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Research Paper

Hypolipidemic and Adipose-reducing Effects of Ethanolic Extract of *Ziziphus Talanai* (Blanco) Merr. in Monosodium Glutamate-Induced Obese Female Albino Rats

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Abstract

Obesity is a global health-related risk factor associated with metabolic disorders characterized by excessive fat accumulation and high lipid serum profile. One major factor contributing to obesity is the chronic consumption of monosodium glutamate (MSG). Generally, this study aimed to evaluate the hypolipidemic and anti-adipogenic effects of Ziziphus talanai ethanolic leaf extract (ZTELE) in MSG-induced obesity in female albino rats. A total of twelve (12) female albino rats were used in the study and divided into four treatment groups: T (distilled water), T+ (simvastatin), T1 (400 mg/kg ZTELE), and T2 (800 mg/kg ZTELE). Before treatment, rats were fed a high-fat diet and MSG for 1 month to induce obesity. Significant reductions in body weight, intrascapular and visceral fats, and selected lipid serum profiles (total cholesterol, high-density lipoproteins, low-density lipoproteins) were observed in the ZTELE-treated groups (T1 and T2), with comparable results to those of simvastatin-treated (T+). Phytochemicals, such as flavonoids, saponins, and tannins, influence metabolic pathways by their antioxidative potential, inhibition of lipid synthesis, and regulation of fat cell differentiation. In conclusion, ZTELE is a promising natural therapeutic agent for managing obesity by regulating fat accumulation and lipid metabolism.

Keywords: *anti-adipogenic, hypolipidemic, monosodium glutamate, obesity, Ziziphus talanai*

INTRODUCTION

Obesity is a global epidemic characterized by excessive fat deposits and is associated with impaired and significant health risks, including but not limited to diabetes and cardiovascular diseases. These conditions are characterized by lipid metabolism problems in which the liver plays a crucial role. In the Philippines, liver disease remains prevalent, and the number of cases continues to rise, emerging as a significant public health issue. Traditional pharmacological treatments are widely used for lipid regulation. This includes the use of statins. However, long-term use is often associated with adverse effects (Bonfim et al. 2015), increasing interest in natural alternatives with lipid-lowering and adipose-reducing properties.

Plants are extensively used in medicinal studies to treat various diseases associated with their phytochemical properties. The use of medicinal plants, along with the exploration of bioactive compounds in endemic plant species, has provided insights into the scientific community. One such plant is the *Ziziphus talanai* (Blanco) Merr. *Z. talanai* is a Philippine endemic plant belonging to the Rhamnaceae family. The study was conducted and confirmed to exhibit anti-necrotic potential (Yamauchi et al., 2023). Numerous studies have been conducted on related species, such as *Z. jujuba* (Mostafa & Labban, 2013) and *Z. mauritiana* (Abubakar et al. 2018), highlighting their potential to regulate lipid profiles and inhibit adipogenesis. Despite extensive research on *Ziziphus* species, few

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studies have investigated the lipid-lowering and adipose-reducing effects of *Z. talanai*, particularly in the context of obesity induced by monosodium glutamate (MSG).

Meanwhile, MSG, a salt form of glutamic acid, is commonly used as a food additive to enhance and add a unique flavor (Quines et al., 2014). However, there are concerns about its chronic administration, which leads to metabolic syndrome and is linked to obesity in experimental animal models (Collison et al. 2012). MSG-induced obesity can be characterized by a high lipid profile and adipose tissue accumulation, mimicking the pathophysiology observed in human obesity. Therefore, the identification of natural products that can mitigate MSG-induced lipid and fat accumulation remains an active research area.

This study aimed to evaluate the hypolipidemic and anti-adipogenic effects of *Z. talanai* ethanolic leaf extract (ZTELE) in MSG-induced obesity in female albino rats. Specifically, this study aimed to assess the weight of adipose tissue (intrascapular and visceral fats) and to measure serum lipid profiles to evaluate ZTELE as a natural therapeutic agent for obesity management and intervention for lipid metabolism disorders.

RESEARCH METHOD

Plant procurement and preparation

Z. talanai was collected from Xevera, Tabun, Mabalacat City, Pampanga, Philippines. We assessed the plant specimen for plant authentication at Jose Vera Santos Memorial Herbarium, Institute of Biology, College of Science, University of the Philippines, Diliman, Quezon City, Philippines. The expert confirmed and labeled the specimen as *Ziziphus talanai* (Blanco) Merr.

Leaf Extract Preparation

A total of two (2) kilograms of mature leaves were used in this study. The washed leaves were maintained at room temperature within one (1) week for air drying. The dried leaves were subjected to homogenization to generate pulverized leaves. Technical grade ethanol was used for three (3) days of soaking, with a 1:4 ratio (Hussain et al., 2014). The solution evaporated at Adamson University, Ermita, Manila, Philippines. The extract was lyophilized until the last day of administration (Oyedeji et al., 2013). Stock solutions of 400mg/kg and 800mg/kg extract were prepared at the Biology Laboratory, Mabalacat City College, Mabalacat City, Pampanga, Philippines.

Animal Model

Animal handling protocols and animal ethics were guided by the Handling Methods of Laboratory Mice and Rats, 1st Edition, and Recommendations of the Philippine Association for Laboratory Animal Sciences (PALAS). This study used 12 (12) female Albino rats to evaluate the effect of ZTELE on lipid profile and visceral fat content. The rats were procured from the University of the Philippines, Manila, Philippines, and were aged 6–8 weeks. All rats were acclimatized for two (2) weeks before the induction of a high-fat diet. The animals were kept in modified animal cages with a dimension of 0.5m x 0.5m x 0.5m, purchased at department stores Hypermarket Dau, Mabalacat City, Pampanga, Philippines. In addition, commercial rodent pellets named Integra 3000" were fed to the rats as a source of nutrition and water *ad libitum*. The composition of the high-fat diet was homogenized Integra 3000 (47%), cholesterol (2%), sodium cholate (1%), dextrose (40%), olive oil (10%), and water (15%). Subsequently, a high-fat diet was introduced to the animal model after the acclimatization period for 1 month to induce obesity and irregularities in lipid profile levels. Animals were maintained in an ideal environment at the Biological Laboratory, Mabalacat City College, Dolores, Mabalacat City, Pampanga, Philippines, with a 12/12 h light/dark cycle (Nolasco et al., 2023; Yamauchi et al., 2023).

Treatment groups

Several treatment groups were established to study the hypolipidemic effects of *Z. talana*i ethanolic leaf extract (ZTELE). Obese albino rats were fed a high-fat diet. This study employed a complete randomized design to assess the regulation of various lipid parameters and visceral fat in rats. The treatment groups are comprehensively described in Table 1.

Table 1. Treatment groups of MSG-induced obese female albino rats

Treatment groups		Description
Treatment symbol	**Treatment name**	
T-	Negative control	Rats received distilled water via oral gavage at a dose of 1 mL/kg body weight (b.w.).
T+	Positive control	Rats were administered simvastatin at 2 mg/100 g b.w. via oral gavage.
T1	400 mg/kg	Rats were treated with ethanolic leaf extract of *Ziziphus talanai* at 400 mg/1000 g b.w. via oral gavage.
T2	800 mg/kg	Rats were treated with ethanolic leaf extract of *Ziziphus talanai* at 800 mg/1000 g b.w. via oral gavage.

Preparation of chemicals and treatment administration

A total of 50 g of monosodium glutamate (MSG) was used in this study. The dosage of 9000mg/kg of MSG was converted to 1.35g/150g b.w. and further diluted to 1.5 mL/20 g (Erhirhie et al., 2014). The solution was administered to the rats via intragastric gavage for 14 days to induce elevation of lipid profile and adipose tissue levels.

Simvastatin (100 mg) was purchased from A.R.A Drugstore, Fiesta, Tabun, Mabalacat, Pampanga. The resulting solution was pulverized and mixed with 20 ml of distilled water. Oral administration was via gavage at a dose of 2 mg/100 g b.w. for 14 days (Biswas et al., 2014; Zhang et al., 2011; Erhirhie et al., 2014).

The obese rats were administered distilled water, simvastatin, and ethanolic leaf extract between 7 a.m. and 11 a.m. before food refilling (Nolasco et al., 2023). Rat weights were assessed weekly to obtain accurate chemical dosages. The dosage was adjusted proportionally to each rat's body weight. After the final administration on the 14th day, all rats were fasted for 24 h prior to euthanasia. On the 15th day, necropsy was performed. Fats and blood samples were collected for adipose and lipid profiling (Hagihara et al., 2009; Erhirhie et al., 2014).

Visceral and interscapular fat extraction

All rats were euthanized 24 h after the final administration of distilled water, simvastatin, and ethanolic leaf extract. Visceral white fats and subcutaneous (interscapular) fats were collected and weighed (Scudamore, 2014; Berry et al., 2013) using a digital weight scale.

Extraction of Blood

The rats were fasted for 10 h before blood collection via open-cardiac puncture. Euthanasia was performed via cervical dislocation, and blood was extracted using a 3-cc syringe. The collected blood samples were centrifuged at 4000 rpm for 15 min to separate the serum. Serum samples were sent to Hi-Precision Diagnostics laboratory in Angeles City for lipid profiling following the protocols adopted by Parasuraman et al. (2010) and Scudamore (2014).

Statistical Analysis

Data collected in the experiment are presented as mean ± standard deviation. Group comparisons among treatments, including body weight and adipose fat, were evaluated using a parametric test of the paired t-test one-way Analysis of Variance (ANOVA) followed by a *post-hoc* analysis of Tukey's multiple comparison test, respectively. Statistical significance was set at $p< 0.05$ and was conducted using GraphPad Prism.

FINDINGS AND DISCUSSION

Body weight of female albino rats

Table 2 summarizes the mean body weights of the rats across the established treatment groups during the 2-week observation period. In the negative control group (T-), body weight remained stable from 154.0 g in Week 0 to 153.7 g by Week 2. In the simvastatin-treated group (T+), the weight decreased from 192.0 g in Week 0 to 151.3 g in Week 2. For the T1 (400mg/kg ZTELE), body weight decreased from 186.0 g to 145.7 g, and in T2 (800 mg/kg ZTELE), weight decreased from 172.3 g to 143.0 g by Week 2.

Table 2. Mean body weight of rats in different treatment groups over a 2-week observation period

Treatment		Week 0 (g)	Week 1 (g)	Week 2 (g)
Symbol	Name			
T-	Negative control	154.0±8	154.0±9	153.7±8
T+	Positive control	192.3±12	171±5	151.3±4*
T1	400 mg/kg ZTELE	186.0±11	160.7±5	145.7±9*
T2	800 mg/kg ZTELE	172.3±16	151±11	143.0±3*

* Significant difference between Weeks 0 and Week 2 ($p<0.05$)

Statistical treatment showed no significant change in T- ($p=0.9982$). Meanwhile, T+ showed significant weight reduction ($p=0.0051$). Notably, significant declines in body weight were observed in the ZTELE-treated groups of T1 ($p=0.0020$) and T2 ($p=0.0323$). The changes in body weight across treatments are illustrated in a line graph (refer to Figure 1). Suneetha et al. (2013) reported that water alone did not induce obesity in rats, which is consistent with the findings of this study. Similarly, Banda et al. (2013) observed the same results, further supporting the aforementioned observations. Meanwhile, the simvastatin-treated group was consistent with the findings of Al-Rasheed et al. (2017), who highlighted the antioxidative potential of simvastatin in diabetic rats, suggesting that it can suppress oxidative stress caused by MSG-induced metabolic syndrome. Bonfim et al. (2015) reported that weight loss accounted for the inhibitory effect of simvastatin on the enzyme of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. The significant reductions in body weight observed in the ZTELE-treated groups at 400 mg/kg and 800 mg/kg were attributed to the extract's antioxidant properties. This treatment may suppress MSG-induced oxidative stress linked to metabolic syndrome. Aquino Jr (2018) demonstrated that methanolic extract from the leaves of *Z. talanai* possesses antioxidant activity using DPPH assays and accounted mainly for the presence of flavonoids. Other related species, such as *Z. jujube*, *Z. mauritiana,* and *Z. xylopyrus*, have been found to contain secondary metabolites, particularly flavonoid compounds, with antioxidant properties (Prabhu et al., 2021; Taraneh Esteki & Asna Urooj, 2012; Zohra et al., 2016; Abalaka et al., 2011).

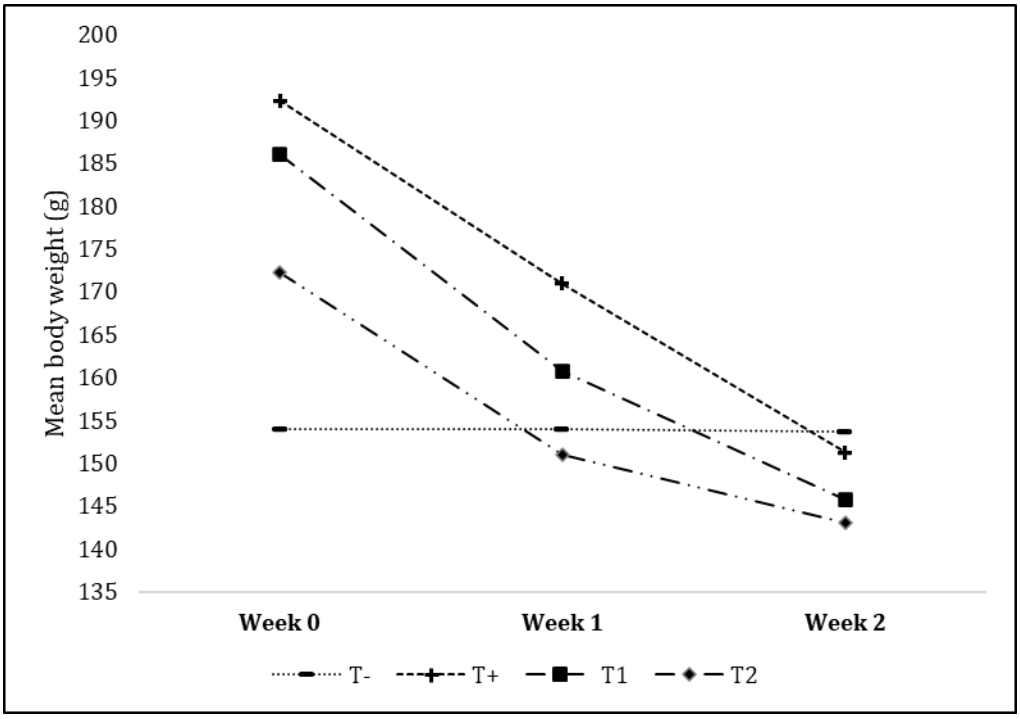

Figure 1. Line graph showing the mean body weight (± SD) of albino rats treated with different treatments.

Intrascapular and visceral fat of female albino rats

Table 3 presents the mean intrascapular and visceral fat weights of the rats in each treatment group. The T- group had the highest mean weights for the intrascapular and visceral fats, with 48.46±1 g and 51.99±1 g, respectively. Meanwhile, T+ had the lowest mean weight for intrascapular fat with 37.67±2 g and T2 has the lowest mean weight for visceral fats with 30.50±1 g. As revealed by one-way ANOVA, significant differences among the treatments were observed for both intrascapular and visceral fats.

Table 3. Mean intrascapular and visceral fat weights among the different treatment groups

Treatment		Intrascapular fats (g)*	Visceral fat (g)*
Symbol	Name		
T-	Negative control	48.46±1	51.99±1
T+	Positive control	37.67±2	38.13±1
T1	400 mg/kg ZTELE	44.99±2	31.28. ±1
T2	800 mg/kg ZTELE	38.11±3	30.50±1

* Significant difference among treatments ($p<0.05$)

A comparison of intrascapular and visceral fats is presented in the bar graph below (refer to Figure 2). *Post-hoc* analysis revealed significant differences in intrascapular fats observed between T and T+, T+ and T1, T1 and T2, and T and T2. The results also revealed significant differences between T- and T1 and between T- and T2 in visceral fats. This reduction is plausible because the extract starts in the intestine near the visceral fats. This allows the rapid utilization of key secondary metabolites. *Z. talanai* contains tannin compounds that play crucial roles in suppressing adipogenesis. Lafontan et al. (2005) cited by Deshpande et al. (2013) stated that tannins amplify the expression of Adiponectin R2, which is associated with reduced rat adiposity. Moreover, the tannins present in the extract likely reduce fat by suppressing lipid accumulation and glycerol-3-

phosphate dehydrogenase and altering the expression of genes crucial to fat cell differentiation, such as *PPAR-γ* and *C/EBPs,* as demonstrated in related species of *Z. jujuba* (Patra et al. 2015). Additionally, Lafontan et al. (2005) also stated that tannins enhance the expression of adiponectin R2, which is associated with reduced fat accumulation.

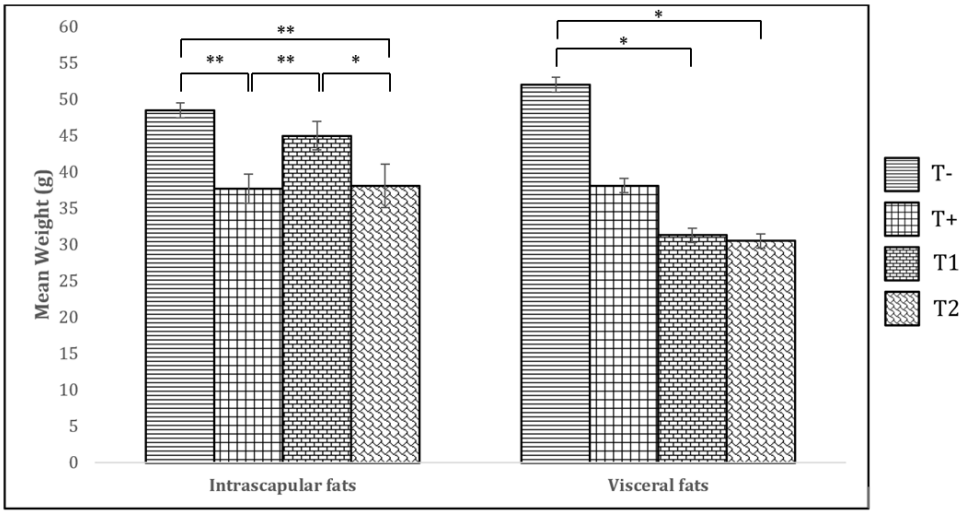

Figure 2. Bar graph showing the mean intrascapular and visceral fat weight (± SD) of albino rats in different treatments.
*- p≤0.05 to 0.01, ** - 0.01≤ p > 0.001, *** - p ≤0.001

Lipid serum profile of female albino rats

Table 4 presents the lipid profile parameters measured in rats across different treatments (a comparative illustration of lipid profile parameters can be seen in Figure 3). Significant differences were observed in the serum lipid profile parameters, including TC, TAG, HDL, and LDL. A significant difference was observed between T- and T+ cholesterol levels. No significant difference was observed between T2 and T+ patients, suggesting that ZTELE at 800 mg/kg dose had comparable effects on those of simvastatin in reducing total cholesterol levels. Regarding HDL, significant differences were observed between the T- and ZTELE-treated (T1 and T2) groups. Although ZTELE treatment did not improve HDL levels compared with T+, it still demonstrated the ability to lower HDL levels. Notably, a significant reduction in LDL levels was observed more than that of T+, suggesting that the ZTELE-treated groups had a stronger LDL-lowering effect. However, ZTELE-treated rats exhibited higher TAG levels compared to T+. Finally, no significant differences were observed for VLDL. However, a trend toward higher VLDL levels in T- was noticeable compared to T+. These alleviated results are relative to the results of the rats` weight. Weight loss in rats induces notable changes in serum lipid profiles, which are driven by enhanced lipolysis and fatty acid oxidation. As adipose tissue stores are mobilized to meet energy needs, serum triglyceride levels decline because of increased fatty acid uptake by peripheral tissues and hepatic metabolism. Concurrently, hepatic lipid regulation shifts often lead to reduced low-density-lipoprotein (LDL) cholesterol levels as demand for cholesterol transport decreases. High-density lipoprotein (HDL) levels frequently increase or remain stable, facilitating reverse cholesterol transport and promoting cholesterol clearance from the circulation. These lipid profile adjustments reflect the metabolic adaptations that accompany weight loss and improved lipid handling. Moreover, these values are consistent with the findings of Kwape et al. (2013), whose rats treated with water alone exhibited no decrease in TC, TAG, LDL, and VLDL and no increase in HDL. Meanwhile, T+ rats exhibited low

TC, TAG, LDL, and VLDL values. These results confirm the efficacy of simvastatin in lowering cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase, which catalyzes the conversion of HMG-CoA to mevalonate, a precursor for cholesterol production, supporting the findings of Bonfim et al. (2015), in which reduction to all lipoprotein molecules was observed. On the other hand, the ZTELE-treated groups (T1 and T2) also exhibited lower values of lipid profile parameters in comparison to T-. These results also align with those of Kwape et al. (2013) and Dahiru and Obidoa (2009), in which extracts of related species of *Z. mucronat*a and *Z. mauritiana* exhibited reductions in serum parameters. Additionally, Mostafa and Labban (2013) reported a decrease in serum lipid profiles in obese rats treated with an extract of *Z. jujube*. Further corroborated results from Niamat et al. (2012) were also observed in various *Ziziphus* species, including *Z. vulgaris*, *Z. mauritiana*, *Z. jujube*, and *Z. spina-christi,* which reduced the serum lipid profiles of obese rats.

Table 4. Lipid profiles of albino rats across different treatments

Treatment		TC*	TAG*	HDL*	LDL*	VLDL
Symbol	Name	(mg/dl)	(mg/dl)	(mg/dl)	(mg/dl)	(mg/dl)
T-	Negative control	64.86±5.7	62.84±2.8	41.31±1.9	10.81±2.2	12.69±3.0
T+	Positive control	36.68±6.6	45.14±3.3	18.53±3.5	9.27±2.9	9.23±2.5
T1	400 mg/kg ZTELE	55.60±5.1	73.46±4.1	34.75±3.1	6.18±2.4	14.61±2.7
T2	800 mg/kg ZTELE	48.26±4.9	63.72±2.3	32.82±4.0	2.70±3.1	12.69±2.2

TC, total cholesterol; TAG, triacylglycerides; HDL, high-density lipoproteins (good cholesterol); LDL, low-density lipoproteins (bad cholesterol); VLDL, very low-density lipoproteins (bad cholesterol)

* Significant difference among treatments (p<0.05)

The potential lipid-lowering effect of ZTELE can be accounted for in the presence of saponin compounds. Marrelli et al. (2016) reported that saponins can inhibit the synthesis of triacylglyceride and other pathways of lipoproteins by suppressing pancreatic lipase, a key enzyme involved in hyperlipidemia. Moreover, Aquino Jr (2018) demonstrated that the methanolic leaf extract of *Z. talanai* possesses antioxidant properties that suggest the extract's ability to neutralize the harmful effects of MSG that can lead to metabolic syndrome.

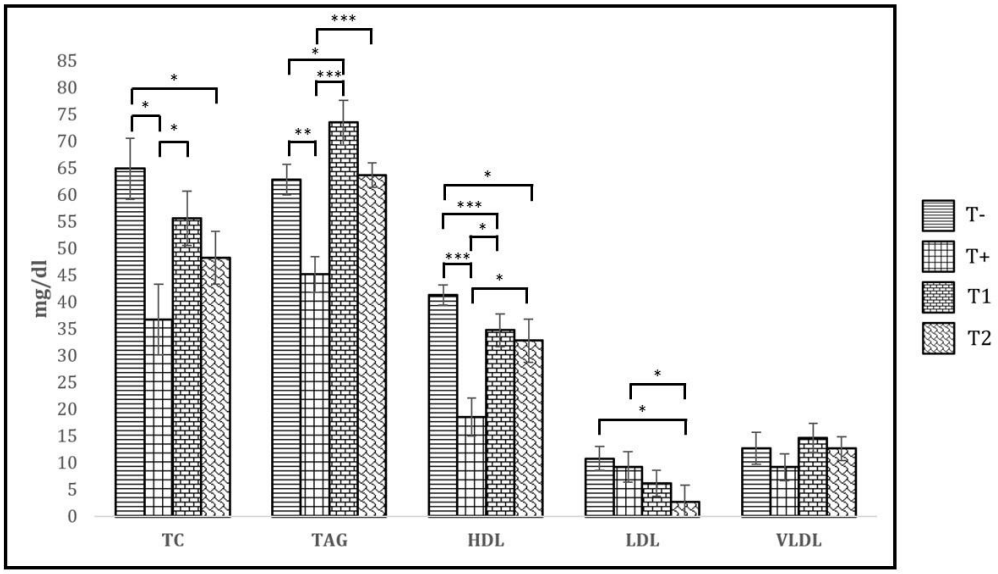

Figure 3. Bar graph showing the lipid profile parameters (TC, TAG, HDL, LDL, and VLDL) in the rats.

*- p≤0.05 to 0.01, ** - 0.01≤ p > 0.001, *** - p ≤ 0.001

CONCLUSION

Compared with simvastatin, ZTELE revealed a significant decline in the body weight of obese female albino rats. The observed weight reduction can be attributed to the antioxidant properties of ZTELE flavonoids, which alleviate the oxidative stress associated with MSG-induced metabolic syndrome. In addition, ZTELE revealed a significant decrease, similar to simvastatin, in both intrascapular and visceral fats, which accounted for the suppression of key genes involved in fat cell differentiation and accumulation. Lastly, ZTELE also exhibited comparable results with the positive control (T+) and a significant reduction compared with the negative control (T-) in lipid profile parameters, which also accounted for the bioactive compounds inhibiting the synthesis of triacylglyceride and lipoproteins. In conclusion, ZTELE has hypolipidemic and antiadipogenic effects against MSG-induced obesity, offering a promising insight into natural product-based therapies for metabolic disorders related to lipid metabolism.

LIMITATION & FURTHER RESEARCH

The current study was limited to female albino rats, which may not fully represent human lipid metabolism. The doses of ZTELE and its duration may also not reflect optimal therapeutic doses. The formulation is now being developed. Other important metabolic indicators, such as blood glucose levels and inflammation markers, are also recommended for further research.

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