Journal of Pharmacy & Allied Medicine

JPAM, 3(1), 01-09, 2025
https://doi.org/10.58985/jpam.2025.v03i01.26
ISSN (Print): 3005-2726

*Research Article*

# Ethanol leaf extract of *Ficus exasperata* mitigates cardiometabolic risk factors in olanzapine-induced obese female Wistar rats

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***Article Information***
*Received:* 09 December 2024
*Revised:* 01 January 2025
*Accepted:* 02 January 2025
*Published:* 07 January 2025

***Academic Editor***
Prof. Dr. Christian Celia

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***Keywords***
*Ficus exasperate*, electrolytes, lipid profiles, olanzapine-induced obesity, ethanol leaf extract.

## Abstract

Obesity is a major public health concern characterized by excessive body fat, which increases the risk of numerous health conditions, including heart disease, diabetes, high blood pressure, and certain cancers. Addressing obesity is crucial for improving overall health and well-being. In this study, thirty female albino Wistar rats, weighing between 190-200 g, were utilized to investigate the effects of *Ficus exasperata* on olanzapine-induced obesity. After a two-week acclimatization period, obesity was induced in the designated group using olanzapine (4 mg/kg) via oral gavage for 28 days. The rats were then divided into five groups (n=6): normal control, obese-untreated, non-obese treated with *Ficus exasperata* (100 mg/kg), obese treated with *Ficus exasperata* (100 mg/kg), and obese treated with orlistat (100 mg/kg). Treatments were administered orally for 28 days. At the end of the study, the animals were sacrificed, and blood samples were collected for serum analysis. The extract of *Ficus exasperata* demonstrates significant potential in improving various cardiometabolic indexes, BMI [Underweight: BMI less than 18.5; normal weight: BMI 18.5 - 24.9; overweight: BMI 25.0 - 29.9; obesity (Class 1): BMI 30.0 - 34.9; obesity (Class 2): BMI 35.0 - 39.9; extreme obesity (Class 3): BMI 40.0 and above], weight management, and leptin regulation. *Ficus exasperata* extract offers promising therapeutic benefits for improving cardiometabolic health, managing body weight, and regulating leptin, making it a valuable addition to natural health interventions.

## 1. Introduction

Cardiometabolic risk factors are a group of conditions that increase the likelihood of developing cardiovascular diseases (CVD) and metabolic disorders. Obesity is a major cardiometabolic risk factor. It is commonly assessed using the Body Mass Index (BMI), a simple index of weight for height. High BMI is associated with an increased risk of hypertension, dyslipidemia, and type 2 diabetes. A study has shown that weight loss interventions can significantly reduce cardiometabolic risk factors [1]. Obesity has emerged as a global pandemic, impacting millions of people across diverse age groups and socioeconomic backgrounds. It is characterized by excessive body fat that increases the risk of numerous health problems, including cardiovascular diseases, diabetes, and certain cancers like breast and colorectal cancer [2]. The prevalence of obesity has risen sharply due to a combination of factors such as sedentary

lifestyles, poor dietary habits, and genetic predispositions [3]. Its prevalence has increased dramatically over the past few decades. In 2022, approximately 890 million adults and 160 million children and adolescents were living with obesity [4-7].

The Castelli Index 1 (CRI-I) represents the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol. It is used as an indicator of cardiovascular risk. A higher CRI-I suggests a higher risk of developing cardiovascular diseases, while a lower CRI-I indicates a lower risk [8]. The Castelli Index 2 (CRI-II), or LDL/HDL ratio, provides insight into cardiovascular risk by comparing the levels of "bad" low-density lipoprotein (LDL) cholesterol to "good" high-density lipoprotein (HDL) cholesterol [9, 10].

Atherogenic index of plasma (AIP) reflects the balance between pro-atherogenic (triglycerides) and anti-atherogenic (HDL cholesterol) lipoproteins in the blood. A higher AIP indicates a higher risk of atherosclerosis and cardiovascular diseases, while a lower AIP suggests a healthier lipid profile. Studies have shown that AIP is strongly associated with obesity and cardiovascular risk beyond traditional risk factors like smoking, hyperlipidemia and diabetes. It predicts cardiovascular events and mortality better than conventional lipid components [11].

Leptin is an adipocyte-derived hormone that plays a role in regulating energy balance, metabolism, and body weight. It is referred to as the "satiety hormone" because it helps to suppress appetite and increase energy expenditure. However, in individuals with obesity, leptin resistance can occur, leading to an inability to respond to the hormone's signals, which contributes to further weight gain and metabolic complications [12]. It is produced by adipose (fat) cells and signals the brain to reduce appetite and increase energy expenditure. In a healthy individual, increased fat mass leads to higher leptin levels, suppressing hunger and promoting weight loss [13].

*Ficus exasperata*, commonly known as the sandpaper fig, is a species of fig tree belonging to the Moraceae family. This plant has been widely studied for its traditional medicinal uses and pharmacological potential. *Ficus exasperata* has been used in traditional medicine across various regions, particularly in Africa. Different parts of the plant, including the bark, leaves, and roots, are employed for treating a range of ailments. The leaves are particularly significant and are used as analgesics, antiarthritics, diuretics, wound healers, antiparasitics, vermifuges, abortifacients, and for treating haemorrhoids and venereal diseases. Additionally, the plant parts are used as animal fodder [14]. Phytochemical screening of *Ficus exasperata* has revealed the presence of various bioactive compounds, including tannins, flavonoids, alkaloids, anthraquinones, steroids, and cardiac glycosides. These compounds contribute to the plant's medicinal properties and have been the focus of numerous studies [15]. Research has demonstrated that *Ficus exasperata* exhibits a wide range of pharmacological activities. Studies have shown its antidiabetic, anticonvulsant, anti-inflammatory, antimicrobial, hypolipidemic, antioxidant, anti-ulcer, anxiolytic, and hypotensive properties [1]. For instance, aqueous extracts of the leaves have been found to inhibit alpha-amylase and alpha-glucosidase activities, which are key enzymes involved in carbohydrate digestion, making it a potential candidate for managing diabetes mellitus [16]. This study evaluated the effect of ethanol leaf extract of *Ficus exasperata* on cardiometabolic risk factors in olanzapine-induced obese female Wistar rats.

## 2. Materials and methods

### *2.1 Materials*

Olanzapine USP 10 mg Tablets (10 mg, oral, 10 tabs, N05AH03, B4-7395) were obtained from Chez Resources Pharmaceutical LTD. Orlistat (A08AB01), manufactured by Getz Pharma (Private) Limited, was also acquired. Both orlistat and olanzapine drugs were sourced from City Medics Pharmacy in Abuja, Nigeria. Orlistat is marketed under the trade name Xenical, while Olanzapine is marketed under the trade name Zyprexa.

### *2.2 Plants collection*

*Ficus exasperata* leaves were collected from the environment of the University of Abuja, Abuja, Nigeria. They were identified at the National Institute of Pharmaceutical Research and Development (NIPRD) herbarium in Abuja, with voucher specimen number NIPRD/H/7268. The leaves were dried and blended into powder using an electric blender. The


https://doi.org/10.58985/jpam.2025.v03i01.26

powdered leaves were then weighed using an SJ-30KWP weighing scale, manufactured by Ohaus Corporation, Pine Brook, NJ, USA.

*2.3 Preparation of extract*

Forty grams of *Ficus exasperata* leaf powder was dissolved in 200 ml of ethanol and left covered for 48 hours. After this period, the mixture was filtered through a nylon sieve into a small container, and the remaining residue was spread out to dry. The residue was then re-extracted with an additional 200 ml of fresh ethanol for 24 hours. The combined dried extract from these processes was used for this study [17].

*2.4 Experimental animals*

For this study, 30 female albino Wistar rats, each weighing between 190-200 g, were used. The animals were sourced from the animal facility of the Faculty of Veterinary Medicine at the University of Abuja. They were housed in plastic cages in the Department of Human Physiology at the same university. The rats were allowed to acclimate to the laboratory environment for two weeks, with conditions maintained at a temperature range of 24-28°C, relative humidity of 60-70%, and a 12-hour light-dark cycle. They had free access to food and water throughout the acclimatization period.

*2.5 Experimental induction of obesity*

Obesity was induced by administering olanzapine 4 mg/kg dissolved in normal saline using 2 ml disposable needles and syringes through oral gavage for 28 days. The weight and naso-anal length (using meter rule) of the Wistar rats were measured. The body mass index (BMI) of each Wistar rat was obtained by dividing the weight of each rat by the square of naso-anal length. Wistar rats with body mass index greater than 0.68 g/cm² were considered obese [18].

*2.6 Experimental design*

Rats were divided into five groups of six rats each (n=6). Group 1 served as the normal control and was given normal saline (1 ml/kg). Group 2 was designated as the obese-untreated. Group 3 was non-obese and was given *Ficus exasperata* extract 100 mg/kg. Groups 4 and 5 were obese and were given *Ficus exasperata* extract 100 mg/kg and orlistat 100 mg/kg, respectively. Administration was done orally for 28 days.

*2.7 Animal sacrifice*

The animals were sacrificed after 28 days of administration. Animals were anaesthetized with sodium phenobarbital 60 mg/kg [19]. Blood samples were collected via cardiac puncture. The blood samples were dispensed in a plain serum bottle. The serum was prepared by using a bench centrifuge to spin blood samples for 20 minutes at a speed of 3500. A clear supernatant was used.

*2.8 Body Mass Index Assessment*

Each rat was weighed using an electronic scale and the body weight was recorded (BW) in grams (g). The naso-anal length of each rat was measured using a flexible ruler and recorded in centimetres (cm). The BMI was calculated according to the method described by Novelli *et al* [18]. Using the provided mathematical relationship:

$$\text{BMI} = \frac{\text{Body weight (g)}}{\text{Naso} - \text{anal length cm}^2}$$

*2.9 Assessment of lipid profile indexes*

The Castelli risk index-I was calculated from total cholesterol and high-density lipoprotein obtained from the blood sample. It was calculated by dividing the total cholesterol (TC) by the high-density lipoprotein cholesterol (HDL-C) [20].

$$\text{Castelli Risk Index} - \text{I} = \frac{\text{Total Cholesterol (TC)}}{\text{High Density Lipoprotein (HDL}-\text{c)}}$$

The Castelli risk index-II was calculated by dividing the low-density lipoprotein cholesterol (LDL-C) by the HDL-C [20].

$$\text{Castelli Risk Index} - \text{II} = \frac{\text{Low Density Lipoprotein (LDL}-\text{c)}}{\text{High Density Lipoprotein (HDL}-\text{c)}}$$

The atherogenic index was calculated as the Log of triglycerides divided by high-density lipoprotein [20].

$$\text{Atherogenic Index} = \text{Log}\ \frac{\text{Triglyceride (TG)}}{\text{High Density Lipoprotein (HDL}-\text{c)}}$$

*2.10 Serum Leptin assessment*

Assessment of serum leptin level was carried out using a commercially available rat-species-specific ELISA kit; (Fine Test; Catalogue Number: ER0115, Range: 0.156-10 ng/mL, Sensitivity: 0.09ng/ mL).



https://doi.org/10.58985/jpam.2025.v03i01.26

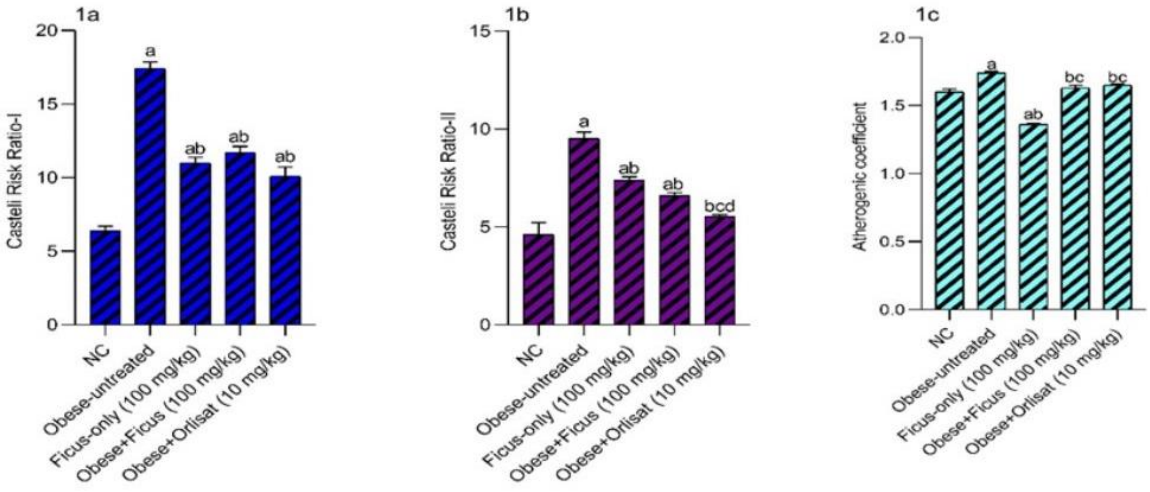


**Figure 1.** Results of Castelli risk index I (1a), Castelli risk index-II (1b) and atherogenic coefficient (1c). NC= normal control. Superscripts a=p<0.05 vs NC; b=P<0.05 vs Obese-untreated; c=p<0.05 vs Ficus-only; d=p<0.05 vs Obese+Ficus. Data presented as Mean ± SEM.

*2.11 Statistical Analysis*

The data obtained were analysed using one-way analysis of variance (ANOVA) on Graph Pad Prism version 9.3.1 and statistical significance was set at P<0.05. The results were presented as Mean ± SEM.

## 3. Results

*3.1 Castelli risk index I, II and atherogenic coefficient*

Fig. 1 showed the Castelli risk index-I was significantly higher ($p < 0.05$) in the obese-untreated group than in the NC (1a). In the non-obese group treated with Ficus, Castelli risk index-I was significantly ($p < 0.05$) higher compared to the NC. However, it was significantly lower ($p < 0.05$) compared to the obese-untreated group. In the obese groups treated with Ficus and orlistat, the Castelli risk index-I was significantly higher ($p < 0.05$) than that of the NC, and significantly lower ($p < 0.05$) compared to the obese-untreated group. In Fig. 1b, the Castelli risk index-II was significantly higher ($p < 0.05$) in the obese-untreated group compared to the NC. Both in the Ficus-only and the obese+Ficus groups, the Castelli risk index-II was significantly higher compared to the NC and lower ($p < 0.05$) compared to the obese-untreated group. In the obese+orlistat treated group, the Castelli risk index-II was significantly lower compared to the obese-untreated, Ficus-only and obese+Ficus groups. In Fig. 1c, the atherogenic coefficient was significantly ($p< 0.05$) higher in the obese-untreated group compared to the NC. In the Ficus-only group, it was lower significantly compared to both NC, obese-untreated, obese+Ficus and obese+orlistat groups. The atherogenic coefficient in the obese groups treated with Ficus and orlistat was significantly ($p < 0.05$) lower compared to the obese-untreated group.

*3.2 Percentage of body weight change, body mass index and serum leptin*

Percentage body weight (Fig. 2a) was significantly higher ($p < 0.05$) in the obese-untreated group compared to the NC and Ficus-only groups. In the obese groups treated with Ficus and orlistat, the percentage of body weight was significantly decreased ($p < 0.05$) compared to the NC, obese-untreated and Ficus-only groups. BMI in Fig. 2b was significantly higher ($p < 0.05$) in the obese-untreated group compared to the NC. In all the other groups, BMI was lower significantly ($p < 0.05$) compared to the obese-untreated group. Serum leptin level was significantly higher in the obese-untreated group compared to the NC. However, in all the other treated groups, serum leptin was significantly lower ($p < 0.05$) compared to the NC and obese-untreated groups. In the group treated with orlistat, the leptin level was significantly ($p < 0.05$) higher compared to the Ficus-only treated group.

## 4. Discussion

Obesity often leads to dyslipidemia, characterized by abnormal levels of lipids in the blood. This includes


https://doi.org/10.58985/jpam.2025.v03i01.26

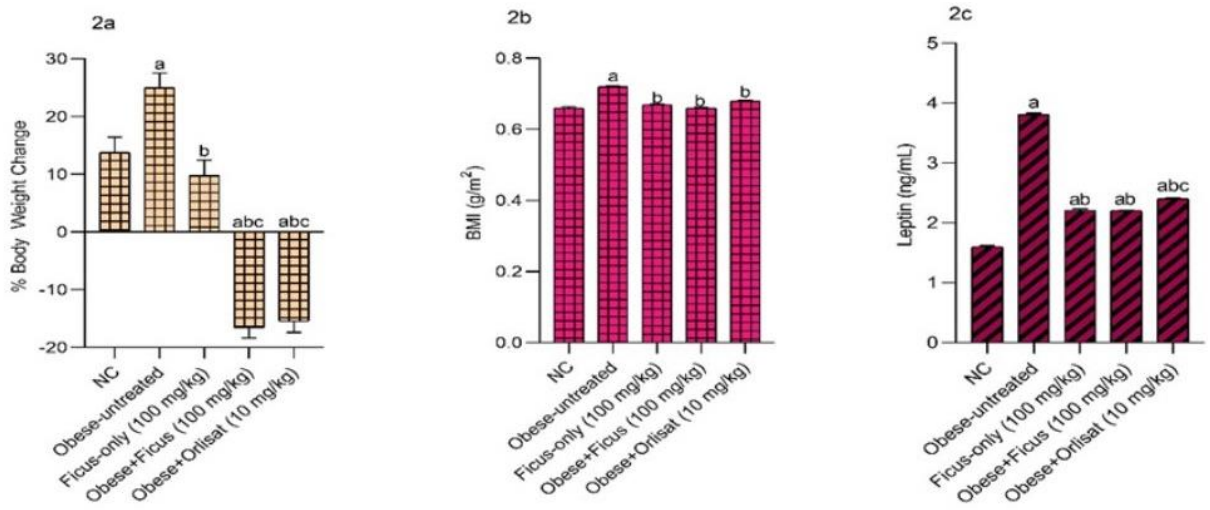


**Figure 2.** Results of percentage body weight change (2a), BMI (2b), and Leptin (2c). NC= normal control; TRIG= triglyceride. Superscripts a=p<0.05 vs NC; b=P<0.05 vs Obese-untreated; c=p<0.05 vs Ficus-only; d=p<0.05 vs Obese+Ficus.

increased triglycerides (TG) and LDL cholesterol, which further exacerbate the imbalance between TC and HDL-C [21]. Obesity often leads to dyslipidemia, characterized by abnormal levels of lipids in the blood. This includes increased triglycerides (TG) and LDL cholesterol, which further exacerbates the imbalance between TC and HDL-C [22, 23]. These changes could account for the significant increase in the Castelli risk index-I observed in the obese-untreated group in this study. In this study, Castelli risk index-II was significantly higher in the obese-untreated group compared to the NC. Obesity has been shown to increase Castelli Risk Index II (CRI-II), which is the ratio of low-density lipoprotein cholesterol (LDL-C) to high-density lipoprotein cholesterol (HDL-C). Obesity, as confirmed by the results of BMI in this group, has been shown to affect Castelli risk indexes I and II by increasing total cholesterol, decreasing high-density lipoprotein, and dyslipidemia [24]. These are consistent with the findings of this study. Elevated leptin levels are often associated with obesity and can impact lipid metabolism, which in turn affects the Castelli Indexes [25]. Elevated leptin is consistent with the findings of this present study in the obese-untreated group. A higher CRI-I and II means that the balance is tilted unfavourably towards more cholesterol which can potentially contribute to plaque buildup in the arteries, leading to atherosclerosis, heart attacks, and strokes [10]. Thus, the result of *Ficus* administration in this current study on Catelli risk index-I and II suggests its potential effect in the prevention of plaque accumulation in the arteries. *Ficus exasperata* extracts contain compounds like flavonoids, tannins, and phenols, which have strong antioxidant properties. Antioxidants help reduce oxidative stress, which can damage lipids and lead to higher cholesterol levels [26, 27]. The extracts have been shown to reduce levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) while increasing high-density lipoprotein cholesterol (HDL-C). This shift in lipid profile directly lowers the CRI-I and II [27].

In the present study, the atherogenic index (AI) was significantly higher in the obese-untreated group compared to the NC. Obesity is often associated with higher levels of triglycerides, which contribute to AI. Elevated TG levels are a key component in the calculation of AI, leading to a higher index [21, 28]. Obesity is linked to lower levels of high-density lipoprotein cholesterol (HDL-C), which is considered "good" cholesterol. Since HDL-C helps remove excess cholesterol from the bloodstream, lower levels result in a higher AI [29]. Obesity often leads to insulin resistance, which can result in increased production of very low-density lipoprotein (VLDL) and decreased clearance of triglycerides. This imbalance further elevates the AI [30-32]. Thus, the significant effect of Ficus extract on AI in the present study could be


https://doi.org/10.58985/jpam.2025.v03i01.26

attributed to reduced triglycerides and improved HDL-c levels. The action of this extract on AI in the present study could also have been due to its ability to improve insulin sensitivity [33]. Elevated leptin levels as observed in the present study are linked to insulin resistance, which can lead to dyslipidemia (abnormal lipid levels) and increased AI. Insulin resistance results in higher levels of triglycerides and LDL-C, contributing to atherogenesis [34-36]. Therefore, the extract in the present study reduced AI via leptin-related pathway.

The percentage of body weight was significantly higher in the obese-untreated group compared to the NC in this study. Olanzapine increases appetite and food consumption, leading to weight gain. This is partly due to its antagonistic effects on histamine H1 receptors, which play a role in regulating hunger and satiety [37]. Olanzapine can decrease metabolic rate, reducing the amount of energy expended by the body. This contributes to the accumulation of excess calories as fat [38, 39]. Studies have shown that olanzapine promotes the proliferation of adipocytes (fat cells), leading to increased fat mass [40]. In the present study, the administration of *Ficus exasperata* significantly reduced the percentage of body weight gain. This action could have been via normal regulation of appetite and food consumption by an agonistic action on histamine H1 receptors, as well as increasing metabolic rate. Plant extracts have been shown to modulate the expression of genes involved in adipogenesis (the formation of fat cells), such as peroxisome proliferator-activated receptor gamma (PPAR$\gamma$) and CCAAT enhancer binding protein alpha (CEBP$\alpha$), which can reduce the proliferation of adipocytes [41, 42].

Polyphenols can inhibit the differentiation of pre-adipocytes into mature adipocytes (fat cells), which helps reduce fat accumulation [43]. They can stimulate the breakdown of fat (lipolysis), leading to a reduction in body fat [44]. These could account for the effect of *Ficus exasperata* administration in the current study on body mass index, which was significantly reduced in the obese+Ficus group compared to the obese-untreated group. Hormones like leptin and insulin play crucial roles in regulating appetite and metabolism. Imbalances in these hormones can lead to overeating and weight gain, increasing BMI [45, 46].

Serum leptin in the current study was significantly increased in the obese-untreated group compared to the NC. Olanzapine may affect the function of adipocytes (fat cells), leading to increased fat storage and higher leptin production [47]. With increased fat mass, the body produces more leptin. However, in some cases, the body becomes resistant to leptin, leading to higher circulating levels of the hormone [48]. Treatment with *Ficus exasperata* and orlistat significantly reduced circulating leptin levels. Oxidative stress is linked to obesity and metabolic disorders, which can affect leptin levels. The antioxidant properties of *Ficus exasperata* might help mitigate oxidative stress, potentially influencing leptin production and function [49]. The phytochemicals in *Ficus exasperata* could modulate metabolic pathways involved in fat storage and energy balance, indirectly affecting leptin levels. Additionally, by enhancing insulin sensitivity, *Ficus exasperata* extract might help regulate leptin levels, as insulin and leptin are closely related to energy homeostasis.

## 5. Conclusions

The extract of *Ficus exasperata* demonstrates significant potential in improving various cardiometabolic indexes, BMI, weight management, and leptin regulation. *Ficus exasperata* extract offers promising therapeutic benefits for improving cardiometabolic health, managing body weight, and regulating leptin, making it a valuable addition to natural health interventions.

## Ethical consent

Ethical approval was obtained from the University of Abuja Ethics Committee on Animal Use (UAECAU), with a reference number (UAECAU/2021/0001). Animals were handled per protocols approved by the Institutional Guidelines on Animal Care and Use Committee and conformed to guidelines set by the National Institutes of Health on experiments involving the use of animals.

## Authors' contributions

Conceptualization, O.O., B.R.B.; Methodology, O.O.; Software, O.O.; Validation, O.O., B.R.B., E.D.E.; Formal analysis, O.O.; Investigation, O.O.; Resources,


https://doi.org/10.58985/jpam.2025.v03i01.26

O.O.; Data curation, O.O.; Writing – original draft preparation, O.O.; Writing – review & editing, O.O., E.N.S.; Visualization, O.O.; Supervision, O.O.; Project Administration, O.O.; Funding acquisition, B.R.B., E.N.S.

## Acknowledgements

We acknowledge the staff of the Department of Human Physiology, Faculty of Basic Medical Sciences, University of Abuja. Nigeria and the Department of Physiology, University of Ilesa, Ilesa, Osun State, Nigeria.

## Funding

"This research received no specific grant from any funding agency "(the public, commercial, or not-for-profit sectors)".

## Availability of data and materials

All relevant data are within the paper and its supporting information files. Additional data will be made available on request according to the journal policy.

## Conflicts of interest

The authors declare no conflict of interest.

## References

1. Landi, F.; Calvani, R.; Picca, A.; Tosato, M.; Martone, A.M.; Ortolani, E.; Sisto, A.; Serafini, E.; Desideri, G.; Fuga, M.T.; Marzetti, E. Body mass index is strongly associated with hypertension: results from the longevity check-up 7+ study. Nutrients. 2018, 10(12), 1976. https://doi.org/10.3390/nu10121976
2. Lin, X.; Li, H. Obesity: Epidemiology, pathophysiology, and therapeutics. frontiers in endocrinology. 2021, 12, 706978. https://doi.org/10.3389/fendo.2021.706978
3. Shafiee, A.; Nakhaee, Z.; Bahri, R.A.; et al. Global prevalence of obesity and overweight among medical students: a systematic review and meta-analysis. BMC Public Health. 2024, 24, 1673. https://doi.org/10.1186/s12889-024-19184-4
4. Kranjac, A.W.; Kranjac, D. Explaining adult obesity, severe obesity, and BMI: Five decades of change. Heliyon. 2024, 9(5), e16210. https://doi.org/10.1016/j.heliyon.2023.e16210
5. Jaacks, LM.; Vandevijvere, S.; Pan A, McGowan, C.J.; Wallace, C.; Imamura, F.; Mozaffarian, D.; Swinburn, B.; Ezzati, M. The obesity transition: stages of the global epidemic. Lancet Diabet. Endocrinol. 2019, 7(3), 231-240. https://doi.org/10.1016/S2213-8587(19)30026-9
6. Haththotuwa, R.N.; Wijeyaratne, C.N.; Senarath, U. Worldwide epidemic of obesity. Obesity and Obstetrics (Second Edition). 2019, 3-8. https://doi.org/10.1016/B978-0-12-817921-5.00001-1
7. Boutari, C.; Mantzoros, C.S. A 2022 update on the epidemiology of obesity and a call to action: As its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism. 2022, 133, 155217. https://doi.org/10.1016/j.metabol.2022.155217
8. Lumu, W.; Bahendeka, S.; Wesonga, R.; Kibirige, D.; Kasoma, R.M.; Ssendikwanawa, E. Atherogenic index of plasma and its cardiovascular risk factor correlates among patients with type 2 diabetes in Uganda. Afr. Health Sci. 2023, 23(1), 515. https://doi.org/10.4314/ahs.v23i1.54
9. Csige, I.; Ujvárosy, D.; Szabó, Z.; Lőrincz, I.; Paragh, G.; Harangi, M.; Somodi, S. The impact of obesity on the cardiovascular system. J. Diabet. Res. 2018, 3407306. https://doi.org/10.1155/2018/3407306
10. Drwiła, D.; Rostoff, P.; Nessler, J.; Konduracka, E. Prognostic value of non-traditional lipid parameters: Castelli risk index I, castelli risk index II, and triglycerides to high-density lipoprotein cholesterol ratio among patients with non-ST-segment elevation myocardial infarction during 1 year follow-up. Kardiologiia. 2022, 62(9), 60-66. https://doi.org/10.18087/cardio.2022.9.n2037
11. Qin, M.; Chen, B. Association of atherogenic index of plasma with cardiovascular disease mortality and all-cause mortality in the general US adult population: results from NHANES 2005–2018. Cardiovas. Diabetol. 2024, 23, 255. https://doi.org/10.1186/s12933-024-02359-z
12. Picó, C.; Palou, M.; Pomar, C.A.; et al. Leptin as a key regulator of the adipose organ. Rev. Endocr. Metabol. Disord. 2022, 23, 13–30. https://doi.org/10.1007/s11154-021-09687-5
13. Obradovic, M.; Sudar-Milovanovic, E.; Soskic, S.; Essack, M.; Arya, S.; Stewart, A. J.; Gojobori, T.; Isenovic, E. R. Leptin and obesity: role and clinical implication. Front. Endocrinol. 2021, 12, 585887. https://doi.org/10.3389/fendo.2021.585887
14. Abotsi, W.M.K.; Woode, E.; Ainooson, G.K.; Amo-Barimah, A.K.; Boakye-Gyasi, E. Antiarthritic and antioxidant effects of the leaf extract of *Ficus exasperata* P. Beauv. (Moraceae). Pharmacog. Res. 2010, 2(2), 89. https://doi.org/10.4103/0974-8490.62958
15. Lawal, I.O.; Borokini, T.I.; Oyeleye, A.; Williams, O.A.; Olayemi, J.O. Evaluation of extract of *Ficus exasperata*

Vahl root bark for antimicrobial activities against some strains of clinical isolates of bacterial and fungi. Int. J. Modern Bot. 2012, 2(1), 6-12. https://doi.org/10.5923/j.ijmb.20120201.02

16. Akinloye, D.I.; Ugbaja, R. N. Potential nutritional benefits of *Ficus exasperata* Vahl leaf extract. Nutrire. 2022, 47, 6. https://doi.org/10.1186/s41110-022-00157-9.
17. Kofie, W.; Osman, H.; Bekoe, S.O. Phytochemical properties of extracts and isolated fractions of leaves and stem bark of *Ficus exasperata.* World J. Pharm. Pharm. Sci. 2015, 4(12), 91-101.
18. Novelli, E.L.B.; Diniz, Y.S.; Novelli Filho, J.L.V. et al. Anthropometrical parameters and markers of obesity in rats. Lab. Animal. 2007, 41(1), 37-41. https://doi.org/10.1258/002367707779399518
19. Tobar Leitão, S.A.; Soares, D.D.S.; Carvas, J.N.; Zimmer, R.; Ludwig, N.F.; Andrades, M. Study of anaesthetics for euthanasia in rats and mice: A systematic review and meta-analysis on the impact upon biological outcomes (SAFE-RM). Life Sci. 2021, 284, 119916. https://doi.org/10.1016/j.lfs.2021.119916
20. Bhardwaj, S.; Bhattacharjee, J.; Bhatnagar, M.K.; Tyagi, S. Atherogenic Index of plasma, castelli risk index and atherogenic coefficient- new parameters in assessing cardiovascular risk. Int. J. Pharm. Biol. Sci. 2013, 3(3), 359-364. https://doi.org/10.5923/j.ijpbs.20120201.02
21. Klop, B.; Elte, J.W.; Cabezas, M.C. Dyslipidemia in obesity: Mechanisms and potential targets. Nutrients. 2013, 5(4), 1218. https://doi.org/10.3390/nu5041218
22. Vargas, H.O.; Nunes, S.O.V.; Barbosa, D.S.; Vargas, M.M.; Cestari, A.; Dodd, S.; Venugopal, K.; Maes, M.; Berk, M. Castelli risk indexes 1 and 2 are higher in major depression but other characteristics of the metabolic syndrome are not specific to mood disorders. Life Sci. 2014, 102(1), 65-71. https://doi.org/10.1016/j.lfs.2014.02.033
23. Raaj, I.; Thalamati, M.; Gowda, M.N.V.; et al. The role of the atherogenic index of plasma and the castelli risk Index I and II in Cardiovascular Disease. Cureus. 2024, 16(11), e74644. https://doi.org/10.7759/cureus.74644
24. Anandkumar, M.H.; Chandrashekhar, D.M.; Jayalakshmi, M.K.; Prashanth, B.G. Anthropometric measures of obesity as correlates of atherogenic index of plasma in young adult females. Nat. J. Physiol. Pharm. Pharmacol. 2019, 10(1). https://doi.org/10.5455/njppp.2020.10.0933518112019
25. Wang, C.; Chang, L.; Wang, J.; Xia, L.; Cao, L.; Wang, W.; Xu, J.; Gao, H. Leptin and risk factors for atherosclerosis: A review. Medicine. 2023, 102(46), e36076. https://doi.org/10.1097/MD.0000000000036076
26. Anigboro, A.A.; Avwioroko, O.J.; Ohwokevwo, O.A.; Pessu, B. Bioactive components of *Ficus exasperata*, *Moringa oleifera* and *Jatropha tanjorensis* leaf extracts and evaluation of their antioxidant properties. Eur. Asian J. BioSci. 2019, 13, 1763-1769
27. Wani, P.A.; Adesina, O.F.; Wahid, S.; Salami, O.R.; Jan, N. Antioxidant phytochemical screening and antimicrobial activity of *Ficus exasperata* against pathogens in Nigeria. Asian J. Biol. Sci. 2019, 12(3), 251-257. https://doi.org/10.3923/ajbs.2019.251.257
28. Bays, H.E.; Toth, P.P.; Kris-Etherton, P.M.; Abate, N.; Aronne, L.J.; Brown, W.V.; Gonzalez-Campoy, J.M.; Jones, S.R.; Kumar, R.; La Forge, R.; Samuel, V.T. Obesity, adiposity, and dyslipidemia: A consensus statement from the National Lipid Association. J. Clin. Lipidol. 2013, 7(4), 304-383. https://doi.org/10.1016/j.jacl.2013.04.001
29. Stadler, J.T.; Marsche, G. Obesity-related changes in high-density lipoprotein metabolism and function. Int. J. Mol. Sci. 2020 Nov 26, 21(23), 8985. https://doi.org/10.3390/ijms21238985
30. Ye, J. Mechanisms of insulin resistance in obesity. Fron. Med. 2013, 7(1), 14-24. https://doi.org/10.1007/s11684-013-0262-6
31. Ahmed, B.; Sultana, R.; Greene, M.W. Adipose tissue and insulin resistance in obese. Biomed. Pharmacother. 2021, 137, 111315. https://doi.org/10.1016/j.biopha.2021.111315
32. Tong, Y.; Xu, S.; Huang, L.; Chen, C. Obesity and insulin resistance: Pathophysiology and treatment. Drug Discov. Today. 2022, 27(3), 822-830. https://doi.org/10.1016/j.drudis.2021.11.001
33. Taiwo, I.A.; Adebesin, O.A.; Shittu, A.F.; Lawal, R.I.; Odeigah, P.G.C. Glycaemic activity of *Ficus exasperata* in fructose-induced glucose intolerance in rats. Researcher. 2010, 2(1), 80.
34. Moonishaa, T.M.; Nanda, S.K.; Shamraj, M.; Sivaa, R.; Sivakumar, P.; Ravichandran, K. Evaluation of leptin as a marker of insulin resistance in type 2 diabetes mellitus. Int. J. Appl. Basic Med. Res. 2017, 7(3), 176. https://doi.org/10.4103/ijabmr.IJABMR_278_16
35. Gruzdeva, O.; Borodkina, D.; Uchasova, E.; Dyleva, Y.; Barbarash, O. Leptin resistance: Underlying mechanisms and diagnosis. Diabet. Metabol. Syndr. Obes. 2019, 12, 191-198. https://doi.org/ 10.2147/DMSO.S182406
36. Kumar, R.; Mal, K.; Razaq, M.K.; Magsi, M.; Memon, M.K.; Memon, S.; Afroz, M.N.; Siddiqui, H.F.; Rizwan, A. Association of leptin with obesity and insulin resistance. Cureus. 2020, 12(12), e12178. https://doi.org/10.7759/cureus.12178
37. Huang, J.; Hei, G.; Yang, Y.; Liu, C.; Xiao, J.; Long, Y.; et al. Increased appetite plays a key role in olanzapine-induced weight gain in first-episode schizophrenia

patients. Front. Pharmacol. 2020, 11, 540469. https://doi.org/10.3389/fphar.2020.00739

38. Graham, K.A.; Perkins, D.O.; Edwards, L.J.; Barrier, R.C.J.; Lieberman, J.A.; Harp, J.B. Effect of olanzapine on body composition and energy expenditure in adults with first-episode psychosis. Am. J. Psychiat. 2005, 162(1), 118-23. https://doi.org/10.1176/appi.ajp.162.1.118
39. Park, S.; Yi, K. K.; Kim, S.; Hong, J.P. Effects of ziprasidone and olanzapine on body composition and metabolic parameters: An open-label comparative pilot study. Behav. Brain Func. 2013, 9, 27. https://doi.org/10.1186/1744-9081-9-27
40. Nimura, S.; Yamaguchi, T.; Ueda, K.; Kadokura, K.; Aiuchi, T.; Kato, R.; Obama, T.; Itabe, H. Olanzapine promotes the accumulation of lipid droplets and the expression of multiple perilipins in human adipocytes. Biochem. Biophys. Res. Commun. 2015, 467(4), 906-912. https://doi.org/10.1016/j.bbrc.2015.10.045
41. Moseti, D.; Regassa, A.; Kim, K. Molecular regulation of adipogenesis and potential anti-adipogenic bioactive molecules. Int. J. Mol. Sci. 2016, 17(1), 124. https://doi.org/10.3390/ijms17010124
42. Mota de Sá, P.; Richard, A.J.; Hang, H.; Stephens, J.M. Transcriptional regulation of adipogenesis. Comprehens. Physiol. 2017, 7(2), 635-674. https://doi.org/10.1002/cphy.c160022
43. He, L.; Su, Z.; Wang, S. The anti-obesity effects of polyphenols: A comprehensive review of molecular mechanisms and signal pathways in regulating adipocytes. Front. Nutr. 2024, 11, 1393575. https://doi.org/10.3389/fnut.2024.1393575
44. Langin, D. Adipose tissue lipolysis as a metabolic pathway to define pharmacological strategies against obesity and the metabolic syndrome. Pharmacol. Res. 2006, 53(6), 482-91. https://doi.org/10.1016/j.phrs.2006.03.009
45. Klok, M.D.; Jakobsdottir, S.; Drent, M.L. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: A review. Obes. Rev. 2007, 8(1), 21-34. https://doi.org/10.1111/j.1467-789X.2006.00270.x
46. Miller, G.D. Appetite Regulation: Hormones, peptides, and neurotransmitters and their role in obesity. Am. J. Lifest. Med. 2017, 13(6), 586-601. https://doi.org/10.1177/1559827617716376.
47. Matsuo, T.; Omori, Y.; Tomita, T.; Sadzuka, Y. Olanzapine enhances adipogenesis and suppresses lipolysis in 3T3 L1 adipocytes under low glucose and weak differentiation/maturation conditions. Exp. Ther. Med. 2022, 24(5), 647. https://doi.org/10.3892/etm.2022.11584
48. Murawska-Ciałowicz, E. Leptin—a potential bridge between fat metabolism and the brain's vulnerability to neuropsychiatric disorders: A systematic review. J. Clin. Med. 2021, 10(23), 5714. https://doi.org/10.3390/jcm10235714
49. Čolak, E.; Pap, D. The role of oxidative stress in the development of obesity and obesity-related metabolic disorders. J. Med. Biochem. 2021, 26, 40(1), 1-9. https://doi.org/10.5937/jomb0-24652