EGYPTIAN ACADEMIC JOURNAL OF

BIOLOGICAL SCIENCES ZOOLOGY

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ISSN
2090-0759

WWW.EAJBS.EG.NET

Vol. 15 No. 1 (2023)

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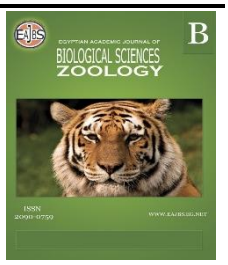
www.eajbs.eg.net

Citation: *Egypt. Acad. J. Biolog. Sci. (B. Zoology) Vol. 15(1) pp: 83-104(2023)*
DOI: 10.21608/EAJBSZ.2023.288784

Egypt. Acad. J. Biolog. Sci., 15(1):83-104(2023)

Egyptian Academic Journal of Biological Sciences
B. Zoology
ISSN: 2090 – 0759
http://eajbsz.journals.ekb.eg/



In Vivo *Salvia officinalis* Extract and Orlistat Provides a Multimechanistic Strategy for Preventing Obesity

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ARTICLE INFO

Article History
Received:23/1/2023
Accepted:27/2/2023
Available:3/3/2023

Keywords:
Obesity. *Salvia officinalis*. Orlistat. Ovariectomy. Leptin. Adiponectin.
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ABSTRACT

Obesity remains one of the main issues in public health. It is a sign of menopause in women, in addition to being connected to metabolic problems. This work was constructed to assess the in *Vivo* possible therapeutic effects as well as physiological mechanisms of *Salvia officinalis* extract and Orlistat in preventing obesity. The obesity model was created by rats ovariectomy, a three-month postoperative period was applied to reach a remarkable decline in estrogen levels and ensuing obesity. Ovariectomy (Ovx) rats were treated with *Salvia officinalis* extract (10 ml /Kg orally) and Orlistat (12 mg/kg orally) daily over 6 weeks. SOE and OR-treated rats exhibited significant decreases in body weight, visceral fat, blood glucose, triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), liver enzymes (AST, ALT), Malondialdehyde (MDA) content, leptin, adiponectin, and pancreatic lipase with a considerable increase in high-density lipoprotein (HDL), total glutathione (GSH), and total antioxidant capacity (TAC) comparable to OVX rats. The histopathological analysis also supported these findings. Co-administration of SOE and OR regained body weight, liver, and adipose histological changes to levels close to normal and reversed all the biochemical markers examined. SOE and OR exhibited anti-obesity potential in OVX rats as evidenced by improving insulin sensitivity, inhibiting lipid synthesis in adipocytes, and reducing oxidative stress according to normal lipid levels. SOE provides a secure and efficient treatment for obesity when used alone or in combination with orlistat, particularly menopausal-related obesity**.**

INTRODUCTION

Obesity is a chronic illness described as a condition in which severe health problems are caused by excessive fat accumulation in white adipose tissue (Safaei *et al*., 2021). It has been linked with the progression of a variety of disorders, including diabetes mellitus, dyslipidemia, atherosclerosis, osteoporosis, clinical depression, and heart disease (Afshin et al., 2017 and Martins *et al*., 2022). Abdominal fat tissue and subcutaneous adipose tissue, together with multiple metabolic characteristics, make up the storage of fats (Nishioa *et al.,* 2019). obesity results when calorie intake surpasses energy usage.

Numerous factors, such as changes in the hypothalamus's signals regulating feeding behavior, leptin levels, the adipokines white adipose tissue (WAT) secretes, neuropeptides and neurotransmitters that regulate behavior, hormonal changes related to aging, inflammatory signals in adipose tissue, stress, and others, have an impact on the occurrence of obesity (Dai et al., 2021). Several studies in animals have consistently shown ovariectomy (OVX) enhances obesity and its metabolic complications due to the loss of protective effects of estrogen, so ovariectomized animals have been used to test postmenopausal metabolic changes and have been reported to gain weight due to changes in lipid metabolism (Nishioa *et al.*, 2019).

The use of slimming drugs as a quick and efficient anti-obesity medication has increased awareness of obesity which affects up to one-third of the population. These medications varied concerning the efficacy, mode of action, and side effects of treatment. Orlistat is an anti-obesity pharmaceutical that helps obese people lose weight. To prevent triglycerides from being broken down in the intestine, it inhibits pancreatic and gastric lipases (Seyedan *et al*., 2015). When lipase activity is suppressed, dietary triglycerides are excreted unchanged rather than being hydrolyzed into absorbable free fatty acids. (Mirja *et al*., 2004 and Zakaria *et al.*, 2021). Because of this, orlistat has shown promise in treating the symptoms of obesity, including vascular dysfunction in humans and metabolic syndrome as well as parameters like white adipocyte size, lipid profiles, BMI, and fecal fat excretion in animal models (Gomaa *et al*., 2019 and Da Silva *et al.*, 2020). Given its ease of accessibility, affordability, and significant impact on weight loss, it has joined a new category of medications for the treatment of overweight (Othman *et al.*, 2021). Despite OR has been permitted by FDA, some experiments have shown it has unfavorable side effects and causes major health concerns because it is unable to effectively restore the metabolic equilibrium lost to obesity (Rodgers *et al.*, 2012). Gastrointestinal disturbances, such as diarrhea, stomach problems, dyspepsia, and serious hepatic damage, are the most frequently reported side effects (Ionnides-Demos *et al.*, 2010 and Deng *et al.*, 2022). The recent interest in medicinal herbs as a healthier alternative to slimming medicines in the treatment of obesity has increased due to the unfavorable side effects and major health concerns effects of orlistat. This is because these plants contain chemicals with antioxidant characteristics (Kim *et al.*, 2014).

Sage *(Salvia officinalis L*.) a perfumed plant and one of the most widely used members of the Lamiaceae family has been utilized as a traditional herb for several disorders. According to some studies, S. *officinalis* L. is a significant anti-diabetic, anti-inflammatory, antioxidant, and antimicrobial agent with potential benefits in the prevention of cancer and cardiovascular diseases (Ghorbani & Esmaeilizadeh, 2017; Jakovljevi´c *et al.*, 2019 and Mot *et al.*, 2022). Flavonoids and polyphenolic substances found in sage have antioxidant properties. Numerous studies have shown that the phenolic and flavonoid components in medicinal plants are what give them their anti-diabetic, antioxidant, and free radical-scavenging effects (Medjahed *et al.*, 2016). Studies in rat and mouse livers show it lowers blood sugar and improves oxidative status, which are two benefits of using it as a traditional herb for treating diabetes (Etsassala *et al.*, 2021).

Therefore, the persistence of this inquiry is to assess the alleviating impacts of SOE and OR alone or their combination therapy on obesity prevention generated by ovariectomy in female rats.

MATERIALS AND METHODS

Animals:

Adult female Wistar rats who are 8 weeks old (n=40, about 190–200 g) were bought from the Animal House Colony of the Faculty of Women for Arts, Science, and Education, Ain Shams University, Heliopolis, Egypt. The rats were quarantined in the animal house for one week within fixed temperatures (22 ± 2 ◦C) and 12 h light/dark cycles, with 70% humidity levels, food provided, and water. All experimental procedures were carried out following the guidelines of the Committee for the Care of Animal House Colony of the Faculty of Women for Arts, Science, and Education, Ain Shams University, Egypt (approval no.ASU/W/Sci-5R/23-2-26).

Model of Obesity and Experimental Procedures:

After anesthesia with ketamine/xylazine (75 mg/kg b.w. and 10 mg/kg b.w.) respectively, the rats had either sham or bilateral OVX procedures (Oršolic et al., 2018). The rats were split into five groups after three months following surgery to achieve a significant estrogen depletion and subsequent obesity Sham rats received nothing more than the identical method of dissolving the medicines as the treated groups (Sham; n = 8); (2) Rats with ovariectomies getting only the identical medication delivery system as the treated groups without any further treatment (OVX; n = 8); (2) Rats with ovariectomies getting only the identical medication delivery system as the treated groups without any further treatment (OVX; n = 8); (3)Ovariectomized rats treated with 10 mg *Saliva Officinalis* extract /kg/day orally (OVX+SOE) (Amin and Hamza, 2005); (4)Rats with ovariectomies have been delivered an intraperitoneal dose of 12 mg/kg of orlistat (Amin *et al.,* 2015). (OVX+OR). (6) Rats with ovariectomies were taken an oral dose of 10 ml /Kg of SOE and then given an intraperitoneal dose of 12 mg/kg of orlistat (OVX+SOE+OR). Every treatment was given every day for 6 weeks.

Plant Materials and Aqueous Extract Preparation:

The dried SO leaves were bought at a herbal shop run by the agriculture faculty at Ain Shams University in Egypt. 10 grams of the dry plant were slowly simmered in 100 mL of distilled water for 30 minutes. The extract was subsequently maintained in a freezer (-40°C) until it was employed in the biological test **(**Amin and Hamza, 2005).

Collection of Sample

Rats were slaughtered under anesthesia after the trial period. Blood samples were transferred into clean microcentrifuge tubes that could coagulate at room temperature to obtain serum, and these tubes were subsequently centrifuged at 3000 rpm for 20 minutes. To preserve them for further examination, the clear, non-hemolyzed supernatant sera were rapidly taken out and stored at -200C.

Biochemical Evaluation:

Evaluation of Lipid Profiles and Glucose:

Serum triglycerides, total cholesterol, and high-density lipoprotein cholesterol were analyzed based on the methods described by Young and Friedman (2002). Low-density lipoprotein cholesterol was calculated as per Freidewald's equation: LDL-Chol. = Total Chol. – [TG/5 – HDL- Chol.] (Tsuzuki *et al.,* 2004). Blood glucose was measured utilizing kits by UV spectrophotometer with an absorbance of 505 nm as per to manufacturer's instructions.

Evaluation of Serum Leptin, Adiponectin, and Pancreatic Lipase:

Leptin was measured by using a Rat leptin assay kit (MyBioSource, USA) and Adiponectin level was estimated by Rat Adiponectin ELISA Kit (ab239421). The pancreatic lipase activity was made rendering to the earlier described technique by Tsuzuki *et al*., (2004) and was expressed in nanograms per milliliter (ng/ mL).

Evaluation of Liver Enzymes:

The activity of serum alanine and aspartate aminotransferases was calculated giving (Wang *et al*., 2012).

Evaluation of Oxidative Stress Markers:

Lipid peroxidation was measured by way of the colorimetric method using commercially available kits according to the procedure of Ohkawa *et al.* (1979). Total antioxidant ability (TAC) and reduced glutathione (GSH) were calculated using commercial kits obtained from Bio diagnostic Co., Egypt according to the method of Koracevic *et al* (2001).

Histopathological Studies:

Fine sections (4-5 μm) from the liver and white adipocytes (preserved in 10% buffer formalin) were organized and stained using hematoxylin and eosin (H&E). After that, an optical microscope was used to examine the stained areas (Banchroft *et al.*,1996).

Statistical Evaluation:

Results for the eight rats in each group are obtainable in the current study by the mean ± S.E. of the mean. To measure the significance among each pair of groups, the Statistical Package for the Social Sciences (SPSS) application, version 20.0 (SPSS Inc., USA), was used. A p-value ≤0.05 is being used to test the significance of the difference.

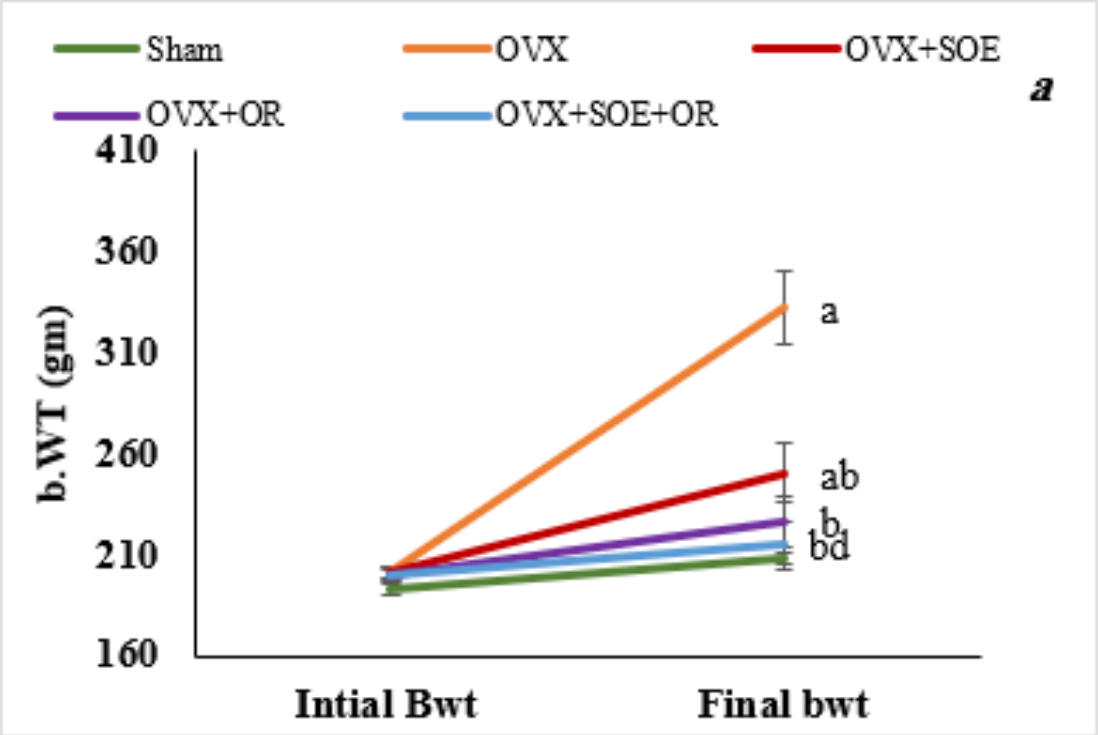
RESULTS

Effect of SOE, OR, and Their Combination Therapy on Body Weight, and Visceral Fat Weight in The Sham and OVX Rats:

Figures 1 and 2 depict the mean body weights and visceral fat weights of the Sham, OVX, and all treated groups. All of the animals had similar body weights (190± 10 g) beginning with the experiment. Additionally, the OVX group's body weight gradually increased until a peak weight gain ($P < 0.05$) at the end of the experimental period relative to the sham group (Fig. 1A). Also, higher raise in the visceral fat weight was noticed in the OVX group compared to the Sham group (Figure 1B) and (Fig. 2B). Conversely, the final body weight, as well as visceral fat weight of the OVX group treated with SOE or OR, were lowered pronouncedly ($P < 0.05$) more than the OVX group (Fig. 1A, B). Whereas the OVX group treated with the combination therapy of SOE and OR restored each the body weight and visceral fat weight to their normal values relative to the Sham group (Figure 1A, B) and (Fig. 2).

Influence of SOE, OR, and Their Combination Therapy on Lipid Profiles, And Adipokine Biomarkers in The Sham and OVX Rats:

The findings of the lipid profile, glucose, leptin, adiponectin, and pancreatic lipase assessments in Sham and other groups are shown in Table (1). In contrast to the Sham group, the values of TG, TC, LDL, glucose, leptin, adiponectin, and pancreatic lipase in the OVX groups demonstrated a significant rise ($p\leq 0.05$). However, when compared to the sham group, the level of HDL in the OVX groups was considerably lower ($P \leq 0.05$). In contrast, treatment with SOE, OR, or combining SOE and OR led to a remarkable improvement ($P\leq 0.05$) in the measured parameters TG, TC, LDL, glucose, leptin, adiponectin, and pancreatic lipase along with a significant rise ($P \leq 0.05$) in HDL when compared to OVX group (Table 1).



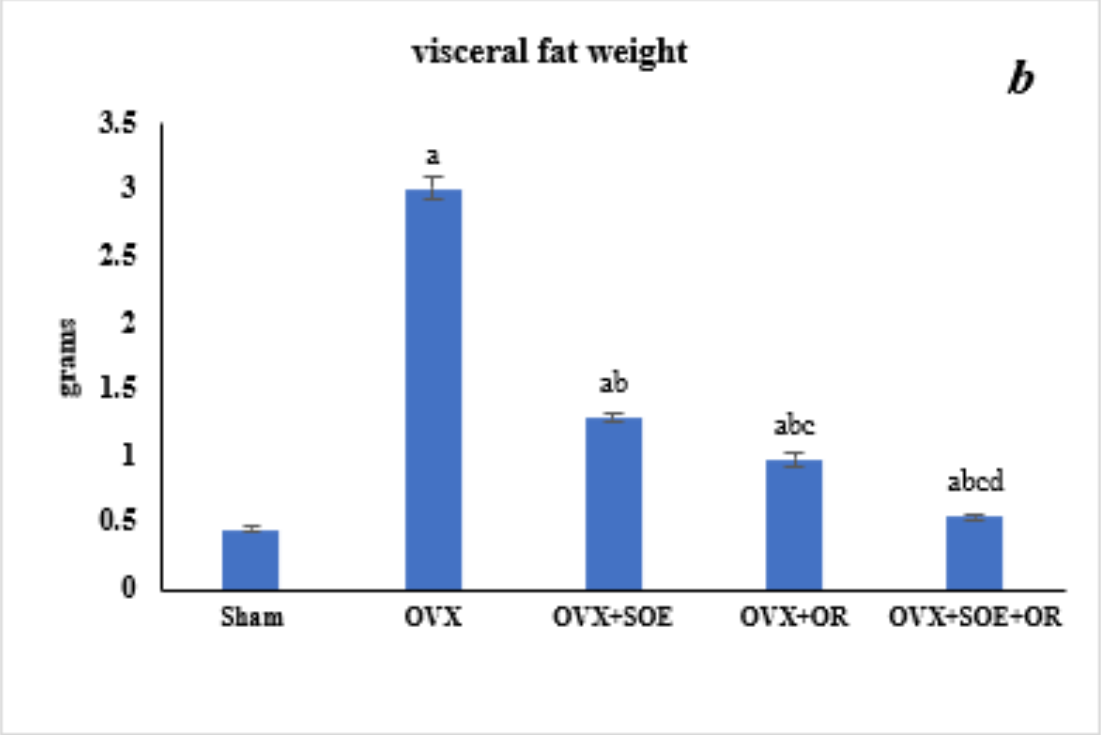


Fig. 1-Effect of *Saliva Officinalis* extract and orlistat on body weight gains and visceral fat tissue in ovariectomized rats. A)- Initial and final body weight. B)-Visceral fat tissue. Values are represented as Mean ± S.E of 8 rats /group. a: Significant change at P< 0.05 compared to the Sham group; b: Significant change at P< 0.05 versus the OVX group. c: Significant change at P< 0.05 versus the SOE group; d: Significant change at P< 0.05 against the OR group. Sham: Sham control; OVX: ovariectomy; SOE: *Salvia officinalis* extract; OR: Orlistat.

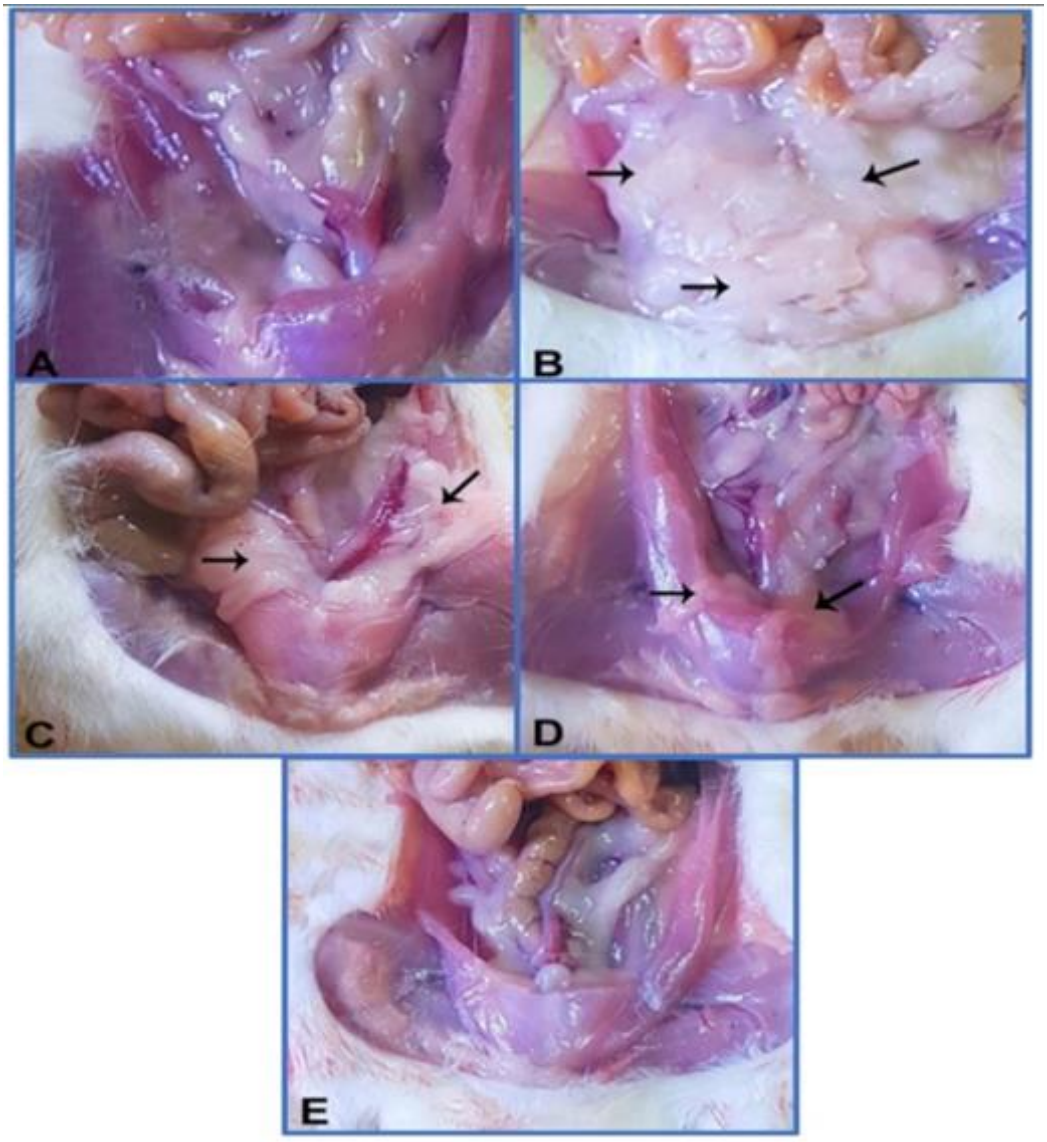


Fig. 2. Gross anatomical examination of visceral fat tissue (A) Photograph of Sham group showing no fats;(B) OVX group showing extensive gross of fats (black arrows) (C); SOE group showing a moderate amount of fats (black arrows); (D)OR group displaying less gross of visceral fats (black arrows); (E) SOE+OR group revealing minor fats.

Table 1-Effect of SOE extract and OR on lipid profile, glucose level, and Adipokine markers in the sham and OVX groups

Groups / Parameters	Sham	OVX	OVX+SOE	OVX+OR	OVX+SOE+OR
TG (mg/dl)	42.29±0.65	171.02±1.5^{a}	129.42±1.7^{b}	91.54±1.38^{ac}	59.35±1.43^{abcd}
TC (mg/dl)	70.14±0.81	227.78±2.0^{a}	181.61±1.6^{b}	99.81±1.18^{abc}	80.29±1.26^{abcd}
HDL (mg/dl)	40.33±0.49	15.46±0.70^{a}	26.38±0.26^{ab}	31.65±0.51^{abc}	36.12±0.26^{abcd}
LDL (mg/dl)	54.80±0.37	130.57±0.93^{a}	97.81±0.69^{ab}	82.09±0.46^{abc}	59.21±0.49^{abcd}
Glucose (mg/dl)	83.97±0.97	160.87±2.09^{a}	121.86±1.68^{ab}	100.77±1.77^{abc}	91.04±1.72^{abcd}
Leptin (ng/ml)	3.92±0.07	9.52±0.21^{a}	7.03±0.06^{ab}	6.15±0.08^{abc}	4.95±0.04^{abcd}
Adiponectin(ng/ml)	10.18±0.15	15.96±0.18^{a}	14.26±0.12^{ab}	12.96±0.07^{abc}	10.45±0.13^{bcd}
Pancreatic Lipase(ng/ml)	21.44±0.36	65.47±0.75^{a}	51.91±0.82^{ab}	39.26±0.80^{abc}	29.04±0.43^{abcd}

Available data are offered as mean ± S.E for groups of 8 rats. a: Significant change with P-value < 0.05 vs the Sham group; b: Significant change with P-value < 0.05 against the OVX group. c: Significant change with P-value < 0.05 vs the SOE group; d: Significant change with P-value < 0.05 vs. the OR group. Sham: Sham control; OVX: ovariectomy; SOE: *Salvia officinalis* extract; OR: Orlistat. TG: Triglyceride; TC: Total Cholesterol; HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol.

Influence of SOE, OR, and Their Combination on The Levels of Liver Enzyme and Markers of Oxidative Stress in The Sham and OVX Rats:

The outcomes existing in Table 2 exhibited a substantial rise (P< 0.05) in AST, ALT, and MDA levels in the OVX group versus the Sham group. However, levels of TAC and GSH were considerably depleted (P< 0.05) in OVX groups compared to sham rats. Comparatively to the OVX group, SOE, OR, or combined SOE and OR treatment in the OVX groups led to a considerable decrease (P< 0.05) in AST, ALT, and MDA concentrations along with a significant increase (P< 0.05) in TAC and GSH levels.

Table 2: Effect of SOE and OR on liver enzymes and oxidative stress markers in OVX rats.

Groups / Parameters	Sham	OVX	OVX+SOE	OVX+OR	OVX+SOE+OR
AST (U/ml)	36.70±0.54	151.98±1.60 ^{a}	108.37±0.91 ^{ab}	81.27±0.54 ^{abc}	47.03±0.67 ^{abcd}
ALT (U/ml)	27.34±0.72	132.60±1.85 ^{a}	90.45±0.61 ^{ab}	68.71±0.62 ^{abc}	35.69±0.68 ^{abcd}
MDA (nmol/mg protein)	0.37±0.01	8.10±0.13^{a}	3.11±0.05^{ab}	1.76±0.07^{abc}	0.66±0.04^{abcd}
GSH (mmol/mg protein)	105.25±0.40	13.28±0.22^{a}	54.99±0.21^{ab}	74.80±0.33^{abc}	97.12±0.43^{abcd}
TAC (mmol/mg protein)	152.94±0.63	30.64±0.45^{a}	77.11±0.76 ^{ab}	111.67±0.89^{abc}	140.51±0.72^{abcd}

Available data are offered as mean ± S.E for groups of 8 rats. a: Significant change with P-value < 0.05 vs the Sham group; b: Significant change with P-value < 0.05 against the OVX group. c: Significant change with P-value < 0.05 vs the SOE group; d: Significant change with P-value < 0.05 vs. the OR group. Sham: Sham control; OVX: ovariectomy; SOE: *Salvia officinalis* extract; OR: Orlistat.

Histopathological Results:

Hepatic parenchyma in the control group had a normal histological structure (Fig.3 A). However, group OVX showed various histopathological alterations in the hepatic lobules. The hepatocytes showed excessive accumulation of glycogen which is characterized by pale cytoplasm and central to eccentric nuclei accompanied by sporadic cell necrosis in some instances. The hepatic parenchyma showed steatosis that appeared as well as circumscribed clear intra cytoplasmic vacuole (Fig. 3B). While the hepatic tissue of group OVX + SOE showed moderate enhancement regarding the alterations that were detected in the examined hepatic sections. The hepatic sections showed mild vacuolated hepatocytes and fatty changes in other affected cells (Fig. 3C).

The less protective effect was recorded in group OVX + OR compared to the OVX treated group which showed multifocal inflammatory areas among the hepatic tissue of some individuals also noticed characterized by extensive vacuolated hepatocytes (Fig. 3D), while others showed mildly enlarged to normal hepatocytes. On the other hand, the highest protection was scored by group OVX + SOE + OR. The hepatic parenchyma showed normal hepatocytes (Fig. 3E). Moreover, the adipose tissue of the control group showed normal mature adipocytes that appeared approximately uniform in size with clear cytoplasm and the nucleus pushed toward the periphery at one side of the adipocyte (Fig. 4A).

Meanwhile, group OVX showed a marked increased size of adipocytes with over-accumulation of fat inside the cells and marked variation in size (Fig. 4B). Whereas groups OVX + SOE and OVX + OR showed a moderate increase in adipocyte size with uniform size in most examined sections (Fig. 4C& 4D). The adipocytes of group OVX + SOE + OR showed a marked reduction in size compared to group OVX and the adipose tissue appeared normal and closely resemble to control group (Fig. 4E). Likewise, the area (m2) of adipocytes in group OVX was significantly higher than other groups. In the meantime, there was no discernible difference between the OVX +SOE and OVX + OR groups. Contrary to the other groups that were treated, the OVX + SOE + OR group demonstrated a considerable reduction in adipocyte area (Fig. 5).

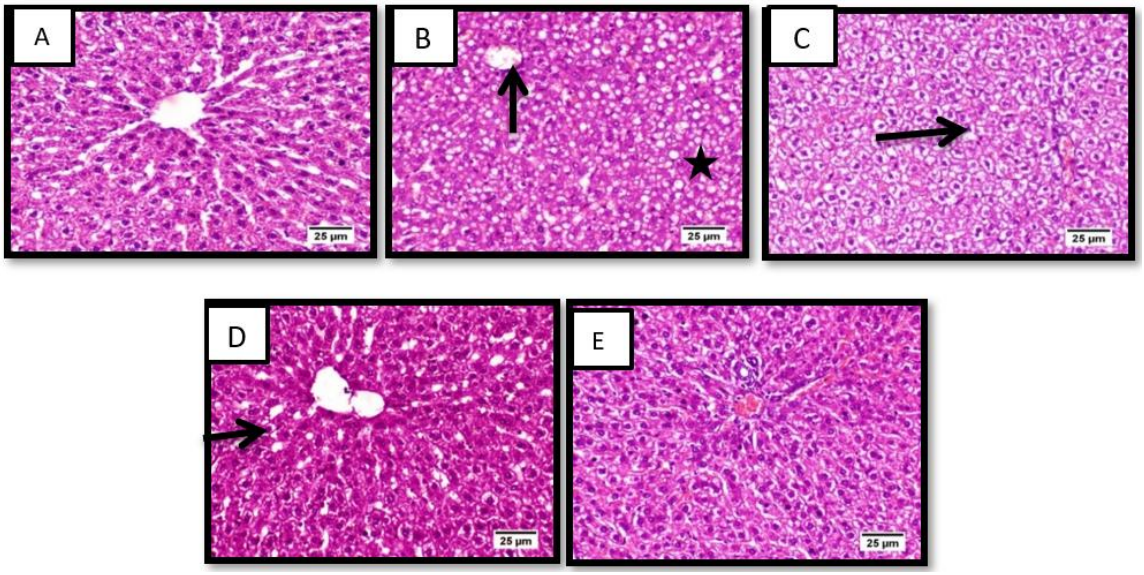


Fig. 3: Histological examination of liver tissue(A-E), **A**: liver tissue from the control group showed a normal central vein bounded by radiating hepatic cords (arrow). **B**: liver tissue from group Ovx showing hepatic steatosis(black arrow) that appeared as well-circumscribed clear intracytoplasmic vacuole (*). **C**: liver tissue from group OVX + SOE showing moderate swelling and vacuolation in the hepatocytes (arrow). **D**: liver tissue from group OVX + OR showing mild vacuolated hepatocytes (arrow). **E**: liver tissue from group OVX + SOE + OR showing normal hepatocytes surrounding normal portal triad (H&E).

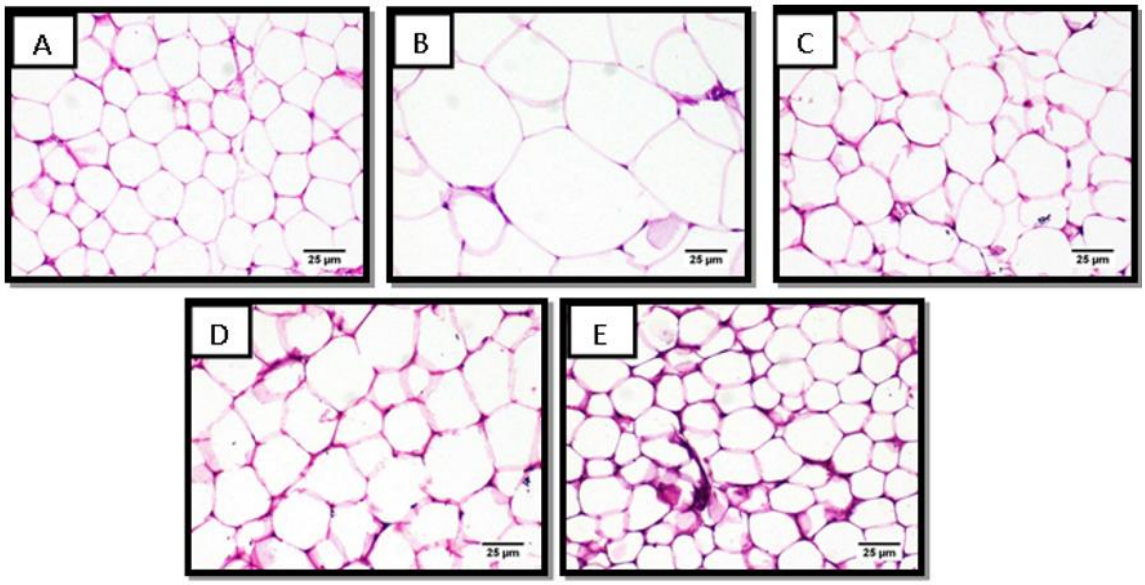


Fig. 4. A: adipose tissue from the control group showed higher power of normal histological structure of mature adipocytes that appeared uniform in size. **B**: adipose tissue from group OVX showing over distension of adipocytes with fat storage. **C**: adipose tissue from group OVX + SOE showing the uniform size of adipocytes. **D**: adipose tissue from group OVX + OR showing a moderate increase in the size of adipocytes with approximately uniform size. **E:** adipose tissue from group OVX + SOE + OR showing normal mature adipose tissue with normal size (H&E).

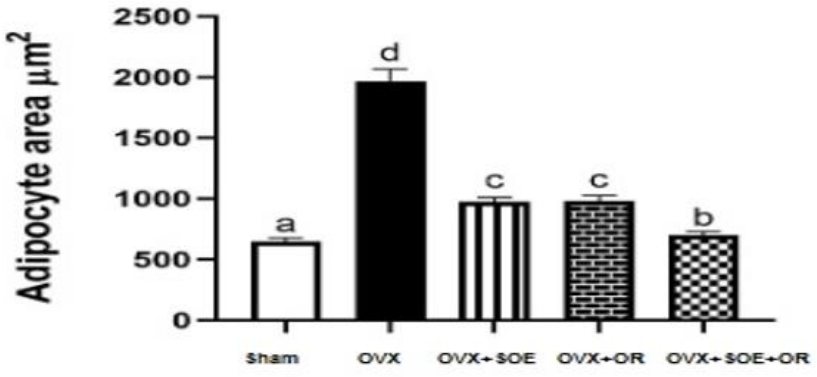


Fig. 5: adipocyte area (μm^2) in different test groups. Data are expressed as means ± SE. a, b, c, and d above the error bar indicate a significant difference at $p<0.05$.

DISCUSSION

Obesity prevalence is a global health issue that has gotten worse significantly over the past few decades. In this study, the model of ovariectomy enhanced body weight mirrored by aggravation in the levels of lipid profile except for HDL, leptin, adiponectin, pancreatic lipase activity, and glucose. Ovariectomy also induced an increment in liver enzymes and MDA matched by a decline in levels of GSH and TAC activity compared to the sham control group. Consequently, these findings support the theory that ovariectomy raises the risk of obesity, metabolic complications, and cardiovascular diseases (Nishioa *et al.*, 2019; Tsai *et al.*, 2019). In ovariectomized rats estradiol levels are reduced, resulting in the development of insulin resistance and overweight (Sharma *et al.*, 2018). Numerous studies demonstrate that a lack of estradiol causes weight gain, increased food intake, and body fat storage (Ke *et al.*, 2015). Body fat increase and excessive blood triglyceride levels are significant risk factors for vascular problems (Marques *et al.*, 2015). According to our results, ovariectomy causes obesity through increasing visceral adiposity (Lima-Mendoza *et al.*, 2014; Palmisano *et al.*, 2017). This visceral adiposity is linked to higher body fat content and BM, as well as levels of TG, TC, and LDL that caused metabolic impairments and ROS production which can be exacerbated by the fall in the production of E2 from the ovaries (Goettems-Fiorin *et al.*, 2019). E2 has anti-inflammatory, antioxidant, cardioprotective, and Vasoprotective functions and its decrease is associated with oxidative stress and dyslipidemia (Stice *et al.*, 2011).

According to reports, the cytokines leptin and adiponectin, which are mostly released by WAT, are crucial for controlling energy balance and body weight. Adipocyte dysfunctions brought on by adipocyte hypertrophy and inflammation, which lead to obesity, are exacerbated by an excessive buildup of WAT. This also affects endocrine function and causes a release of proinflammatory adipokines like interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-alpha (TNF-α) (Fontana *et al.*, 2007 and Ludgero-Correia *et al.*, 2012). Also, cytokines cause persistent inflammation because of decreased triglyceride deposition and enhanced lipolysis. Elevating blood triglycerides and free fatty acids promote the formation of activated lipids in skeletal muscle, the liver, and pancreatic beta-cells, which leads to insulin resistance (Jeong & Yoon, 2009; Chen *et al.*, 2015). Our findings support these reports since OVX rats increased circulating triglycerides, and induced lipid accumulation through increasing leptin, adiponectin levels and pancreatic lipase activity, AST, ALT as well as glucose levels than sham control rats.

Moreover, the existing study confirmed that the weight increases of obese rats dramatically reduced following therapy with either SOE or for 6 weeks. And most importantly, when SOE was combined with OR the inhibitory effect was enhanced, and the body weight was restored to its normal weight. This finding is highly confirmed by the work of Amini *et al.* (2020) who found that SOE treatment leads to a statistically significant lessening in body weight, waist circumference (WC), body mass index (BMI), and insulin resistance markers in people with polycystic ovary syndrome strongly support this finding (PCOS). Moreover, the anti-obesity effect of SOE in body weight loss was attributed to its capacity to suppress the function of pancreatic lipase, which aids in fat digestion thus reducing all lipid levels and leading to a decrease in total body weight (Ninomiya *et al.,* 2004; EI-Serwy & Abd EI-Hameid, 2012). Our results concur with those of Hernandez-Saavedra *et al.* (2016) who found that the various SOE extracts reduced excess weight and the amount of abdominal fat in obese rats. According to some research, quercetin from S. Officinalis can prevent animals fed a high-fat chow from developing hyperglycemia, hyperinsulinemia, dyslipidemia, liver fat, and body weight gain. It can also prevent the buildup of visceral fat (Imessaoudene *et al.,* 2016; Porras *et al.,* 2017). The moderating power and mechanism of SOE in reducing obesity are evident in the manner that their physiologically active metabolites, flavonoids, can either directly or indirectly suppress weight increase (Song *et al.,* 2019). Some bioactive components from SOE such as epigallocatechin gallate were shown to reduce food consumption by boosting the formation and release of cholecystokinin, which has appetite-suppressing effects. consumption and absorption of lipids by lowering the activity of digestive enzymes and lipid emulsification (Grove *et al.,* 2012). Additionally, epigallocatechin gallate activates AMPK, limits acetyl-CoA carboxylase activity, as well as downregulates the activation of lipogenic genes such as FAS, SREBP-1c, and SCD1to reduce fat storage in adipocytes (Hwang *et al.,* 2005).

Furthermore, our study delineates that administration with OR or adding to SOE considerably decreased the main visceral fat weight and body weight in contrast to the OVX group. This finding may be due to the that OR inhibits pancreatic lipase which can lower obesity. Some studies have reported that treatment with OR alone or in combination with *Allium sativum* ameliorates the body weight of HFD rats (Mathus-Vliegen *et al.,* 2004; Caroline *et al.,* 2021). Also, the current results are compatible with the results of Bhattacharjee *et al.* (2021) who found that Co-administration of OR with AEBN resulted in an improvement in general health and a notable recovery of body weight that was comparable to controls of the same age and gender.

Surprisingly, our findings demonstrated that SOE and OR both administrations produced a substantial decrement in TC, TG, LDL, and blood glucose as well as a considerable rise in the level of HDL when compared to OVX rats. Those findings were consistent with Plana *et al.* (2008) and Marrelli *et al.* (2016) who suggested that the cause could be due to effective SOE compounds like single turbines, the most important of which, and Thujone in the plant, which play a role in hypolipidemia by inhibiting triglyceride synthesis. Also, the hypocholesterolemic action of SOE could be attributable to flavonoid components that lower cholesterol absorption or production, such as catechins. In diet-induced obese rats, SOE was already proven to lower TG, TC, and LDL with increased HDL (Hernandez-Saavedra *et al.,* 2016). Due to its impact on decreasing cholesterol levels, function in improving lipid profiles, and antioxidant defenses, it is very crucial for the avoidance of cardiovascular illnesses (Sa *et al.,* 2009; Christensen *et al.,* 2010).

The flavonoids found in SOE may be responsible for the herb's positive effects on dyslipidemia. For instance, therapy with rosmarinic acid lowers TG and TC levels in

diabetic rats induced by streptozotocin and HFD. In addition, rutin reduced body weight and adipose tissue mass of obese rats fed HFD (Govindaraj et al., 2015). Additionally, that antioxidant raises DNA content, mitochondrial size, and gene expression associated with mitochondrial biogenesis (Seo *et al.,* 2015). Many hypothesized mechanisms of action include suppression of adipocyte differentiation, fatty acid synthesis digestive enzymes, but increased fatty acid oxidation, thermogenesis, and energy expenditure (Ahmed *et al.,* 2016; Andrad *et al.,* 2020).

Moreover, the significant decrement of TC, TG, LDL and increase in HDL levels following OR administration may have been attributed to the main ingredient in OR, lipstatin, which has an inhibitory action on the enzyme lipase, which in turn prevents the digestion of lipids in the stomach and intestines, restricting their transformation into free fatty acids and monoglycerides, and thus lowering intestinal fat absorption (Sladic *et al.,* 2014; Da Silva *et al.,* 2020; Othman *et al.,* 2021). The mechanism by which OR lowers TC, TG, and LDL and boosts the HDL level may be explained by the inhibitory action of the OR to the 3-Methyl Glutaryl-Coenzyme A reductase (HMG-CoA) which is primarily responsible for cholesterol synthesis (Al-Kuraishy & Al-Gareeb, 2016). It also inhibits Cholecystokinin (CCK) secretion, which causes the bile sac to contract and the pancreatic hepatic to loosen, allowing bile and enzyme-rich pancreatic amyloid to pass through to the duodenum. As a result, reducing the CCK hormone affects bile and pancreatic enzyme secretion, resulting in a slowdown in the fat-digesting process (Alqahtani *et al.,* 2015).

Furthermore, the current data showed the SOE treatment significantly reduced serum glucose levels as compared to OVX rats. This may be elucidated by the fact that SOE possesses hypoglycemic properties to decrease glucose levels because of their components quercetin, lutein, and kaempferol, which inhibit gluconeogenesis by enhancing hepatocyte insulin sensitivity and decreasing glucokinase and glucose 6-phosphatase enzyme activity through the stimulus of peroxisome proliferator-activated receptor γ (PPARγ (Lima *et al.,* 2007; Wang *et al.,* 2011). These results concurred with previous studies which confirmed that SOE exhibited significant hypoglycemic effects by reducing postprandial blood glucose in an experimental rat model via inhibiting intestinal α-glycoside activity, in addition to their inhibitory effects on digestive enzymes and strong effect on insulin sensitivity and glucose metabolism in long-term use (Zhang *et al.,* 2014; Moradabadi *et al.,* 2013; Ben Khedher *et al.,* 2018; Mahdi *et al.,* 2020). On alloxan-induced diabetic rats, aqueous and alcoholic extracts from SOE leaves showed a considerable decline in blood glucose, TC, and TG levels more than glibenclamide medication (Khashan & Al-Khefaji, 2015). Our findings are also, consistent with earlier research that demonstrated flavonoids were beneficial in improving the glycemic profile and considerably up-regulating insulin-stimulated glucose absorption, which was found to be abolished in palmitate-treated circumstances (Chen *et al.,* 2009; Chen *et al.,* 2011; Sano *et al.,* 2017). Correspondingly, OR therapy for OVX rats resulted in a reduction in glucose levels. Many studies have demonstrated that OR improves fasting serum insulin and fasting blood glucose in diabetic and non-diabetic obese people (Ballinger &Peikin, 2002). OR also, increases glucose tolerance and lowers the rate of diabetes development in obese people, according to a separate study (Heymsfield *et al.,* 2000).

More importantly, the present findings showed that SOE supplementation with or without OR restored the high levels of leptin, adiponectin, and pancreatic lipase activity to their normal levels. These results have been linked to the probable inhibitory action of SOE, which contains four abietane-type diterpenes: carnosic acid, carnosol, royleanonic acid, and 7-methoxy-romano (Ninomiya *et al.,* 2004). Carnosic acid has demonstrated that it reduces adipogenesis-related gene expression in 3T3-L1 adipocytes, by reducing the mRNA expression of the proteins sterol regulatory element-binding protein 1,

CCAAT/enhancer-binding protein 1, and peroxisome proliferator-activated receptor-gamma, hence inhibiting lipid synthesis (Park & Sung, 2015). The infusion made from *S. officinalis* has been found to include several flavonoids, including ellagic acid, epicatechin, epigallocatechin gallate, quercetin, rosmarinic acid, rutin, luteolin-7-glucoside, as well as several volatile substances, including cineole, borneol, camphor, and thujone. The two flavonoids that are most prevalent in the S. *Officinalis* infusion extract are rosmarinic acid and ellagic acid, followed by rutin, chlorogenic acid, and quercetin (Lima *et al.,* 2005; Hernandez-Saavedra *et al.,* 2016). Modern phytochemicals and adipose lipogenesis management have demonstrated that resveratrol, quercetin, and ellagic acid have an anti-lipogenic effect by blocking AKT signaling and lowering the level of adiponectin (Borah *et al.,* 2021).

Conversely, there was also a greatly substantial decrease in the leptin, adiponectin, and pancreatic lipase levels after OR treatment. By covalently attaching to a serine residue, OR a chemically synthesized derivative of the natural product Lipstatin, specifically inhibits lipase at its catalytic triad of serine 153-histidine 264-aspartate 177. The catalytic triad is a highly conserved feature of many biological lipases; the lipases in the gastrointestinal tract, are gastric lipase, pancreatic lipase, and carboxyl ester lipase. The covalent bonding of OR to the serine residue of the lipase active site is what causes the decrease in enzymatic activity (Iqbal & Hussain, 2009; Asler et al., 2007). Even though a rise in fat mass is correlated with an elevation in leptin, making leptin an indicator of total fat mass, serum leptin concentration is directly related to the level of obesity (Lopez *et al.,* 2005). Leptin's impact in lowering total body fat mass and managing obesity is illustrated by the current study's lowered levels of leptin in response to OR. Leptin is furthermore synthesized by adipose tissue to reveal the body's stored fat and controls long-term appetitive regulation (Faggioni *et al.,* 2000).

From our data, it was clear that the administration of SOE markedly succeeds to reduce ALT, AST, and MDA and improving GSH, and TAC levels as compared to OVX groups. The decreased level of liver enzymes after SOE administration may be due to SOE having compelling antioxidant activities that boost the sensitivity of rat hepatocytes to oxidative stress and shield them from hydrogen peroxide and dimethoxy naphthoquinone-induced DNA damage (Kolac *et al.,* 2017; Essawy *et al.,* 2019). This may be a consequence of the phenolic and monoterpene compounds of SOE, which are the basis for all its various biological functions. SOE is a natural source of several phenolic acids and flavonoids (Medjahed *et al.,* 2016; Sotiropoulou *et al.,* 2020).

The bioactive components of SOE polyphenols, such as rosmarinic acid, carnosol, rosmanol, and have been discovered to have antioxidant properties, donating hydrogen to reactive species, thus protecting fatty acid and phospholipid membrane lipids from oxidative and enhancing the antioxidant status (Kolac *et al.,* 2017; Pavic *et al.,* 2019). Likewise, Sadeghnia *et al.* (2013) found that flavonoids of SOE, especially quercetin and rutin, have high antioxidant properties that prevented the hexachlorobutadiene-produced rise of lipid peroxidation and lessening of thiol level in the kidney of rodents. SOE is notable for its capacity to have an increased impact on the GSH level of brain tissues. Additionally, the primary protection against oxidative damage is the enzymatic antioxidant defense system, which includes SOD and CAT and may degrade superoxide and hydrogen peroxide in the cells (Tripathi *et al.,* 2009). Also, the most common phenolic substance in SOE is rosmarinic acid. The ability to scavenge reactive oxygen species was used to explain its action as having antioxidant capabilities (Zheng *et al.,* 2004; Govindaraj *et al.,* 2015).

Furthermore, our study showed that the OR treatment effectively decreased the levels of ALT, AST, and MDA and strongly improved GSH and TAC in OVX rats. More

crucially, the therapeutic effect was stronger, and the antioxidant status was improved when OR was mixed with SOE, indicating the effective therapeutic role of SOE and OR in combination contributes to modifying many crucial physiological functions, including antioxidants (Zimmermann *et al.,* 2011; EI-Serwyl & Abd EI-Hameid, 2012). Our results support earlier studies that showed OR reduced SGOT, SGPT, ALP, and LDH blood levels in HFD rats and prevented liver damage when combined with melatonin rather than therapy alone (Annamalai *et al.,* 2016). The reduction in oxidative stress could be attributed to OR's capacity to stop pro-atherogenic LDL cholesterol from oxidizing (Osaretin & Bukola, 2016) In our study, OVX rats revealed a clear disturbance of hepatic architecture with deformed hepatocytes, numerous intracytoplasmic vacuoles demarcated as microvesicular steatosis with extensive diffuse intracytoplasmic vacuoles, pyknotic nuclei, leukocyte infiltration, dilatation and congestion of blood vessels, in addition, damaged blood sinusoids with dense Kupffer cells. Moreover, the adipose tissues of OVX rats also afforded critical support for biochemical analysis (increased LPO and decreased antioxidant enzymes activity) and liver sections which recorded enlarged adipocytes and more fat deposits compared to the sham group (Jain, 2018; Tanaka *et al.,* 2019; Sorour *et. al.,* 2021). The current data showed that groups receiving SOE or treatment decreased hepatic fat accumulation, relieved hepatocyte enlargement, and decreased the development of steatosis. Our data are in accord with prior exploration displays that OVX animals treated with SOE for four weeks had significant evidence of recovery. In addition, hepatocytes were seen to have improved nuclei, a more defined shape, and less vacuolated cytoplasm (Krentz, 2016; Jain, 2018). Furthermore, SOE extract was previously shown to inhibit lipid droplet buildup in mature adipocytes at the highest two concentrations (25 and 50 g/ml), or even at the lowest concentration (0.2 and 1 g/ml), in a general concentration-dependent manner. However, in *vivo* animal studies revealed that it was more effective in the avoidance of lipid accumulation within 3T3-L1 adipocytes, which is compatible with its ability to minimize body weight increase (Ben Khedher *et al.,* 2018).

Our histological finding concluded that the co-supplementation with SOE and OR was more efficient than SOE or OR alone in repressing obesity and this was more noticeable through lessening adipocyte deposition in the hepatocytes and white adipose tissue, which resulted in a practically normal appearance contrasted to the OVX group. These outcomes are in line with research that shows that the combination of A. *Sativum* extract and OR decreased body weight, serum glucose levels, physiological hormones, and insulin sensitivity in HFD rats more effectively than OR alone or AS alone (Caroline *et al.,* 2021). Al-kuraishy and Al-Gareeb (2016) demonstrated that the addition of *Garcinia cambogia* to OR had a more profound impact on improving visceral adiposity and the cardiometabolic profile in obese patients than in OR alone. According to the same theory, Diallyl trisulphide (DATS) and its mixture with OR treatment in obese rats reduced body weight and erased the severe histological abnormalities that were brought on by HFD both within the adipose tissue and liver (Annamalai *et al.,* 2017).

Corroborating our findings many investigators suggested that an intake of monoterpene phenolic SOE component contributes to the browned of white adipose tissue, enhancement of fat oxidation, lipolysis, and thermogenesis (Choi, 2016). This finding also supports previous observations that SOE has a high degree of repair and improvement in the organization of the hepatocytes and the proliferation of the majority of hepatic cells, together with being protective of the liver tissue from degradation after being imperiled by a high-fat diet. This improvement was caused by the potency of the flavonoids in SOE, which actively protect the cellular membranes of the liver by triggering the production of the antioxidants CAT, SOD, and GSH as a consequence of their ability to reduce oxidative damage and prevent lipid peroxidation (Placha *et al.,* 2015; Van *et al.,* 2017). The phenolic

compounds of the plant were shown to diminish the quantity of fatty infiltration in the hepatic tissue and the size of adipocytes in the adipose tissues of obese rats (Sunil, 2017).

Conclusion

Finally, our findings showed that SOE and OR therapy was effective in combating obesity in OVX rats through their bioactive substances, which have pharmacologic properties and mechanism action comprising inhibition of pancreatic lipase action, appetite suppression, inhibiting lipogenesis in adipocytes, suppressing lipid peroxidation and oxidative stress and improving insulin sensitivity as indicated by normal lipid levels. SOE provides a secure and efficient treatment for obesity when used alone or in combination with orlistat, particularly menopausal-related obesity. However, more clinical studies are needed to confirm the effectiveness and safety of SOE in animal models.

Conflicts of interest: There are no conflicts of interest

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