypothalamic malonyl CoA levels, resulting in increased AMP kinase concentrations which further drives food intake [43]. Indirect effects of fructose on the central nervous system include hypertriglyceridemia, which reduces leptin transport across the blood–brain barrier [44], and hyperinsulinemia, which blocks the leptin signal transduction pathway, resulting in a sense of starvation. Obesity, characterized by abnormal or excessive fat accumulation, is an important contributor to inflammation, altered glucose metabolism, dyslipidemia, hypertension and MS [45]. Adiponectin and leptin are important signals regulating energy balance associated with high-fructose diet feeding and obesity [46,47]. Adiponectin, produced by adipocytes, plays a vital role in regulating hepatic glucose production, insulin sensitivity, and inflammatory cytokines [48]. Elevated adiponectin levels following *P. alliaceae* leaf extract administration could enhance insulin sensitivity and lower blood glucose levels in high-fructose diet-fed rats. Adiponectin is important in suppressing hepatic glucose production and hepatic lipogenesis while stimulating glucose uptake by skeletal muscle, fatty acid oxidation in the liver and skeletal muscle, insulin secretion and inhibition of pro-inflammatory cytokines (IL-6 and TNFα) [49]. Plasma adiponectin inversely correlates with insulin resistance resulting from obesity or lipodystrophy [50]. Indeed, adiponectin treatment was reported to improve insulin action and metabolic disturbances associated with insulin resistance. The significant reduction in adiponectin level reported in this study could contribute to elevated blood glucose, vascular inflammation, insulin resistance, vascular stiffness and impaired relaxation [51, 52].

Leptin, another metabolic hormone, interacts with receptors in various tissues like the central nervous system and peripheral tissues including the liver and is associated with obesity-related conditions like non-alcoholic fatty liver disease [53]. The extract reversed high-fructose diet-induced leptin increases, potentially contributing to improved glucose levels and insulin sensitivity, and consistent with prior research on medicinal plants and phenolic compounds [54]. The concentration of leptin is proportional to body adiposity [55]. In excess energy, leptin inhibits food intake and increases energy expenditure through hypothalamic pathways. Furthermore, it suppresses hepatic glucose production and fatty acid synthesis while stimulating fatty acid oxidation. The increased leptin as observed in this study is consistent with data from obese and non-alcoholic fatty liver disease which could have resulted from leptin resistance [56].

Inflammation, one of the second hit events of MS, has been reported in high-fructose diet-induced MS model. Pro-inflammatory cytokines including (TNF-α), IL-6 and IL-8 are critical in the development of insulin resistance in MS. Increased pro-inflammatory cytokines is proportional to increased visceral adiposity common in MS and is related to the pathogenesis of obesity induced insulin resistance [57]. Adiponectin has been shown to suppress these cytokines by inhibiting Kupffer cell activation [58]. The ability of the extract to reduce TNF-α levels could enhance glucose utilization and contribute to reduced blood glucose levels [59]. Increased (TNF-α) observed in high-fructose diet-induced MS may lead to reduced glucose utilization and fatty acid oxidation with increased *de novo* synthesis of cholesterol and fatty acids [60] while the reversal of high-fructose diet-fed rat mediated increase in TNF-α could increase glucose utilization. This may be responsible for the reduced blood glucose level following the administration of aqueous extract derived from *P. alliaceae*. Furthermore, the reversal might have contributed to the enhanced insulin sensitivity by reducing the phosphorylation of insulin receptor-1 and 2 [61]. The role of IL-6 and IL-8 is clearly defined in the pathogenesis of MS [62]. The reversal of high-fructose diet-mediated increase in IL-6 and IL-8 observed in this study has been reported previously with medicinal plants and secondary metabolites [63]. This reversal suggests the anti-inflammatory activity of aqueous leaf extract derived from *P. alliaceae* and improved insulin sensitivity already documented in this study and confirmed by previous work [64].

## 5. Conclusion

This study has shown that the aqueous leaf extract of *Petiveria alliaceae* contains phytochemicals that demonstrate therapeutic potential in managing fructose-induced MS with 400 mg/kg BW demonstrating the best activity. The bioactive compounds present in the aqueous leaf extract could serve as a promising foundation for drug development, offering innovative solutions for addressing the disorders associated with MS.

## 6. References

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