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ETHANOL LEAF EXTRACT OF *FICUS EXASPERATA* ATTENUATES CHANGES IN ELECTROLYTES AND LIPID PROFILES IN A RAT MODEL OF OLANZAPINE-INDUCED OBESITY

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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 Wistar rats, weighing between 190 and 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 study demonstrated that Ficus exasperata significantly ($P< 0.05$) increases bicarbonate and potassium while reducing sodium and calcium ($P< 0.05$). Ficus exasperata significantly ($P< 0.05$) reduces HDL with a significant ($P< 0.05$) increase in TC, TG and LDL. These findings suggest that Ficus exasperata influences both electrolyte balance and lipid metabolism in obese animals.

Keywords: *Ficus exasperata*, Electrolytes, Lipid profiles, Olanzapine-induced obesity, Ethanol leaf extract

INTRODUCTION

Obesity is a global epidemic, with its prevalence increasing dramatically over the past few decades. In 2022, approximately 890 million adults and 160 million children and adolescents were living with obesity (Okunogbe et al., 2022; Lingvay et al., 2024; NCD Risk Factor Collaboration, 2024). Olanzapine-induced obesity is a significant concern for patients treated with this atypical antipsychotic medication. Olanzapine is commonly used to manage schizophrenia, bipolar disorder, and other serious mental illnesses. However, one of the most troubling side effects is weight gain, which can lead to obesity and associated metabolic disturbances (Laguado & Saklad, 2022). The increasing prevalence of metabolic disturbances associated with the use of antipsychotic medications, such as olanzapine, poses significant health risks for 7% of patients undergoing treatment for psychiatric disorders (Chang et al., 2021; Yang et al., 2022; Yang and Wu, 2025). Obesity is often associated with dyslipidemia, characterized by elevated levels of triglycerides, low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C). Changes in lipid levels can provide insights into the success of these interventions (Hasan et al., 2020). Olanzapine, an atypical antipsychotic, is frequently prescribed for the management of schizophrenia and bipolar disorder due to its efficacy in symptom control (Narasimhan et al., 2007; Lund & Perry, 2000). However, its use is often accompanied by adverse metabolic effects, including dyslipidemia, weight gain, and electrolyte imbalances, which contribute to a heightened risk of cardiovascular diseases and diabetes (Balbão et al., 2014; Awoyemi et al., 2024).

In response to these challenges, there is growing interest in exploring natural alternatives and complementary therapies that can mitigate the side effects of pharmaceutical agents (Ekor, 2014). Ficus exasperata, commonly known as the "sandpaper tree," is a plant that has been traditionally used in various regions for its medicinal properties. Its leaves, in particular, have demonstrated potential therapeutic benefits, including anti-inflammatory, antioxidant, and hepatoprotective effects (Abotsi et al., 2010; Nworu et al., 2013; Hasnat et al., 2024). The present study focuses on the ethanol leaf extract of Ficus exasperata and its potential to modulate the metabolic alterations induced by olanzapine in female Wistar rats. Previous research has shown that Ficus exasperata leaf extract contains bioactive compounds such as flavonoids, tannins, and phenolic acids, which are known to possess significant antioxidant and lipid-lowering properties (Nworu et al., 2013; Nawaz et al., 2019). In this study, we aim to investigate the effects of Ficus exasperata on the electrolyte and lipid profiles of olanzapine-induced obese female Wistar rats. Olanzapine-induced obesity in animal models is a well-established method for studying the metabolic side effects of antipsychotic medications (Lian et al., 2014; Chen et al., 2022). By examining the changes in serum electrolyte levels (sodium, potassium, chloride, calcium) and lipid profiles (total cholesterol, triglycerides, LDL, HDL), this research seeks to determine whether Ficus exasperata leaf extract can ameliorate the metabolic disturbances caused by olanzapine treatment. The potential findings from this study could have significant implications for the development of complementary therapeutic strategies that incorporate natural products to enhance the safety and efficacy of antipsychotic medications. Understanding the mechanisms through which Ficus exasperata exerts its effects may also provide valuable insights into the broader applications of herbal medicine in managing drug-induced metabolic disorders.

MATERIALS AND METHODS

Materials

Olanzapine USP 10 mg Tablets 10mg Oral 10 tabs N05AH03 B4-7395 Drug POM Chez Resources Pharmaceutical LTD. Orlisat (A08AB01) Getz Pharma (Private) Limited. Orlistat and Olanzapine drugs were obtained from City Medics Pharmacy in Abuja, Nigeria. orlistat was sold under the trade name Xenical while Olanzapine was sold under the trade name Zyprexa.

Plants Collection

The leaves of Ficus exasperata were collected from the University of Abuja environment, Abuja, Nigeria. They were identified at the National Institute of Pharmaceutical Research and Development (NIPRD) Herbarium Abuja with voucher specimen Number (NIPRD/H/7268). The leaves were dried and blended with an electric blender into powder. It was weighed using a weighing scale (SJ- 30KWP) manufactured by Ohaus Corporation, Pine Brook, NJ USA.

Ethical Approval

Ethical approval was obtained from the University of Abuja Ethics Committee on Animal Use (UAECAU) with reference number (UAECAU/2021/0001).

Preparation of Extract

The Ficus exasperata leaf powder (40 g) was dissolved in 200 mL of ethanol and covered. After 48 hours, the mixture was filtered through a nylon sieve into a small container, and the residue was spread out in another container and allowed to dry. Re-extraction with fresh 200 mL of ethanol was conducted for 24 hours. The pooled and dried extract (19.5 g), constituting a 48.75% yield, was used for this study (Kofie et al., 2015).

Experimental Animals

For this study, thirty (30) female albino Wistar rats, weighing between 190-200 g, were utilized. The animals were obtained from the animal facility of the University of Abuja's Faculty of Veterinary Medicine. They were housed in plastic cages within the Department of Human Physiology at the University of Abuja. The rats were allowed to acclimatize to laboratory conditions for two weeks, with a temperature range of 24-28°C, relative humidity of 60-70%, and a 12-hour light-dark cycle. They were provided with access to food and water ad libitum.

Experimental Induction of Obesity

Wistar rats in the obesity-untreated group were given olanzapine (4 mg/kg) dissolved in normal saline using 2 ml disposable needles and syringes via oral gavage for 28 days. The weight and naso-anal length of the Wistar rats were measured. The body mass index (BMI) of each Wistar rat was calculated by dividing the weight of each rat by the square of the naso-anal length. Wistar rats with a BMI greater than 0.68 g/cm² were considered obese and used for the study (Novelli et al., 2007; Mutiso et al., 2014; Alptekin et al., 2024).

Experimental Design

Rats were randomly divided (Mutiso et al., 2014) into five groups of six rats each (n = 6). Group 1 served as the normal control and was given normal saline. 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. The administration was conducted orally for 28 days.

Animal Sacrifice

After 28 days of administration, the animals were sacrificed. They were anaesthetized using sodium phenobarbital (60 mg/kg) (Tobar Leitão et al., 2021). Blood samples were collected via cardiac puncture and placed in a plain serum bottle. The serum was prepared by spinning blood samples for 20 minutes at a speed of 3500 rpm using a bench centrifuge. A clear supernatant was used.

Biochemical Assessment

Electrolyte analysis was performed on serum sodium, potassium, calcium, and bicarbonate ions. The determination of sodium and potassium was carried out using photometry (Model 410 C, Sherwood Scientific Ltd, Petracourt Ltd, England). Lipid profiles, including total cholesterol (TC) and triglycerides (TG), were analyzed using an enzymatic colourimetric method with a kit (Labtest). High-density lipoprotein cholesterol (HDL-C) levels were determined using the kinetic method with the Labtest kit. Low-density lipoprotein (LDL) was estimated using the method described by Islam et al. (2021).

Statistical Analysis

The data obtained were analyzed 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.

RESULTS AND DISCUSSION

Results

Effect of Ficus exasperata and Orlistat on Serum Electrolytes

Figure 1: The serum bicarbonate level was significantly higher ($p< 0.05$) in the obese-untreated group than in the NC (1a). There was no significant difference ($p> 0.05$) in the group that was given Ficus only compared to the NC and the obese-untreated group. However, in the obese + Ficus 100 mg/kg group, serum bicarbonate was significantly ($p< 0.05$) higher compared to NC, the obese-untreated and the obese + Ficus 100 mg/kg groups. Conversely, in the group that was treated with orlistat 10 mg/kg, the serum bicarbonate level was significantly ($p< 0.05$) lower compared to all the other groups. Serum sodium (1b) was significantly increased in the obese-untreated groups compared to the NC. No significant ($p> 0.05$) change was observed in the Ficus only treated group compared to all the other groups. However, serum sodium in the obese groups treated with Ficus and orlistat was significantly ($p< 0.05$) decreased compared to the obese-untreated group. There was a non-significant decrease observed in the level of potassium in the obese-untreated group compared to NC (1c). In the non-obese group that was given Ficus only, the potassium level was significantly decreased compared to both the NC and the obese-untreated groups. In the obese groups that were given Ficus and orlistat, it was significantly ($p< 0.05$) higher compared to the Ficus-only group. Serum calcium (1d) was significantly ($p< 0.05$) reduced in the obese-untreated group compared to the NC. In the Ficus-only group, serum calcium was significantly lower compared to both the NC and the obese-untreated group. In the obese groups given Ficus 100 mg/kg and orlistat 10 mg/kg, the level of serum calcium was significantly ($p< 0.05$) reduced compared to NC and significantly ($p< 0.05$) increased compared to the obese+Ficus 100 mg/kg treated group.

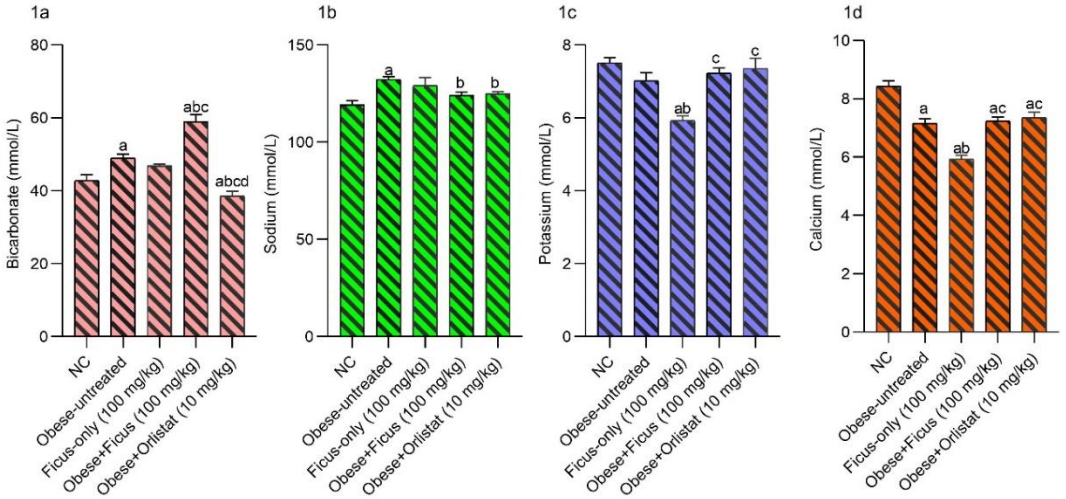

Figure 1: Results of serum bicarbonate (1a), sodium (1b), potassium (1c) and calcium (1d). NC= normal control. Superscripts a=p<0.05 vs NC; b=P<0.05 vs Obese-untreated; c=p<0.05 vs Ficus-only; d=p<0.05 vs Obese+Ficus. Data presented as Mean±SEM

Effect of Ficus exasperata and Orlistat Lipid Profile

Low-density lipoprotein (2a) was significantly (p< 0.05) raised in the obese-untreated group compared to the NC group. In the Ficus-only group and obese + Ficus 100 mg/kg, LDL was significantly (p< 0.05) reduced compared to both NC and the obese-untreated group. Serum LDL in the obese+orlistat 10 mg/kg group was significantly (p< 0.05) reduced compared to all the other groups. HDL (2b) was significantly (p< 0.05) reduced in all the treated groups compared to the NC. Administration of Ficus-only significantly reduced HDL compared to the untreated obese group. Treatment with both Ficus and orlistat significantly (p< 0.05) raised the level of HDL compared to the untreated obese group. In the orlistat 10 mg/kg treated group, HDL was significantly higher compared to all the other treated groups. The level of serum cholesterol (1c) was significantly (p< 0.05) higher in the obese-untreated group compared to the NC. No significant changes were observed in the Ficus-only 100 mg/kg group. However, in the obese group treated with Ficus 100 mg/kg, cholesterol was significantly (p< 0.05) higher compared to the NC and Ficus-only groups and lower compared to the obese-untreated group. Treatment with orlistat significantly (p< 0.05) reduced cholesterol compared to the obese-untreated group. TRIG (2d) in the obese-untreated group was significantly (p< 0.05) increased compared to NC. TRIG in all the other treated groups was significantly reduced (p< 0.05) compared to the obese-untreated group. TRIG in the obese + Ficus 100 mg/kg and orlistat 10 mg/kg was significantly (p< 0.05) higher compared to the Ficus-only group.

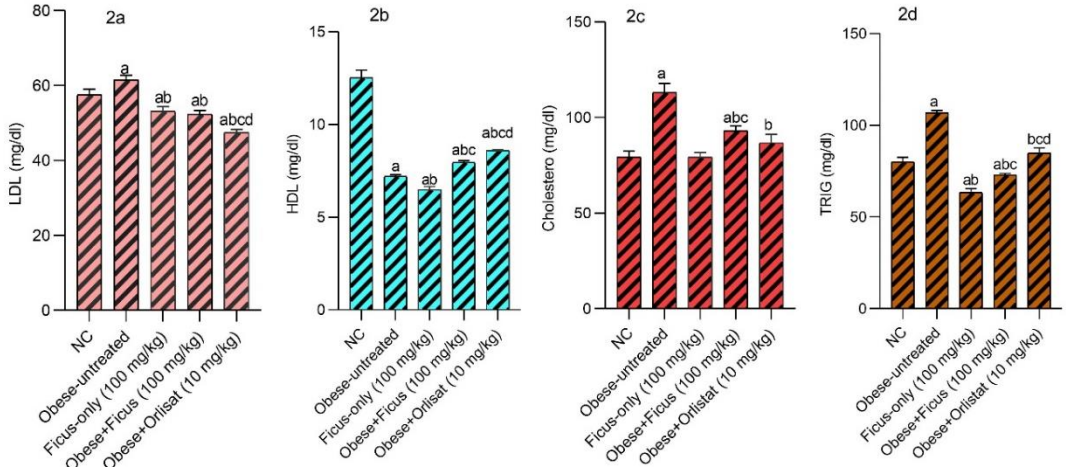

Figure 2: Results of serum LDL (2a), HDL (2b), Cholesterol (2c) and TRIG (2d). NC= normal control; TRIG= triglyceride. Superscripts a=p<0.05 vs NC; b=P<0.05 vs Obese-untreated; c=p<0.05 vs Ficus-only; d=p<0.05 vs Obese+Ficus

Discussion

The study shows that serum bicarbonate levels (Figure 1a) were significantly higher in the obese-untreated group compared to the normal control (NC) group. This aligns with previous research indicating that obesity is often associated with metabolic acidosis, which can elevate serum bicarbonate levels (Bingol et al., 2015). The administration of Ficus exasperata extract (100 mg/kg) further increased serum bicarbonate levels, suggesting a potential buffering effect of the extract. Some plant extracts contain alkaline substances that can neutralize excess acid in the bloodstream, thereby increasing bicarbonate levels (Noce et al., 2021).

The extracts may contain electrolytes like potassium and sodium, which play a role in maintaining acid-base balance. These electrolytes help regulate bicarbonate levels in the blood (Nagami & Kraut, 2024). Furthermore, certain

phytochemicals in extracts can influence metabolic pathways, leading to increased production or retention of bicarbonate (Park, 2023). Extracts that support kidney function can enhance the kidneys' ability to reabsorb bicarbonate and excrete hydrogen ions, thus increasing blood bicarbonate levels (Kuhn et al., 2024). Conversely, orlistat treatment reduced serum bicarbonate levels, which may be due to its impact on fat metabolism and subsequent reduction in acid load (Xie et al., 2024). During fat metabolism, the body produces ketone bodies (acetoacetate, β-hydroxybutyrate, and acetone), which can be converted to bicarbonate in the liver and released into the bloodstream, increasing blood bicarbonate levels (Kolb et al., 2021). Fat metabolism can also lead to the production of organic acids, such as fatty acids and their derivatives. These acids may contribute to metabolic acidosis if not properly buffered. The body compensates by increasing bicarbonate production to neutralize excess acids, thus raising blood bicarbonate levels (Suburu et al., 2013). The kidneys play a crucial role in maintaining acid-base balance. During fat metabolism, increased production of acids can lead to metabolic acidosis, prompting the kidneys to retain bicarbonate and excrete hydrogen ions to maintain pH balance (Hamm et al., 2015).

The study found that serum sodium (Figure 1b) levels were significantly increased in the obese-untreated group compared to the NC group. This is consistent with the literature, which suggests that obesity can lead to alterations in sodium balance and fluid retention (Wójcik & Kozioł-Kozakowska, 2021). Treatment with Ficus exasperata and orlistat both resulted in decreased serum sodium levels, indicating their potential role in modulating sodium homeostasis. Some plant extracts have diuretic properties, promoting the excretion of sodium through urine. For example, extracts from plants like Hibiscus sabdariffa and Allium sativum have been shown to reduce blood pressure by increasing sodium excretion (Ellis et al., 2022).

Plant extracts can influence renal function, enhancing the kidneys' ability to excrete sodium and thus reducing blood sodium levels (Musabayane, 2012). Obesity is often associated with inflammation, which can affect sodium balance. Plant extracts with anti-inflammatory properties, such as those containing flavonoids and polyphenols, may help reduce inflammation and subsequently lower sodium levels (Mahboob et al., 2023). It is also possible that the extract in this study reduced serum sodium via its action on aldosterone (Umaru et al., 2022).

A non-significant decrease in potassium levels in the obese-untreated group compared to the NC group was observed in this study. However, the significant decrease in potassium levels in the non-obese group treated with Ficus suggests that the extract may have a diuretic effect, leading to potassium loss. The phytochemicals in the extract, such as flavonoids and tannins, can affect electrolyte balance, leading to reduced potassium levels (Ghai et al., 2023). However, the increase in potassium levels in the obese groups treated with Ficus and orlistat could be due to compensatory mechanisms to maintain electrolyte balance. Obesity is often associated with inflammation, which can affect potassium balance. Plant extracts with anti-inflammatory properties can help reduce inflammation and improve potassium retention (Ellulu et al., 2017).

The study shows a significant reduction in serum calcium levels in the obese-untreated group compared to the NC group. Obesity has been shown to affect calcium metabolism and bone health (Shapses & Sukumar, 2012). Obesity is often associated with lower levels of vitamin D, which is crucial for calcium absorption. Reduced vitamin D levels can lead to decreased calcium absorption from the diet (Harahap et al., 2022). Obesity can alter the levels of hormones that regulate calcium metabolism, such as parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D. Elevated PTH levels can lead to increased calcium release from bones, potentially reducing bone density (Villarroel et al., 2014).

In the non-obese group, Ficus reduced serum calcium levels, suggesting that the extract might cause a reduction in PTH or increased calcitonin. The further reduction in serum calcium levels with Ficus treatment suggests that the extract may interfere with calcium absorption or metabolism. Some extracts contain compounds that inhibit osteoclast activity, which are cells responsible for breaking down bone tissue and releasing calcium into the bloodstream. By reducing osteoclast activity, these extracts can lower serum calcium levels (Wang et al., 2020). Orlistat treatment, on the other hand, resulted in increased serum calcium levels, possibly due to its effects on fat-soluble vitamin absorption and metabolism.

Obesity is often associated with insulin resistance, which can lead to higher LDL levels. Insulin resistance affects how the body processes fats and cholesterol. Chronic inflammation, which is common in obesity, can contribute to higher LDL levels. Inflammatory markers can alter lipid metabolism, leading to increased LDL (Manna & Jain, 2015). Obesity can also affect the balance of hormones that regulate lipid metabolism, such as leptin and adiponectin, leading to higher LDL levels (Akinloye & Ugbaja, 2022). Ficus exasperata contains bioactive compounds with antioxidant properties, such as phenolic acids and flavonoids, which can prevent the oxidation of LDL. This is in concert with other studies (Adeyi et al., 2012; Omolola & Bukoye, 2019).

The observed increase in HDL in the present study with Ficus exasperata treatment is consistent with the reports of George et al. (2023), which showed increased HDL with Ficus Carica, belonging to the same genus as Ficus exasperata. In obese conditions, high-density lipoprotein (HDL) levels are often reduced, a condition known as low HDL cholesterol (HDL-C). This reduction in HDL is a key component of the dyslipidemia associated with obesity and increases the risk of cardiovascular disease (Zhang et al., 2019). Obesity leads to changes in the morphology and function of adipose tissue, which affects HDL metabolism. Adipose tissue secretes various adipokines that influence lipid metabolism, including HDL levels. In obesity, the secretion of anti-inflammatory adipokines is reduced, while pro-inflammatory adipokines are elevated, contributing to lower HDL levels (Longo et al., 2019).

Obesity is also associated with an overproduction of free fatty acids (FFAs) due to increased lipolysis in adipose tissue. Elevated FFAs lead to the production of triglyceride-rich lipoproteins, which negatively impact HDL levels. HDL plays a crucial role in reverse cholesterol transport, a process where cholesterol is transported from peripheral tissues to the liver for excretion. Obesity can impair this process, reducing cholesterol efflux efficiency and leading to lower HDL levels (Marques *et al*., 2018). These mechanisms likely explain the changes in HDL observed in the obese-untreated group in the present study.

Treatment with Ficus exasperata extract significantly increased HDL relative to the obese-untreated group. Polyphenols modulate lipid metabolism by increasing the expression of genes involved in fatty acid oxidation and reducing the expression of genes involved in lipogenesis, leading to improved HDL levels (Ma *et al*., 2020). Polyphenols also enhance cholesterol efflux, the process by which cholesterol is transported from peripheral tissues to the

liver for excretion, a mechanism that could explain the *Ficus* extract's effect on HDL levels (Berrougui *et al*., 2015).

Olanzapine treatment has been shown to activate lipogenic gene expression in the liver, upregulating genes such as fatty acid synthase and acetyl-CoA carboxylase, which are involved in fatty acid and cholesterol synthesis (Chen *et al*., 2022; Zhu *et al*., 2022). This is consistent with the effect of olanzapine treatment observed in the obese-untreated group in this study. Olanzapine can also modulate adipose tissue accumulation and lipid metabolism via hepatic muscarinic M3 receptor-mediated signaling, leading to increased fat mass and abnormal lipid metabolism (Su *et al*., 2024).

The Ficus exasperata extract in this study significantly reduced serum cholesterol levels (Figure 2c) compared to the obese-untreated group. The extract may contain sterols and stanols that inhibit cholesterol absorption in the intestines, leading to lower serum cholesterol levels (Nguyen, 1999; Oyewole *et al*., 2013). Additionally, the extract may modulate lipid metabolism by downregulating genes involved in fatty acid synthesis while increasing the activity of enzymes involved in fatty acid oxidation, further reducing serum cholesterol levels (Tang *et al*., 2013).

Serum triglyceride levels were significantly higher (Figure 2d) in the obese-untreated group in this study. Olanzapine treatment has been shown to upregulate genes involved in lipogenesis, such as fatty acid synthase and acetyl-CoA carboxylase, leading to increased fatty acid and triglyceride synthesis in the liver (Coccurello *et al*., 2006; Huang *et al*., 2024). Chronic administration of olanzapine can induce insulin resistance, resulting in hyperinsulinemia. Insulin resistance and hyperinsulinemia promote triglyceride synthesis and storage in adipose tissue and the liver (Li *et al*., 2019).

Treatment with Ficus extract reduced serum triglyceride levels in this study. The extract may modulate lipid metabolism by increasing the activity of enzymes involved in fatty acid oxidation while reducing the expression of genes involved in lipogenesis, effectively lowering triglyceride synthesis and accumulation (Park & Han, 2018). Phenolic compounds and flavonoids in the extract have strong antioxidant properties that prevent lipid oxidation and improve lipid profiles, including reducing triglyceride levels (Dai & Mumper, 2010). Furthermore, the extract may contain compounds that inhibit lipid absorption in the intestines, contributing to lower serum triglyceride levels (Koo & Noh, 2007). By enhancing insulin sensitivity, the extract may help regulate lipid metabolism and reduce triglyceride levels in the bloodstream (Qin *et al*., 2010).

In this study, Orlistat compared to Ficus exasperata was effective in correcting sodium imbalance caused by obesity, possibly by improving renal function or reducing sodium loss (Bruijn *et al*., 2024). The elevated bicarbonate in the group given Orlistat may indicate improved acid-base balance, which is often disrupted in obesity-related metabolic dysfunction (Alexander *et al.,* 2023). Orlistat helped restore calcium levels to normal, avoiding potential hypercalcemia, and it did not worsen potassium imbalance compared to Ficus (Mathus-Vliegen et al., 2012). Orlistat inhibits gastrointestinal lipases, reducing fat absorption. This leads to weight loss and improved metabolic profiles, which can positively affect electrolyte balance (Ruban *et al*., 2020). By reducing fat accumulation, Orlistat may alleviate pressure on organs like the kidneys and liver, improving their ability to regulate electrolytes. Orlistat consistently brought values closer to or slightly above normal across all parameters, indicating a balanced therapeutic effect.

CONCLUSION

The observed effects of Ficus exasperata on cholesterol, triglyceride levels, and electrolyte balance in the present study suggest it may offer a natural therapeutic avenue for improving lipid profiles and mitigating cardiovascular risk in obesity-related conditions. Future research involving larger, more diverse populations and extended periods is necessary to validate these preliminary findings.

REFERENCES

Abotsi, W. M., Woode, E., Ainooson, G. K., Amo-Barimah, A. K., & Boakye-Gyasi, E. (2010). Antiarthritic and antioxidant effects of the leaf extract of *Ficus exasperata* P. Beauv. (Moraceae). *Pharmacognosy Research, 2*(2), 89–97. https://doi.org/10.4103/0974-8490.62958

Alexander, S. P. H., Fabbro, D., Kelly, E., Mathie, A. A., Peters, J. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Davies, J. A., Annett, S., Boison, D., Burns, K. E., Dessauer, C., Gertsch, J., Helsby, N. A., Izzo, A. A., Ostrom, R., Papapetropoulos, A., ... Wong, S. S. (2023). The concise guide to PHARMACOLOGY 2023/24: Enzymes. *British Journal of Pharmacology, 180*(S2). https://doi.org/10.1111/bph.16181

Alptekin, İ. M., Çakıroğlu, F. P., Reçber, T., & Nemutlu, E. (2024). Inulin may prevent the high-fat diet induced-obesity via suppressing endocannabinoid system in the prefrontal cortex in Wistar rats. *International Journal of Food Sciences and Nutrition, 75*(8), 800–811. https://doi.org/10.1080/09637486.2024.2408545

Awoyemi, T., Guzman, R. B., & Naveed, A. (2024). Olanzapine-induced cardiomyopathy: A mimicker of obesity cardiomyopathy? *Clinical Cardiology, 47*(5), e24278.

Balbão, M. S., Hallak, J. E. C., Nunes, E. A., Triffoni-Melo, T., Ferreira, S., Chaves, C., Durão, A. M. S., Ramos, A. P. P., Crippa, S., & Costa Queiroz, R. H. (2014). Olanzapine, weight change and metabolic effects: A naturalistic 12-month follow-up. *Therapeutic Advances in Psychopharmacology, 4*(1), 30. https://doi.org/10.1177/2045125313507738

Bingol, Z., Pıhtılı, A., Cagatay, P., Okumus, G., & Kıyan, E. (2015). Clinical predictors of obesity hypoventilation syndrome in obese subjects with obstructive sleep apnea. *Respiratory Care, 60*(5), 666–672. https://doi.org/10.4187/respcare.03733

Bruijn, N., Van Lohuizen, R., Boron, M., Fitzek, M., Gabriele, F., Giuliani, G., Melgarejo, L., Řehulka, P., Sebastianelli, G., Triller, P., Vigneri, S., Özcan, B., & Van Den Brink, A. M. (2024). Influence of metabolic state and body composition on the action of pharmacological treatment of migraine. *The Journal of Headache and Pain, 25*(1). https://doi.org/10.1186/s10194-024-01724-3

Chang, C., Goh, K. K., & Lu, L. (2021). Metabolic disturbances associated with antipsychotic drug treatment in patients with schizophrenia: State-of-the-art and future perspectives. *World Journal of Psychiatry, 11*(10), 696. https://doi.org/10.5498/wjp.v11.i10.696

Chen, C., Nakano, T., Hsu, W., Chu, C. Y., & Huang, T. (2022). Early lipid metabolic effects of the anti-psychotic drug olanzapine on weight gain and associated gene

expression. *Neuropsychiatric Disease and Treatment, 18*, 645. https://doi.org/10.2147/NDT.S345046

Ekor, M. (2014). The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in Pharmacology, 4*, 177. https://doi.org/10.3389/fphar.2013.00177

Ellis, L. R., Zulfiqar, S., Holmes, M., Marshall, L., Dye, L., & Boesch, C. (2022). A systematic review and meta-analysis of the effects of *Hibiscus sabdariffa* on blood pressure and cardiometabolic markers. *Nutrition Reviews, 80*(6), 1723. https://doi.org/10.1093/nutrit/nuab104

Ellulu, M. S., Patimah, I., Khaza'ai, H., Rahmat, A., & Abed, Y. (2017). Obesity and inflammation: The linking mechanism and the complications. *Archives of Medical Science, 13*(4), 851–863. https://doi.org/10.5114/aoms.2016.58928

George, T. T., Oyenihi, A. B., Oyenihi, O. R., & Obilana, A. O. (2023). Composition and health-promoting effects of fig (*Ficus carica*) extracts. In *Fig (Ficus carica): Production, processing, and properties* (pp. 561–578). Springer. https://doi.org/10.1007/978-3-031-16493-4_25

Ghai, R., Chaudhary, S., Nagarajan, K., Goel, R., et al. (2023). An investigative study of medicinal herbs for anti-obesity potential. *Oriental Journal of Chemistry, 39*. https://doi.org/10.13005/ojc/390605

Hamm, L. L., Nakhoul, N., & Hering-Smith, K. S. (2015). Acid-base homeostasis. *Clinical Journal of the American Society of Nephrology, 10*(12), 2232–2242. https://doi.org/10.2215/CJN.07400715

Harahap, I. A., Landrier, J. F., & Suliburska, J. (2022). Interrelationship between Vitamin D and Calcium in obesity and its comorbid conditions. *Nutrients, 14*(15), 3187. https://doi.org/10.3390/nu14153187

Hasan, B., Nayfeh, T., Alzuabi, M., Wang, Z., Kuchkuntla, A. R., Prokop, L. J., Newman, C. B., Murad, M. H., & Rajjo, T. I. (2020). Weight loss and serum lipids in overweight and obese adults: A systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism, 105*(12), dgaa673. https://doi.org/10.1210/clinem/dgaa673

Hasnat, H., Alam, S., Shompa, S. A., et al. (2024). Phyto-pharmacological wonders of genus *Ficus*: Ethnopharmacological insights and phytochemical treasures from natural products. *Saudi Pharmaceutical Journal.* https://doi.org/10.1016/j.jsps.2024.102211

Islam, S. U., Ahmed, M. B., Ahsan, H., & Lee, Y. S. (2021). Recent molecular mechanisms and beneficial effects of phytochemicals and plant-based whole foods in reducing LDL-C and preventing cardiovascular disease. *Antioxidants (Basel), 10*(5), 784. https://doi.org/10.3390/antiox10050784

Kofie, W., Osman, H., & Bekoe, S. O. (2015). Phytochemical properties of extracts and isolated fractions of leaves and stem bark of *Ficus exasperata*. *World Journal of Pharmacy and Pharmaceutical Sciences, 4*.

Kolb, H., Kempf, K., & Röhling, M. (2021). Ketone bodies: From enemy to friend and guardian angel. *BMC Medicine, 19*, 313. https://doi.org/10.1186/s12916-021-02185-0

Kuhn, C., Mohebbi, N., & Ritter, A. (2024). Metabolic acidosis in chronic kidney disease: Mere consequence or also culprit? *Pflügers Archiv - European Journal of Physiology, 476*, 579–592. https://doi.org/10.1007/s00424-024-02912-5

Laguado, S. A., & Saklad, S. R. (2022). Opioid antagonists to prevent olanzapine-induced weight gain: A systematic review. *Mental Health Clinician, 12*(4), 254–262. https://doi.org/10.9740/mhc.2022.08.254

Lian, J., Huang, F., Pai, N., & Deng, C. (2014). Preventing olanzapine-induced weight gain using betahistine: A study in a rat model with chronic olanzapine treatment. *PLOS ONE, 9*(8), e104160. https://doi.org/10.1371/journal.pone.0104160

Lingvay, I., Cohen, R. V., le Roux, C. W., & Sumithran, P. (2024). Obesity in adults. *The Lancet, 404*(10456), 972–987.
Lund, B. C., & Perry, P. J. (2000). Olanzapine: An atypical antipsychotic for schizophrenia. *Expert Opinion on Pharmacotherapy, 1*(2), 305–323. https://doi.org/10.1517/14656566.1.2.305

Mahboob, A., Samuel, S. M., Mohamed, A., Wani, M. Y., et al. (2023). Role of flavonoids in controlling obesity: Molecular targets and mechanisms. *Frontiers in Nutrition, 10*, 1177897. https://doi.org/10.3389/fnut.2023.1177897

Mathus-Vliegen, L., Toouli, J., Fried, M., Khan, A. G., Garisch, J., Hunt, R., Fedail, S., Štimac, D., Lemair, T., Krabshuis, J., Kaufmann, P., Roberts, E., & Riccardi, G. (2012). World Gastroenterology Organisation global guidelines on obesity. *Journal of Clinical Gastroenterology, 46*(7), 555–561. https://doi.org/10.1097/mcg.0b013e318259bd04

Musabayane, C. T. (2012). The effects of medicinal plants on renal function and blood pressure in diabetes mellitus. *Cardiovascular Journal of Africa, 23*(8), 462–468. https://doi.org/10.5830/CVJA-2012-025

Mutiso, S. K., Rono, D. K., & Bukachi, F. (2014). Relationship between anthropometric measures and early electrocardiographic changes in obese rats. *BMC Research Notes, 7*, 931. https://doi.org/10.1186/1756-0500-7-931

Nagami, G. T., & Kraut, J. A. (2024). The role of the endocrine system in the regulation of acid–base balance by the kidney and the progression of chronic kidney disease. *International Journal of Molecular Sciences, 25*(4), 2420. https://doi.org/10.3390/ijms25042420

Narasimhan, M., Bruce, T. O., & Masand, P. (2007). Review of olanzapine in the management of bipolar disorders. *Neuropsychiatric Disease and Treatment, 3*(5), 579. https://pmc.ncbi.nlm.nih.gov/articles/PMC2656294

Nawaz, H., Waheed, R., & Nawaz, M. (2020). Phytochemical composition, antioxidant potential, and medicinal significance of ficus. In *IntechOpen eBooks*. https://doi.org/10.5772/intechopen.86562

NCD Risk Factor Collaboration (NCD-RisC). (2024). Worldwide trends in underweight and obesity from 1990 to 2022: A pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *The Lancet, 403*(10431), 1027–1050.

Noce, A., Marrone, G., Jones, G. W., Lauro, M. D., Zaitseva, A. P., Ramadori, L., Celotto, R., Mitterhofer, A. P., & Daniele, N. D. (2021). Nutritional approaches for the management of metabolic acidosis in chronic kidney disease. *Nutrients, 13*(8), 2534. https://doi.org/10.3390/nu13082534

Novelli, E. L. B., Diniz, Y. S., Galhardi, C. M., Ebaid, G. M. X., Rodrigues, H. G., Mani, F., Fernandes, A. A. H., Cicogna, A. C., & Novelli Filho, J. L. V. B. (2007). Anthropometrical parameters and markers of obesity in rats. *Laboratory Animals, 41*(1), 111–119. https://doi.org/10.1258/002367707779399518

Nworu, C. S., Nwuke, H. C., Akah, P. A., Okoye, F. B., & Esimone, C. O. (2013). Extracts of *Ficus exasperata* leaf inhibit topical and systemic inflammation in rodents and suppress LPS-induced expression of mediators of inflammation in macrophages. *Journal of Immunotoxicology, 10*(3), 302–310. https://doi.org/10.3109/1547691X.2012.732121

Okunogbe, A., Nugent, R., Spencer, G., Powis, J., Ralston, J., & Wilding, J. (2022). Economic impacts of overweight and obesity: Current and future estimates for 161 countries. *BMJ Global Health, 7*(9), e009773. https://doi.org/10.1136/bmjgh-2022-009773

Park, K. (2023). The role of dietary phytochemicals: Evidence from epidemiological studies. *Nutrients, 15*(6), 1371. https://doi.org/10.3390/nu15061371

Ruban, A., Glaysher, M. A., Miras, A. D., Goldstone, A. P., Prechtl, C. G., Johnson, N., Li, J., Aldhwayan, M., Aldubaikhi, G., Glover, B., Lord, J., Onyimadu, O., Falaschetti, E., Klimowska-Nassar, N., Ashrafian, H., Byrne, J., & Teare, J. P. (2020). A duodenal sleeve bypass device added to intensive medical therapy for obesity with type 2 diabetes: A RCT. *Efficacy and Mechanism Evaluation, 7*(6), 1–130. https://doi.org/10.3310/eme07060

Shapses, S. A., & Sukumar, D. (2012). Bone metabolism in obesity and weight loss. *Annual Review of Nutrition, 32*, 287–309. https://doi.org/10.1146/annurev.nutr.012809.104655

Suburu, J., Gu, Z., Chen, H., Chen, W., Zhang, H., Chen, Y. Q. (2013). Fatty acid metabolism: Implications for diet, genetic variation, and disease. *Food Bioscience, 4*, 1–12. https://doi.org/10.1016/j.fbio.2013.07.003

Tobar Leitão, S. A., Soares, D. D. S., Carvas Junior, N., Zimmer, R., Ludwig, N. F., & Andrades, M. (2021). Study of anesthetics for euthanasia in rats and mice: A systematic review and meta-analysis on the impact upon biological outcomes (SAFE-RM). *Life Sciences, 284*, 119916. https://doi.org/10.1016/j.lfs.2021.119916

Umaru, I. J., Samuel, O. S., Kerenhappuch, I. U., Yakub, O. E., et al. (2022). Hypertension and plant extract as a solution. *Clinical Cardiovascular Research, 1*(1). https://doi.org/10.58489/2836-5917/004

Wójcik, M., & Kozioł-Kozakowska, A. (2021). Obesity, sodium homeostasis, and arterial hypertension in children and adolescents. *Nutrients, 13*(11), 4032. https://doi.org/10.3390/nu13114032

Xie, P., Shao, T., & Long, Y. (2024). Orlistat for the treatment of antipsychotic-induced weight gain: An eight-week multicenter, randomized, placebo-controlled, double-blind trial. *Lipids in Health and Disease, 23*(225). https://doi.org/10.1186/s12944-024-02214-w

Yang, Y., & Wu, R. (2025). Atypical antipsychotic drugs cause abnormal glucose and lipid metabolism independent of weight gain. *European Archives of Psychiatry and Clinical Neuroscience, 275*, 619–627. https://doi.org/10.1007/s00406-025-01965-6

Yang, Y., Xie, P., & Long, Y. (2022). Previous exposure to antipsychotic drug treatment is an effective predictor of metabolic disturbances experienced with current antipsychotic drug treatments. *BMC Psychiatry, 22*(210). https://doi.org/10.1186/s12888-022-03853-y