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Anti-obesity Efficiency of Papaya Extract on High-fat Diet-induced Obese Male Albino Rats

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As of 2022, obesity was identified as a complex, long-term disorder characterized by excess body fat affects more than 890 million people globally. It significantly increases the risk of diseases, including heart disease, type 2 diabetes, and many cancers, and is brought on by a confluence of lifestyle, environmental, and genetic variables.The goal of the current study is to compare the anti-obesity efficiency of papaya aqueous extract (PAE) with that of orlistat in male rats fed a High-fat diet (HFD). Forty male rats were used in this study; ten of them fed normal diet as the control group (GI), and the remaining thirty rats were fed a HFD for twelve consecutive weeks. The obese rats were divided into three groups at random as follows: GII; ten obese rats were received HFD; GIII: 10 obese rats given an oral intubation dose of 50 mg/kg/day of orlistat(ORL) for 45 days; GIV: PAE (600 mg/kg b.wt.) was given to ten obese rats for forty-five days.Serum oxidative stress marker malondialdehyde (MDA),pro-inflammatory cytokine, interleukin-1ß(IL1-ß), and obesity markers such as serum insulin, Leptin, resistin, and irisin were estimated by ELISA. PAE has a notable effect in decreasing their body weight that was clear by a drop in BMI,a decrease in obesity markers such as resistin, leptin, and insulin levels and a decline in the levels of MDA & IL1-ß reflecting the anti-obesity & antioxidant capacity of PAE.

Keywords: *Carica Papaya L* aqueous extract; Catechin; High-fat diet; Gallic acid; Lipid peroxidation; and Obesity.

Consuming too much fat can cause visceral fat to build up and body weight to rise. Despite the increasing recognition of the need for an active lifestyle and a nutritious diet, obesity remains a widespread health issue.[1] It results from an imbalance between energy expenditure and intake. This imbalance raises the risk of chronic conditions, including diabetes, cancer, and heart disease, in addition to causing abnormal weight gain[2]. *Carica papaya* L. is widely grown in many parts of the world, particularly in Asia, Central and South America, and other tropical nations.[3] After bananas, mangoes, and pineapples, it is the fourth most traded tropical fruit, making it an economically significant crop. Papaya has hepatoprotective, antihypertensive, and antioxidant qualities. [4]

Papaya fruit and other plant parts have a milky juice that is full of the active compounds papain and chymopapain, which are responsible for papaya's many health benefits.[5] These compounds have also been used to make a

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number of pharmaceutical and industrial products that are used to treat a wide range of illnesses[5]. High concentrations of proteolytic enzymes with antifungal, antiviral, and antibacterial properties, as well as vitamins C, A, and B. According to, [6] papaya is high in calcium, magnesium, sodium, and potassium and contains trace amounts of thiamine and riboflavin.[6]Papaya's main constituents include methyl butanoate, ethyl butanoate, 3-methyl-1-butanol, and 1-butanol. Esters of shorter-chain fatty acids were believed to have a major impact on the common flavour of papaya. It includes saponin, which gives the unripe papaya a harsh flavour. [6] Papaya's high soluble dietary fiber content and its tender, easily digested structure, promotes regular bowel movements, reduce constipation, and aids in nutrient absorption. Papaya has a protein content that varies from 0.29 to 14.41 percent. Highlighting that overripe papaya does not serve as a major source of protein, the pulp contained the least crude protein content (0.29%), while the seeds had the highest. The fat content varied from 0.23 to 5.24%, while the carbohydrate content ranged from 9.65 to 32.18%. Chukwuka *et al*., 2013[6] While the brown, dried papaya leaf is the best tonic and blood purifier, as well as having anti-tumor, anti-inflammatory, and nutritional value due to the plant's abundant latex, the green, unripe papaya is well-known for its antiseptic qualities, which rid the intestines of bacteria whereas the brown, dried leaf is the best tonic and blood purifier[5], in addition to its anti-tumor, anti-inflammatory, economic, nutritional value due to the abundant latex produced by the plant it has industrial applications.[7]

The main ingredients of papaya are 1-butanol, 3-methyl-1-butanol, ethyl butanoate, and methyl butanoate. The usual papaya flavour was believed to be largely influenced by the esters of lower fatty acids. According to,[8] it contains saponin, which gives the un ripe papaya a bitter taste.

MATERIALS AND METHODS

Forty healthy adult male albino rats weighing between 150 and 180 grams were acquired from the animal colony at Qassim University's College of Agriculture. Rats was kept in polycarbonate plastic cages (size 60 × 40 × 22 cm) with five rats per each under conventional laboratory settings (19–25°C, 12 hours), with cycles of light and dark and a relative humidity of 50–60%, the floor of the cage filled with wood shavings. Ten rats fed normal diet (special feed for experimental animals is called Fodder No. 1005. Crude protein (20%), crude fat (4%), crude fiber (3.50%), salt (0.50%), calcium (1%), phosphorus (0.6%), and vitamins A (20%), D (2%), and E (70%) were all included in these pellets (international units/g). As well as a few additional trace elements, such as iron, manganese, selenium, copper, iodine, zinc, and cobalt and they are the control group (GI), the remaining thirty rats fed HFD for 12 weeks. The weight and the nose-anus length of each rat in the control and obese groups were recorded at the beginning and the end of the 12th week. After that, the thirty obese rats were partitioned randomly into 3 groups: GII: HFD-fed rats until the end of the study; GIII: obese rats received a daily oral dose of orlistat (dissolved in 0.2ml saline solution) , while group GIV received an oral daily dose of PAE (dissolved in 0.3ml saline solution) by gastric intubation[8].At the end of the experimental period, all animals were fasted for 24 h, anesthetized using sodium phenobarbital (200 mg/kg body weight, intraperitoneal; diluted by 1:3 in phosphate-buffered saline), and sacrificed by decapitation. The anesthetic was administered only once as a terminal procedure immediately before sacrifice and was not used during the exposure period. Blood samples were collected, and sera were separated by centrifugation aliquoted, and stored at -80°C for subsequent biochemical analyses. Serum levels of irisin , resisten, leptin, insulin, and IL1-β were estimated by ELISA while MDA was detected spectrophotometrically using "MyBioSource kits" that were acquired from Ejadah Trading Corporation for Scientific and Laboratory Equipments. Orlistat (ORL) was bought from the pharmacy.

All experimental procedures were conducted using independent samples (n = 10 per group) to ensure reproducibility and statistical validity. Animal carcasses were disposed of at the Qassim University Veterinary Hospital in accordance with international biosafety and ethical guidelines.

Ethics Approval

All experimental procedures were reviewed and approved by the Committee of

Research Ethics at the Deanship of Scientific Research, Qassim University (Approval No. 24-87-15). All protocols were conducted in accordance with institutional guidelines and the ethical principles outlined by the Institutional Animal Care and Use Committee (IACUC).

Induction of obesity

The weight and nose-anus length of each rat in the control and obese groups were measured at the beginning and end of the 12 weeks after 30 rats were given a high-fat diet. The weight (g) was divided by the square of the nose-anus length (cm^2) to determine the BMI. Animals will be deemed obese if their BMI exceeds 0.68 g/cm^2.

$$\text{Body mass index (BMI)} = \text{Body weight (g)} / \text{Length of nose-anus } (cm^2)$$

Preparation of a high-fat diet

46% fat (25.5% maize oil and 20.5% camel lard), 24% carbs, 20.3% proteins, 5% fibre, 3.7% salt mixture, and 1% vitamin mixture are combined to make the diet.[8]

Aqueous plant extract (PAE) preparation

After purchasing a *Carica papaya* from the local market in Qassim, the pulp was chopped into pieces, the skin was peeled off, and the seeds were extracted. After weighing and blending 500g of the fruits into a beaker, the *Carica papaya L.* was soaked in 1.5L of water for the entire night. Whatman filter paper measuring 125 mm was used to filter the juice, which was then freeze-dried and lyophilized using a freeze drier (Christ alpha1-4 Id plus, Germany) at a temperature of -35 to 41 degrees Celsius and a pressure of 0.1 to 0.5 mBar.[9]

Yield Exract

The whole filtrate was poured in an empty quick fit round bottom flask with known weight (W1) and then weighed again (W2) after solvent evaporation; finally, the yield percentage was calculated from the following formula[10]:

$$\text{Extract yield (g/100g crude herb)} = [W_2\text{-}W_1 / W_3] \times 100$$

Where W1is the empty and dry flask in grams
W2 is the weight of flask after freeze-drying in grams
W3 is the weight of the used crude powdered herb in grams.

***Carica papaya* (PAE) aqueous extract pancreatic lipase inhibition experiment (*in vitro*)**

Using p-nitrophenyl butyrate (PNPB) as a substrate, the activity of the lipase supplied by Spectrum Diagnostic Company (L) CAT no.221006, was evaluated in accordance with.[11]

Procedure description

To test lipase activity, PNPB was utilised as a substrate. At -20 °C, lipase stock solutions (1 mg/mL) were prepared in 0.1 mM potassium phosphate buffer (pH 6.0). Lipase inhibitory activity was measured by pre-incubating extracts (7.8, 15.62, 31.25, 62.5, 125, 250, 500, and 1000 ug/mL) or Orlistat (at equivalent concentrations) with Lipase for one hour at 30 °C in a potassium phosphate buffer (0.1 mM, pH 7.2, 0.1% Tween 80) before Lipase activity was assayed. The reaction was initiated by adding 0.1 µL of pNPB as a substrate to a final volume of 100 µL. After five minutes of incubation at 30 °C, a Biosystem 310-plus UV-visible device was used to measure the amount of p-nitrophenol produced in the reaction at 405 nm spectrophotometer.

The calculation for percentage inhibition is expressed calculation for percentage inhibition is expressed as

$$\% \text{ of percentage} = [A_{Control} - A_{Sample} / A_{Control}] \times 100$$

HPLC analysis of *Carica papaya* aqueous extract. (PAE)

An Agilent 1260 series was used for the HPLC analysis. Separation was carried out using a Zorbax Eclipse Plus C8 column (4.6 mm x 250 mm i.d., 5 ìm). The mobile phase was made up of 0.05% trifluoroacetic acid in acetonitrile (B) and 0.9 ml/min of water (A). The mobile phase's sequential linear gradient programming is as follows: 1–11 minutes (75% A); 11–18 minutes (60% A); 18–22 minutes (82% A); 22–24 minutes (82% A); 0–1 minute (82% A); and 0–1 minute (82% A). The multi-wavelength sensor was observed at 280 nm. Each sample solution had an injection volume of five microlitres (ìl). The temperature of the column was kept at 40 °C. Store in dark bottles at -80°C before using.

Stastical analysis

GraphPad Prism software version 11.0.0 (GraphPad Software, San Diego, CA, USA) was used to conduct statistical analyses. Statistical

analysis was performed using one-way ANOVA followed by Tukey's multiple comparisons test. Statistical significance was defined as a probability value of $P < 0.05$. $P < 0.01$ (**), $P < 0.001$ (***), and $P < 0.0001$ (****).

RESULTS

In vitro results

Data of figure 1 should that 100g of *Carica papaya* gives approximately 9.5% yield.

Figure 2"PAE demonstrated lipase inhibitory activity comparable to ORL, with no statistically significant difference observed between the groups ($p > 0.05$).

Data from Figure 3 revealed the ingredients of the PAE, which contains high concentrations of gallic acid, caffeic acid, and other valuable components, reflecting their potential capacity in fighting obesity.

In vivo results

Physiological results

The graph demonstrates a significant increase in body weight gain (%) in the HFD group compared with the control group, indicating the obesogenic effect of a high-fat diet. Treatment with HFD+ORL markedly reduced weight gain relative to the HFD group, confirming the anti-obesity effect of orlistat. Similarly, the HFD+PAE group showed a significant reduction in body weight gain compared with the untreated HFD group, suggesting that PAE exerts a protective effect against HFD-induced obesity ($p < 0.0001$).

HFD Impact: HFD induced a highly significant increase in BMI compared to the Control group. Treatment Efficacy: Both HFD+ORL and HFD+PAE significantly reduced BMI compared to the untreated HFD group. There is no statistically significant difference (ns) between the HFD-ORL and HFD-PAE groups. Neither treatment fully restored BMI back to the normal control level.

Giving male albino rats resulted in a significant decline in the levels of serum irisin when compared to the corresponding values of the control group, indicating that a high-fat diet negatively affects irisin secretion. While the daily oral intubation with orlistat resulted in a significant improvement when compared to the values of the HFD-fed group demonstrating the beneficial effect of orlistat in improving metabolic status. Likewise, administration of PAE to HFD-fed rats significantly increased serum irisin levels compared with the HFD group, suggesting that PAE ameliorates HFD-induced metabolic disturbances. figure 6. Despite the therapeutic upregulation, irisin levels in both treatment groups remained significantly below the normal control baseline.

Figure 7 illustrates a significant elevation in serum leptin levels in the HFD group compared with the control group, indicating the development

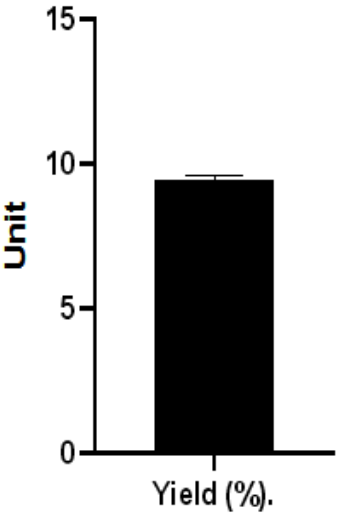


Fig. 1. Yield (%).

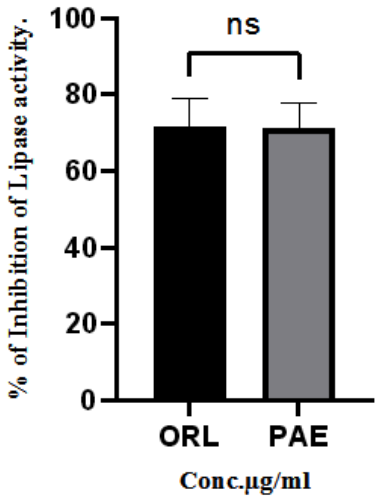


Fig. 2. % Inhibition of Lipase.

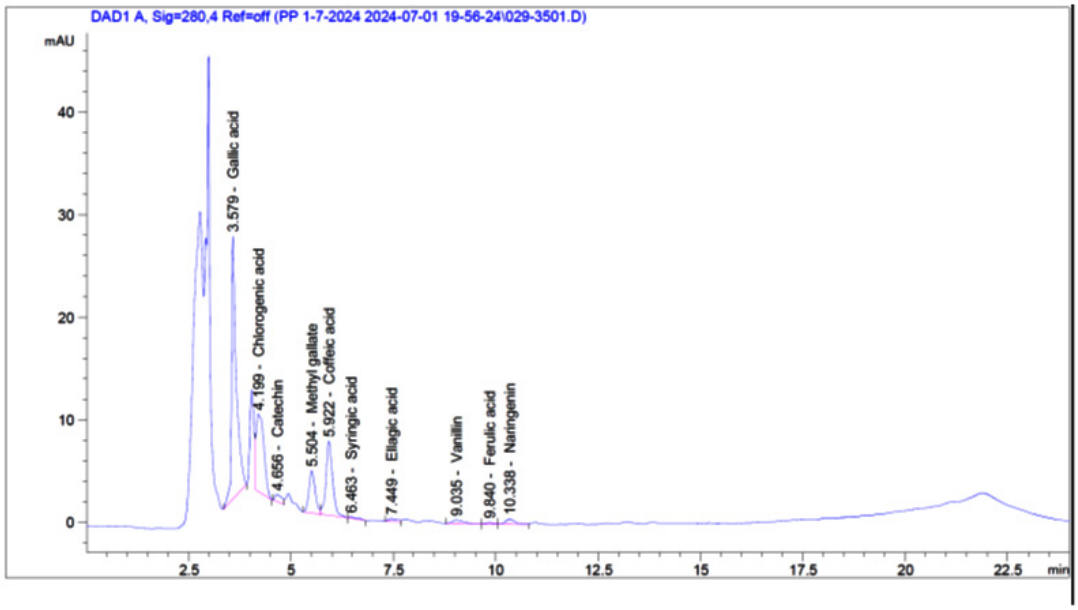


Fig. 3. HPLC fingerprint profile of aqueous extract of *Carica papaya.*10 phenolic compounds were identified.

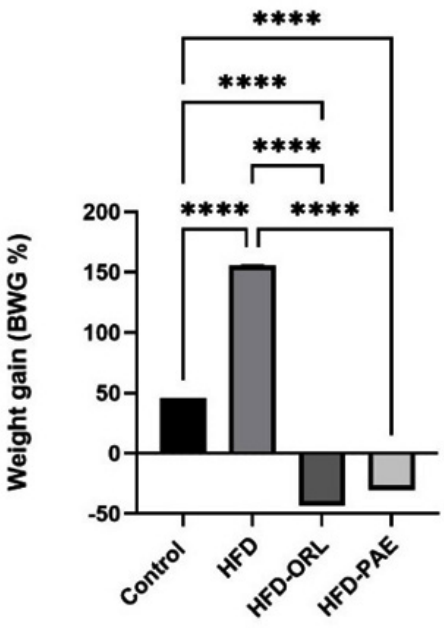


Fig. 4. Shows the effect of consumption of HFD and effect of oral intubation of orlistat and PAE separately body weight. Data are presented as mean ± SEM (n = 10 per group). Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparisons test. ****P < 0.0001.

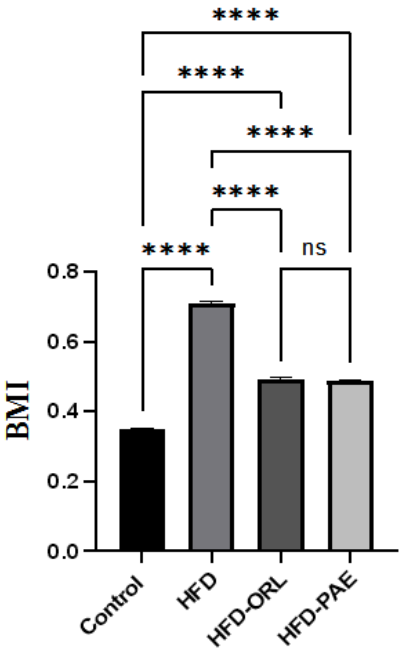


Fig. 5. Shows the effect of consumption of HFD and effect of oral intubation of orlistat and PAE separately Body Mass Index (BMI). Data are presented as mean ± SEM (n = 10 per group). Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparisons test. ****P < 0.0001.

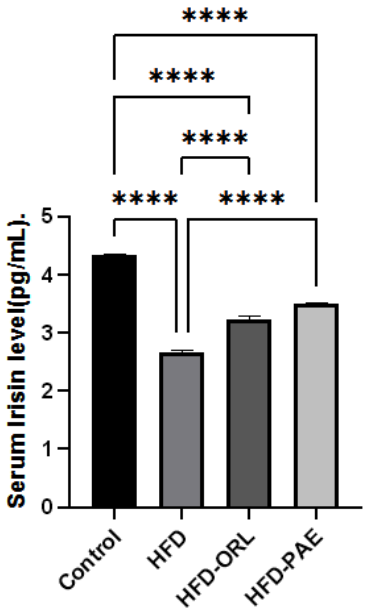


Fig. 6. Serum Irisin level (pg/mL). The Fig. shows the effects of HFD consumption and oral intubation of orlistat and PAE separately. Data are presented as mean ± SEM (n = 10 per group). Statistical analysis was performed using one-way ANOVA followed by Tukey's multiplecomparisons test. ****P < 0.0001.

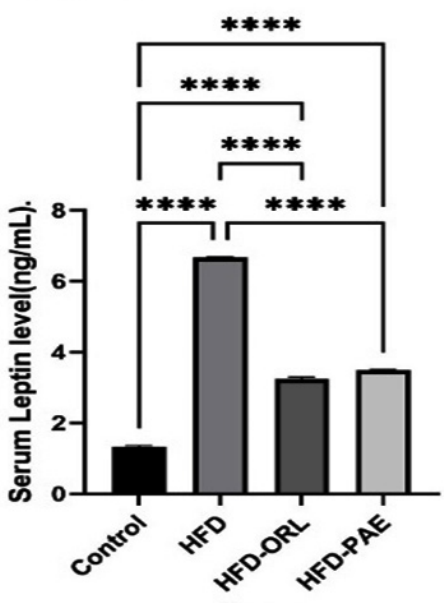


Fig. 7. Serum Leptin level (ng/mL). It shows the effects of HFD consumption and treating obese rats with orlistat and PAE separately. Data are presented as mean ± SEM (n = 10 per group). Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparisons test. ****P < 0.0001.

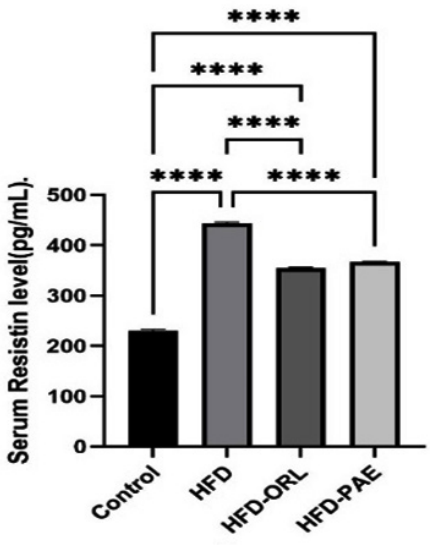


Fig. 8. Serum Resistin level (pg/mL). The fig. shows the effects of HFD consumption and oral intubation with orlistat and PAE separately. Data are presented as mean ± SEM (n = 10 per group). Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparisons test. ****P < 0.0001

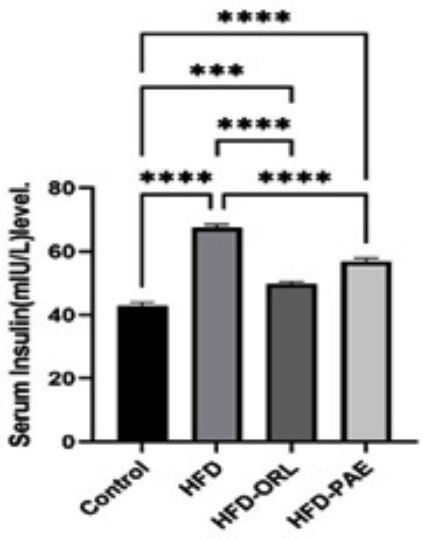


Fig. 9. Serum Insulin (mlU/mL). It shows the effects of HFD consumption and receiving orlistat and PAE separately. Data are presented as mean ± SEM (n = 10 per group). Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparisons test. ****P < 0.0001

of obesity and leptin dysregulation induced by a high-fat diet. Treatment with HFD+ORL markedly reduced serum leptin levels relative to the untreated HFD group, reflecting the anti-obesity and metabolic regulatory effects of orlistat. Similarly, the HFD+PAE group exhibited a significant decrease in serum leptin levels compared with the HFD group, suggesting that PAE ameliorates HFD-induced leptin alterations. Nevertheless, leptin levels in the treated groups remained higher than those of the control group.

The graph demonstrates a significant increase in serum resistin levels in the HFD group compared with the control group, indicating the induction of obesity-associated insulin resistance and metabolic dysfunction by the HFD. Treatment

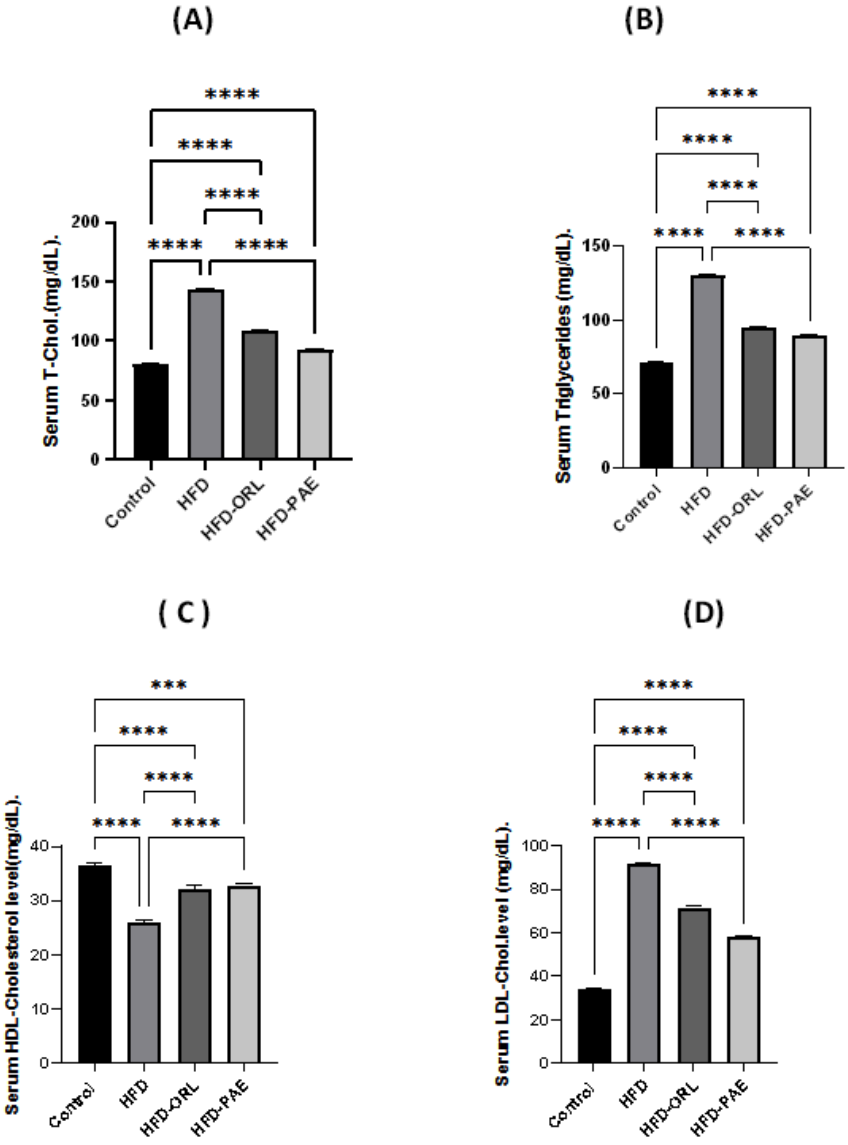


Fig.10. Serum Lipid profile :(A): Total Chol. (B):Trigly. (C)HDL-Chol. (D): LDL-Chol. Figures shows the effects of HFD consumption and receiving orlistat and PAE separately. Data are presented as mean ± SEM (n = 10 per group). Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparisons test. ****P < 0.0001

Table 1. Mean value of serum levels of Malondialdehyde and the pro-inflammatory cytokine IL1-ß of HFD, HFD+ORL and HFD+PAE- treated groups

Parameters Groups		MDA (nmol/mL)	IL-1ß(ng/mL)
Control	M ±SE	23.60±0.2	7.52±0.2
HFD	M ±SE	46±0.1	18±0.3
	% Change A	94.9%	139.4%
HFD+ORL	M ±SE	32.40±0.2	11.75±0.5
	% Change B	-29.6%	-34.7%
HFD + PAE	M ±SE	39.20±0.3	14.57±0.1
	Change B%	-14.8%	-19.1%

of obese rats with HFD significantly reduced serum resistin levels relative to the untreated HFD group, highlighting the beneficial metabolic effect of orlistat. Similarly, the oral intake of PAE showed a marked reduction in serum resistin levels compared with the HFD group, suggesting that PAE alleviates HFD-induced metabolic disturbances and inflammation. However, serum resistin levels in the treated groups remained elevated compared with the control group (figure 8).

The graph shows a significant increase in serum insulin levels in the HFD group compared with the control group, indicating the development of hyperinsulinemia and insulin resistance as a consequence of high-fat diet consumption. Treatment with HFD+ORL significantly decreased serum insulin levels relative to the untreated HFD group, demonstrating the beneficial effect of orlistat in improving insulin sensitivity. Similarly, the HFD+PAE group exhibited a marked reduction in serum insulin levels compared with the HFD group, suggesting that PAE ameliorates HFD-induced insulin dysregulation. Despite these improvements, insulin levels in the treated groups remained slightly elevated compared with the control group(fig.9).

Feeding male albino rats with HFD resulted in a highly significant rise in the levels of serum MDA and IL-1ß when compared with the data of unfed animals indicating increased lipid peroxidation and oxidative stress, resulting in an inflammatory response induced by the HFD, the oral treatment with ORL or PAE separately revealed a significant improvement declaring the antioxidant and anti-inflammatory activity of PAE as shown in table 1.

Feeding male albino rats with HFD for 12 successive weeks resulted in a highly significant rise in the levels of serum Total Chol., Trigly., and LDL-Chol. and a decline in HDL-Chol. indicating hypercholesterolemia, hypertriglyceridemia, impaired lipid metabolism and increased risk of cardiovascular complications. when compared with similar values of control animals. The oral treatment of obese rats with PAE resulted in a significant decline in levels of Total-Chol., Trigly., LDL-Chol. and improvement in levels of HDL-Chol. While the oral administration of ORL to obese rats resulted in a decrease in Total-Chol levels., Tigly., LDL-Chol. and a rise in HDL when compared to the corresponding values of HFD-fed animals, confirming the hypolipidemic effect of ORL and PAE (Figure 10).

DISCUSSION

Research on medicinal plants that may help in the control of obesity and reduce body weight is crucial as the search for new, safe, and effective anti-obesity drugs continues. Pro-inflammatory cytokines and obesity marker hormones were independently reduced when *Carica papaya* aqueous extract was used to treat obesity brought on by a high-fat diet. The anti-lipase action of papaya has been shown to be just as successful in controlling obesity as orilstat by lowering the absorption of fat.[12-16] The anti-lipase activity of PAE was indicated by the presence of gallic acid, caffeic acid, and nargarin, which were mentioned by many researchers to inhibit pancreatic lipase.[17-20] A researcher reported that the existence of gallic acid and quercetin in the crude

extracts contributes to the inhibition of pancreatic lipase, with the highest percentage inhibition of 82% for 1 ml of crude extract used. [16] Conversely, other compounds found in PAE have anti-aging, anti-inflammatory, and cancer-fighting properties, as well as being effective against diabetes, obesity, cardiovascular diseases, and gastrointestinal disorders.[21] The current study discovered that administering a high-fat diet to male albino rats for a consecutive 12 weeks resulted in a significant drop in serum irisin levels. This decline may be consistent with findings from,[9, 12] and it is a critical myokine that increases the risk of obesity and insulin resistance while also impairing metabolic performance.

Increased fat stores raise leptin levels under normal physiological settings, which should reduce appetite and boost energy expenditure. However, long-term consumption of high-fat diets can result in leptin resistance, a condition in which the body is less sensitive to the appetite-suppressive effects of leptin; the inflammatory processes associated with high-fat diets often worsen this resistance, which can also interfere with metabolic control and lead to weight gain. These findings align with. [22-26]

Male albino rats administered HFD orally for 12 consecutive weeks had considerably higher serum resistin levels. There is a strong evidence to support the hypothesis that diets high in fat raise resistin levels, which in turn lead to inflammation and insulin resistance.[27] This discovery highlights resistin as a potential target for therapeutic approaches in obesity-related illnesses and the importance of food composition in managing metabolic health. These results are consistent with a study that found dietary patterns heavy in saturated fats are linked to elevated levels of resistin.[28] In order to explain this increase, he pointed out that adipose tissue also functions as an endocrine organ, producing resistin and other adipokines that are essential for regulating metabolism.

Serum insulin levels significantly increased in male albino rats given a daily oral high-fat diet (HFD) for 12 weeks. These findings are in line with those of, [29-30]who observed that a high-saturated-fat diet increased levels of inflammation, leptin, and serum resistin, all of which promote insulin resistance and inflammation, which in turn compromise appetite control. Additionally, the body secretes more insulin when it consumes more fat, which promotes fat storage and complicates weight loss. This complicated association highlights the challenges in managing obesity in the context of high-fat diets. [31-32]

Because papaya is rich in vitamins, minerals, enzymes, and phytochemicals such flavonoids, phenolic acids, carotenoids, and alkaloids, serum irisin, leptin, resistin, and insulin levels considerably improved in obese rats fed PAE orally.[12] These phenolic chemicals regulate appetite, lipid metabolism, intestinal flora, and energy expenditure. PAE, which is high in flavonoids, may help prevent obesity by enhancing lipolysis and energy expenditure as well as the metabolism of fatty acids and carbohydrates through â-oxidation.[33] For example, Chlorogenic acid (CGA) a polyphenol found abundantly in coffee, tea, and fruits acts as a potent cellular energy regulator. It stimulates [AMP]-activated protein kinase AMPK, which in turn drives the expression and activation of the metabolic coactivator. This cascade is central to metabolic fitness and energy. CGA activates the AMPK/ PGC1á pathway, which causes browning of white adipose tissue (WAT) and increased thermogenic activity in brown adipose tissue (BAT).[34] It also lowers blood sugar by preventing pancreatic lipase and á-amylase from breaking down fats and carbohydrates, respectively. [35-36] PAE is rich in naringenin, a well-known flavonoid has anti-inflammatory and insulin-sensitive properties. These combined advantages raise the potential of PAE in weight loss and obesity prevention strategies. Additionally, naringenin can control resistin, an adipokine associated with insulin resistance.[37] These effects account for naringenin's anti-inflammatory and insulin-sensitizing qualities.

Serum irisin levels significantly improved in male obese albino rats given a daily oral injection of orlistat (50 mg/kg b.wt./day) by gavage for 45 days as compared to the corresponding values of the group of animals that received a HFD. The results of this study are in line with earlier research that discovered that the reduction of body fat caused by orlistat treatment may have an impact on the regulation of hormones and metabolic pathways, particularly those involving irisin, a myokine involved in increased energy expenditure and the browning of white adipose tissue. It has been shown

that irisin, which is produced when the FNDC5 protein is broken down, promotes "browning," or the conversion of white fat into brown fat, which increases thermogenesis and energy expenditure. The relationship between orlistat-induced weight reduction and irisin levels is particularly interesting since body fat loss may impact irisin secretion.[14] While induced significant decline in levels of serum leptin

These findings are consistent with a 2019 study that discovered leptin, a hormone that controls appetite and energy expenditure, is produced by adipose tissue. Increased appetite and a lower resting metabolic rate (RMR) may result from a drop in leptin levels, making weight control more difficult. As fat mass declines due to weight loss, leptin levels usually decrease.[38]

Papain is a powerful proteolytic enzyme found in the white, milky latex of raw, unripe papaya. It is primarily known for its ability to break down proteins into smaller amino acids, making it a key component in food, medical, and industrial applications.

Losing weight lowers resistin levels, suggesting a possible link between adipokine regulation and weight management. A study on mice[39]revealed that in HFD-induced obese mice and 3T3-L1 pre-adipocytes, papain therapy might prevent the development of obesity by controlling lipid accumulation and reducing blood lipid levels by downregulating adipogenic factors such as PPAR, C/EBP, and SREBP-1. Additionally, papain reduced inflammation linked to obesity by blocking leptin, pro-inflammatory cytokines, and increasing adiponectin via AMPK activation. Orlistat, a lipase inhibitor used to treat obesity, may be important in this area because it promotes weight loss, which may indirectly lower resistin levels and improve insulin sensitivity.

The primary cause of the association between orlistat and resistin is the drug's impact on body weight and fat metabolism. Orlistat may indirectly aid in weight loss by reducing the production of resistin by adipocytes, which aids in weight loss. Insulin resistance and related inflammatory states may be lessened by reducing resistin levels with weight-loss techniques like orlistat. Resistin levels affect inflammatory markers linked to obesity, such as TNF-α and IL-6. It has been demonstrated that orlistat administration lowers these inflammatory markers, suggesting a two-pronged mechanism by which orlistat helps with obesity-related weight reduction. [40]

Male albino rats fed HFD on a daily basis showed a significant increase in serum levels of malondialdehyde, the final product of lipid peroxidation. These results are consistent with,[41] which suggests that feeding high-fat diets in unhealthy fats are linked to the elevation of MDA levels through mechanisms involving oxidative stress, lipid peroxidation, and chronic inflammation. A key component of this process is the generation of reactive oxygen species (ROS), which harm cells by destroying polyunsaturated fatty acids in cell membranes and causing a number of health issues.[42]

According to one study, orlistat may indirectly improve psychomotor function by The daily dietary fat intake of male albino rats significantly increased the levels of serum interleukin 1-ß and interleukin-6. These results are consistent with,[28–29] and it has been suggested that this increase may be caused by HFD's alteration of the gut microbiome, which favours bacteria that increase intestinal permeability and promote inflammation, leading to elevated levels of lipopolysaccharides (LPS) in circulation. This mechanism is important because LPS can trigger immunological responses and, by activating NF-kB. This paradox implies that orlistat may lessen oxidative stress by preventing the absorption of fat, but it may potentially raise it in specific metabolic circumstances.

Serum levels of interleukin 1-ß and interleukin-6 were markedly elevated in male albino rats that consumed fat on a daily basis. These findings are in line with ,[43–49] and it has been proposed that this increase could be brought on by HFD's modification of the gut microbiome, which favours bacteria that promote inflammation and increase intestinal permeability, raising blood levels of lipopolysaccharides(LPS).[40]

This process is essential because LPS can provoke immunological reactions and further contribute to the production of pro-inflammatory cytokines such as IL-6 and IL-1β by activating NF-kB.[41,46]

The most common antioxidants in PAE are CGA, Naringenin, ferulic acid, vanillin, ellagic acid, caffeic acid, and methyl gallate in

addition to the high conc. of vitamin c E and beta carotene, which scavenge free radicals, protect cell membrane lipids from oxidation, enhance mitochondrial function, and boost antioxidant enzyme activity. These enzymes detoxify reactive oxygen species before they damage lipids. These findings are consistent with [47–51]. Since oxidative stress is known to play a role in the onset and pro-inflammatory pathways like NF-κB. These findings align with. [42–46] These antioxidant benefits may be especially important in the context of obesity, since oxidative stress is known to contribute to the development and progression of obesity-related issues. [51–53] Steatohepatitis , or inflammation of the liver brought on by obesity, may be lessened by this reduction in inflammatory cytokines.[46,50,51]

CONCLUSION

In conclusion, the present study demonstrated that papaya aqueous extract may have beneficial effects against the metabolic disturbances caused by a high-fat diet in rats. Administration of the extract appeared to improve physiological and biochemical parameters, suggesting its potential antioxidant and protective properties. Rats receiving the papaya extract showed better outcomes compared with untreated high-fat diet groups, indicating that papaya could help reduce the harmful effects associated with obesity and lipid metabolism disorders. These beneficial effects were be evidenced by decreasing the percentage of weight gain, improving obesity hormonal markers, lipid profile due to its anti-lipase activity, due to its high content of vitamins, polyphenols, and flavonoids, including nargirin , caffeic acid, synergic acid, methyl gallate vitamin c , vitamin E and the proteolytic papain enzyme. These polyphenolic components, scavenge free radicals and prevent oxidative stress by decreasing levels of MDA and pro-inflammatory cytokines. Therefore, papaya aqueous extract may serve as a natural therapeutic agent for managing complications induced by high-fat diets. However, further studies are needed to determine the exact mechanisms and evaluate its effectiveness in humans.

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The authors do not have any conflict of interest.

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This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

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Not Applicable.

Author Contributions

Heba Fawzy Gomaa: Designed the experiments, performed the experiments, collected data, discussed the results and strategy, supervised, directed, managed the study and gave final approval of the version to be published; Ruyuf Mohammed AL-foraih: Designed the experiments, performed the experiments, collected data, discussed the results and strategy

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