



Protective role of *Phyllanthus acidus* ethanolic extract in modulating leptin, dyslipidemia, insulin resistance, and oxidative stress in diet-induced obesity: A comparative study with *Zingiber aromaticum*

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ABSTRACT

Obesity is associated with metabolic disturbances, including insulin resistance, dyslipidemia, and leptin dysregulation. Natural compounds with antioxidant and anti-inflammatory properties are being explored as potential alternatives to pharmacological agents. The present work investigated the preventive and attenuating effects of ethanolic extracts of *Phyllanthus acidus* (PA) and *Zingiber aromaticum* (ZA) against metabolic disturbances in a high-fat high-fructose (HFHF) diet-induced obesity model. Rats were divided into groups and given either a normal diet, HFHF diet, or HFHF diet combined with orlistat, PA, or ZA for 12 weeks. Key metabolic parameters were evaluated. The HFHF diet significantly increased BMI, adiposity index, triglycerides, cholesterol, fasting glucose, insulin, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), leptin, and malondialdehyde (MDA) compared with the standard diet. Orlistat reduced leptin and oxidative stress, but had a limited impact on glucose-insulin indices. In contrast, ZA extract attenuated leptin and MDA elevation, with moderate improvements. The ethanolic PA extract consistently demonstrated the most comprehensive effects, attenuating HFHF-induced elevations in fasting glucose, reducing hyperinsulinemia and HOMA-IR, improving lipid profiles, and lowering leptin and MDA to levels comparable with the normal diet and orlistat groups. These findings indicate that the ethanolic PA extract exerts more comprehensive metabolic, hormonal, and oxidative stress-modulating effects than ZA, and shows efficacy comparable to orlistat in several outcomes.

1. INTRODUCTION

Obesity has become a global health concern, with its prevalence gradually rising in both industrialized and developing

countries. In addition to significant weight gain, obesity is closely linked to many metabolic disorders, such as dyslipidemia, insulin resistance, and systemic inflammation, which together elevate the risk of type 2 diabetes mellitus and cardiovascular illnesses. The complex etiology of obesity highlights the necessity for treatment approaches that decrease body weight and address the fundamental metabolic dysfunction [1].

Present pharmacological treatments, including orlistat, exhibit restricted long-term efficacy and frequently entail adverse gastrointestinal side effects that hinder adherence [2]. These constraints have stimulated increasing interest in natural compounds exhibiting pleiotropic bioactivities as safer alternatives

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or complements to traditional anti-obesity pharmaceuticals. Botanical extracts possessing antioxidant, anti-inflammatory, and metabolic-regulating characteristics offer a viable strategy to address the intricate pathophysiology of obesity [3].

Phyllanthus acidus and *Zingiber aromaticum* are traditionally used as edible plants and components of herbal preparations in several Asian countries [4,5]. *Phyllanthus acidus* leaves have been reported to contain diverse bioactive phytochemicals, including flavonoids, phenolic acids, tannins, alkaloids, terpenoids, and steroids, many of which exhibit antioxidant, anti-inflammatory, and metabolic regulatory activities. These compounds are known to scavenge reactive oxygen species, modulate inflammatory mediators, and influence glucose and lipid metabolism [6]. Previous work by Chongsa *et al.* [7] demonstrated that aqueous extracts of *P. acidus* reduced visceral fat and improved lipid profiles in middle-aged healthy rats, supporting its potential role in lipid metabolism. However, its effects on hormonal regulators such as leptin and its mechanisms under diet-induced metabolic stress have not been fully explored [7].

Similarly, *Z. aromaticum* Val. (aromatic ginger) contains terpenoids, phenolic compounds, flavonoids, and essential oil constituents that exhibit antioxidant and anti-inflammatory properties [8]. Members of the *Zingiberaceae* family have been reported to modulate lipid metabolism, improve insulin sensitivity, and attenuate oxidative stress, suggesting that *Z. aromaticum* may offer complementary or distinct mechanisms compared to *P. acidus* [9].

The presence of these phytochemical classes provides a biochemical rationale for investigating PA and ZA as candidates for preventing obesity-associated metabolic disturbances. Although various studies have reported metabolic benefits of *Phyllanthus* and *Zingiber* species, direct comparative *in vivo* studies evaluating both plants under identical metabolic conditions remain scarce, thereby supporting the need for preclinical investigation before clinical translation. Accordingly, this study evaluated the preventive and attenuating effects of ethanolic extracts of *P. acidus* and *Z. aromaticum*, compared with orlistat, on adiposity, lipid metabolism, glucose–insulin homeostasis, leptin regulation, and oxidative stress in a high-fat high-fructose diet-induced metabolic dysfunction model.

2. MATERIALS AND METHODS

2.1. Material and plant extraction

Dried powders of *P. acidus* (*L. Skeels* leaves (PA) and *Z. aromaticum* Val. Rhizomes (ZA) were obtained from the UPT Herbal Laboratory of Materia Medika, Batu, Malang, Indonesia. A total of 900 g of PA leaf powder was macerated with 96% ethanol for 48 hours with occasional stirring, filtered, and the residue was re-macerated twice. The combined filtrates were evaporated to yield 65.7 g of PA extract. Similarly, 1,000 g of ZA rhizome powder was extracted using the same procedure, producing 58 g of ZA extract.

2.2. Qualitative phytochemical analysis

Qualitative phytochemical screening was performed using standard color and precipitation tests. The presence of flavonoids was indicated by an intense yellow color that faded

with dilute 10% NaOH. Phenolic and tannin compounds were detected with 5% and 1% FeCl₃, respectively, resulting in deep blue or greenish-black colors. Alkaloids were assessed using Mayer's and Wagner's reagents, with positive results indicated by cream-colored or reddish-brown precipitates, respectively. Steroids were tested via the Liebermann–Burchard reaction, showing green or blue. Terpenoids were identified using H₂SO₄, evidenced by a reddish-brown layer at the interface. All tests were qualitative, reporting results as positive (+) or negative (–) based on visual indicators, without quantitative measurements [10].

2.3. Animals and experimental protocol

All experimental procedures were approved by the Health Research Ethics Committee, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta, Indonesia (No. 029/EC-HC-KEPK FKIK UMY/IV/2023). Thirty male Wistar rats (8–10 weeks old, 200 ± 20 g) were obtained from the Food and Nutrition Study Center, Universitas Gadjah Mada, Indonesia. Animals were randomly housed in individual cages under controlled conditions (12:12 hours light–dark cycle, room temperature 22°C ± 2°C, relative humidity 60% ± 5%). Animals were acclimatized for 7 days before the experiment.

Rats were randomly allocated into experimental groups using a computer-generated random number sequence after acclimatization. Investigators responsible for biochemical assays and data analysis were blinded to group assignments. There were five groups for the experimental animals (*n* = 6 per group). The groups were divided as (1) Normal diet (ND), rats maintained on standard chow; (2) Obese control (OB), rats induced with a high-fat high-fructose (HFHF) diet without treatment; (3) Orlistat-treated obese group (OB + O), rats fed HFHF diet and administered orlistat at 10 mg/kg BW/day; (4) PA-treated obese group (OB + PA), rats fed HFHF diet and administered *Phyllanthus acidus* extract at 300 mg/kg BW/day; and (5) ZA-treated obese group (OB + ZA), rats fed HFHF diet and administered *Zingiber aromaticum* extract at 500 mg/kg BW/day.

The doses of *P. acidus* and *Z. aromaticum* extracts were based on previously reported effective preclinical ranges and preliminary laboratory observations indicating biological activity without overt toxicity [11,12]. The orlistat dose was selected from established experimental obesity models and corresponds, following body surface area–based conversion, to the therapeutic dose range in humans [13].

The normal diet was prepared according to the AIN-93M standard formulation, providing a total energy content of 3.80 kcal/g. The HFHF diet was developed by modifying the AIN-93M formulation to increase the proportion of fat and by adding 25% (w/v) fructose to the drinking water, resulting in a total energy content of 7.03 kcal/g (Table S1) [14,15]. To induce obesity, both diet and water were supplied *ad libitum* for 12 weeks. The extracts were administered orally once daily, starting concurrently with the initiation of the HFHF diet. Body weight was measured biweekly using a digital precision scale (±0.01 g), while naso-anal length was assessed using a digital

caliper. To measure body mass index (BMI), the formula is body weight (g)/[naso-anal length (cm)]² [16].

The HFHF diet was selected to induce obesity with insulin resistance, dyslipidemia, and oxidative stress, reflecting the pathophysiological features of human metabolic syndrome. Fructose supplementation accelerates hepatic lipogenesis and impairs insulin signaling, while dietary fat promotes adiposity and inflammation.

Finally, the rats were fasted for 8 hours and anesthetized with chloroform. Blood was collected from the orbital vein, and serum was isolated by centrifugation at 3,000 rpm for 20 minutes at 4°C. It was stored at -70°C for subsequent biochemical analyses. Following blood collection, rats were euthanized by cervical dislocation. Epididymal, visceral, and retroperitoneal adipose tissues were excised, rinsed with NaCl, and weighed. The adiposity index was calculated as [(epididymal + visceral + retroperitoneal fat)/final body weight]×100 [17].

2.4. Serum biochemical analysis

Fasting glucose, triglycerides (TG), total cholesterol (TC), low-density cholesterol (LDL), and high-density cholesterol (HDL) levels in serum were measured using a blood chemistry autoanalyzer (Thermo Fisher Scientific) with enzymatic colorimetric assay kits according to the manufacturer's instructions. Serum insulin, leptin, and malondialdehyde (MDA) were measured using commercial ELISA kits (Elabscience; insulin: Cat. No. E-EL-R2466; leptin: Cat. No. E-EL-R0582; MDA: Cat. No. E-EL-0060) following the manufacturers' protocols. The detection ranges were 0.5–30 ng/ml for insulin, 0.1–10 ng/ml for leptin, and 0.1–20 nmol/ml for MDA, with intra- and inter-assay coefficients of variation below 10% and 12%, respectively. Serum samples were diluted (1:5) for insulin and leptin assays when necessary to ensure values fell within the standard curve. MDA concentrations obtained from the standard curve (nmol/mL) were normalized to total protein content and expressed as nmol/mg protein. Insulin resistance was estimated using the HOMA-IR formula: [fasting glucose (mg/dl) × fasting insulin (μU/ml)]/405. Insulin values originally measured in ng/ml were converted to μU/ml using an assay-appropriate conversion factor (1 ng/mL ≈ 28.8 μU/ml) before calculation [18].

2.5. Statistical analysis

Data were analyzed using SPSS. The Shapiro–Wilk test was used to measure normality test. One-way ANOVA followed by Tukey's post hoc test was applied to statistically analyze BMI, adiposity index, and biochemical parameters. The HFHF-fed obese group (OB) served as the primary control for evaluating the effects of *P. acidus* and *Z. aromaticum*, whereas the OB+O (HFHF + orlistat) group was included as a positive pharmacological reference. All analyses were conducted using two-tailed tests. It was presented as mean ± SD (*n* = 6). Data can be stated as statistically significant if the confidence level is above 95% (*p* < 0.05). Superscript letters denote significant differences at *p* < 0.05: a = compared with ND, b = compared with OB, c = compared with OB+O, d = compared with OB+PA.

3. RESULTS

3.1. Qualitative Phytochemical analysis

Qualitative phytochemical analysis indicated that extracts of both *P. acidus* and *Z. aromaticum* comprised flavonoids, phenolic compounds, tannins, alkaloids, terpenoids, and steroids. Colorimetric assays demonstrated the presence (+) or absence (–) of significant secondary metabolites. The intensity of color reactions suggested a greater number of flavonoids and phenolics in *P. acidus*, suggesting a higher concentration of antioxidant elements compared to *Z. aromaticum* (Table 1).

3.1.1. The impact of oral dosages of *P. acidus* and *Z. aromaticum* extracts on the body composition in HFHF diet-induced obese rats

By the end of the 12th week of dietary induction, the OB group showed a significant increase in BMI compared to the ND group (351 ± 3.22 vs. 281.3 ± 3.14, *p* < 0.001). Concomitant oral administration of PA and ZA extracts during HFHF feeding significantly attenuated HFHF-induced BMI elevation relative to the OB group. Notably, the final BMI of the OB+PA group did not differ significantly from that of either the ND or OB+O groups, indicating that PA extract and orlistat comparably attenuated HFHF-associated body weight gain, maintaining BMI at levels similar to normal-diet rats (Fig. 1).

Consistent with BMI changes, the adiposity index was markedly increased in the OB group compared with the ND group (8.74 ± 0.68 vs. 3.0 ± 0.29; *p* < 0.001). Co-administration of PA extract significantly attenuated HFHF-induced adiposity compared with the OB group (3.66 ± 0.31 vs. 8.74 ± 0.68; *p* < 0.001) and produced a greater reduction than ZA extract (3.66 ± 0.31 vs. 6.17 ± 0.35; *p* < 0.001). Furthermore, the adiposity index in the OB+PA group was not significantly different from that observed in the OB+O or ND groups (3.66 ± 0.31 vs. 3.59 ± 0.37 vs. 3.0 ± 0.29; *p* > 0.05), indicating effective attenuation of HFHF-induced fat accumulation (Fig. 2).

3.1.2. The impact of oral dosages of *P. acidus* and *Z. aromaticum* extracts on dyslipidemia and metabolic regulation in obesity model rats

Administration of a HFHF diet induced marked alterations in lipid metabolism compared with the regular

Table 1. Qualitative phytochemical screening of *Phyllanthus acidus* and *Zingiber aromaticum* extracts.

Phytochemical	Reagent/ method	<i>Phyllanthus acidus</i> extract	<i>Zingiber aromaticum</i> extract
Flavonoids	NaOH 10%	++	+
Phenolic	FeCl ₃ 5%	++	+
Tannins	FeCl ₃ 1%	+	+
Alkaloids	Wagner's	+	+
Steroids	H ₂ SO ₄	+	+
Terpenoids	H ₂ SO ₄	+	+

(++) = strong positive reaction; (+) = positive reaction; (–) = absent or negative reaction.

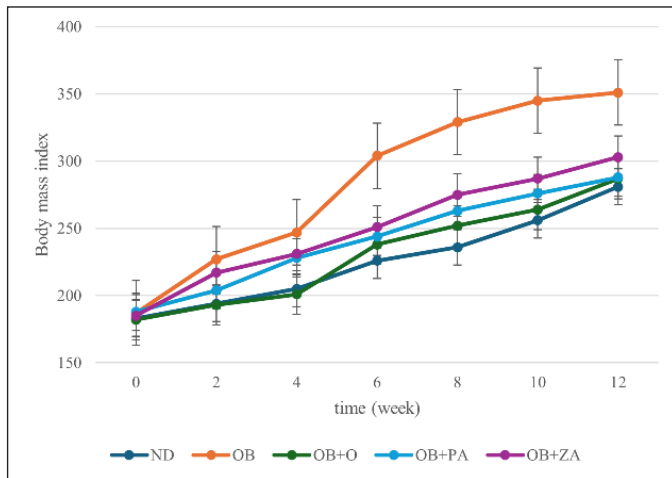


Figure 1. Changes in BMI of Wistar rats over 12 weeks. Data are presented as mean \pm SD ($n = 6$). The OB group showed a significant increase in BMI compared to the ND group, while the OB+O, OB+PA, and OB+ZA groups demonstrated lower BMI values than the OB group.

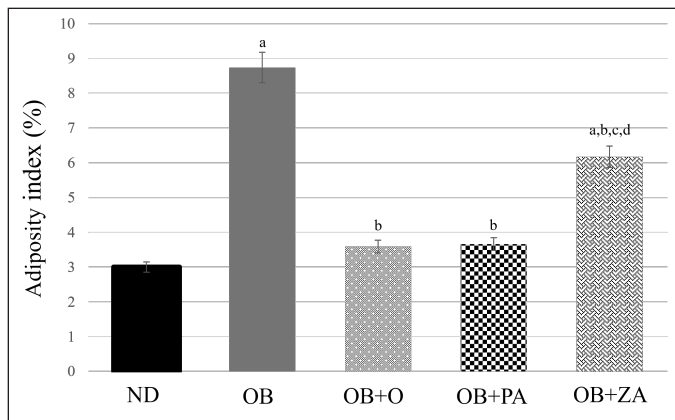


Figure 2. Comparison of adiposity index among Wistar rat groups. Values are presented as mean \pm SD ($n = 6$). Different superscript letters indicate significant differences at $p < 0.001$.

diet (ND) group. OB exhibited significantly elevated serum FFA ($182.4 \pm 1.29 \mu\text{mol/l}$ vs. $60.1 \pm 1.39 \mu\text{mol/l}$, $p < 0.05$), TG (149.67 ± 6.25 vs. $79.50 \pm 2.66 \text{ mg/dl}$, $p < 0.05$), total cholesterol (151.0 ± 4.93 vs. $90.5 \pm 3.27 \text{ mg/dl}$, $p < 0.05$), and LDL (83.69 ± 1.33 vs. $26.22 \pm 2.31 \text{ mg/dl}$, $p < 0.05$), accompanied by a significant reduction in HDL (33.50 ± 3.73 vs. $58.12 \pm 4.07 \text{ mg/dl}$, $p < 0.05$) (Table 2).

Concomitant administration of orlistat during HFHF feeding (OB+O) significantly attenuated HFHF-induced dyslipidemia, with TG, TC, and HDL levels shifting toward normal values. Similarly, co-administration of *P. acidus* extract (OB+PA) and *Z. aromaticum* extract (OB+ZA) significantly attenuated HFHF-induced lipid abnormalities. Notably, the OB+PA group exhibited marked reductions in serum FFA, TG, total cholesterol, and LDL, with HDL levels comparable to those of the ND group. The OB+ZA group also demonstrated favorable effects, although the magnitude of improvements was less pronounced than that observed in the OB+O and OB+PA groups (Table 2).

3.1.3. The impact of oral dosages of *P. acidus* and *Z. aromaticum* extracts on serum glucose and insulin levels in obese rats

Impairment of glucose homeostasis, characterized by elevated fasting blood glucose, serum insulin, and HOMA-IR, was observed in the OB group following HFHF feeding. The fasting blood glucose level in the OB+PA group was significantly lower than in the OB+O and OB+ZA groups, indicating attenuation of HFHF-induced hyperglycemia, and was comparable to that of the ND group. A similar trend was observed for serum insulin and HOMA-IR, with the OB+PA group showing greater reductions than the OB+O and OB+ZA groups, reflecting attenuation of HFHF-induced hyperinsulinemia and insulin resistance, although the values did not fully normalize to those of the ND group (Table 3).

3.1.4. The impact of oral dosages of *P. acidus* and *Z. aromaticum* extracts on serum leptin and oxidative stress markers in obese rats

Rats fed the HFHF diet (OB group) exhibited a significant increase in serum leptin ($2.92 \pm 0.16 \text{ ng/ml}$) and

Table 2. Serum free fatty acids and lipid profile in control and treated obese rats.

Analyzes	ND	OB	OB + O	OB + PA	OB + ZA
FFA ($\mu\text{mol/l}$)	60.1 ± 1.39	182.4 ± 1.29^a	$104.7 \pm 1.79^{a,b}$	$93.0 \pm 1.29^{a,b,c}$	$129.7 \pm 1.19^{a,b,c,d}$
TG (mg/dl)	79.50 ± 2.66	149.67 ± 6.25^a	79.00 ± 3.52^b	$103.17 \pm 7.27^{a,b,c}$	$108.0 \pm 6.78^{a,b,c}$
Total cholesterol (mg/dl)	90.5 ± 3.27	151.0 ± 4.93^a	89.3 ± 5.57^b	92.0 ± 2.96^b	$103.17 \pm 9.15^{a,b,c,d}$
LDL (mg/dl)	26.22 ± 2.31	83.69 ± 1.33^a	$40.88 \pm 3.83^{a,b}$	$41.08 \pm 2.23^{a,b}$	$41.3 \pm 4.07^{a,b}$
HDL (mg/dl)	58.12 ± 4.07	33.50 ± 3.73^a	58.33 ± 2.16^b	57.67 ± 3.26^b	$49.50 \pm 1.87^{a,b,c,d}$

Values are presented as mean \pm SD ($n = 6$). Different superscript letters indicate significant differences at $p < 0.05$.

Table 3. Serum glucose and insulin levels in control and treated obese rats.

Analyzes	ND	OB	OB + O	OB + PA	OB + ZA
FBG (mg/dl)	94.33 ± 2.58	166.0 ± 11.47^a	$121.5 \pm 4.76^{a,b}$	$104.5 \pm 5.99^{b,c}$	$136.0 \pm 2.89^{a,b,c,d}$
Insulin ($\mu\text{U/ml}$) [*]	10.0 ± 0.34	22.3 ± 0.88^a	$15.1 \pm 0.26^{a,b}$	$11.9 \pm 0.27^{a,b,c}$	$16.8 \pm 0.24^{a,b,c,d}$
Homa-IR	2.33 ± 0.06	9.16 ± 0.83^a	$4.53 \pm 0.14^{a,b}$	$3.08 \pm 0.20^{a,b,c}$	$5.66 \pm 0.16^{a,b,c,d}$

^{*}Insulin values were converted from ng/mL to $\mu\text{U/mL}$ prior to HOMA-IR calculation. Values are presented as mean \pm SD ($n = 6$). Different superscript letters indicate significant differences at $p < 0.05$.

Table 4. Serum leptin and MDA levels in control and treated obese rats.

Analyzes	ND	OB	OB+O	OB + PA	OB + ZA
Leptin (ng/ml)	0.48 ± 0.07	2.92 ± 0.16 ^a	2.02 ± 0.38 ^{a,b}	0.66 ± 0.03 ^{b,c}	0.78 ± 0.02 ^{b,c}
MDA (nmol/mg protein)	3.20 ± 0.14	7.31 ± 0.38 ^a	5.92 ± 0.27 ^{a,b}	3.83 ± 0.41 ^{a,b,c}	4.20 ± 0.30 ^{a,b,c}

Values are presented as mean ± SD ($n = 6$). Different superscript letters indicate significant differences at $p < 0.05$.

MDA levels (7.31 ± 0.38 nmol/mg protein) compared with the ND group (0.48 ± 0.07 ng/ml and 3.20 ± 0.14 nmol/mg protein, respectively; $p < 0.05$). The OB+O group demonstrated a significant attenuation of HFHF-induced elevations in leptin (2.02 ± 0.33 ng/ml) and MDA levels (5.92 ± 0.27 nmol/mg protein) relative to the OB group. Both the OB+PA and OB+ZA groups also significantly attenuated HFHF-induced increases in leptin to levels approaching those of the ND group, and more markedly reduced HFHF-induced MDA accumulation compared with the OB and OB+O groups (Table 4).

4. DISCUSSION

Qualitative phytochemical analysis verified the existence of flavonoids, phenolic compounds, tannins, alkaloids, terpenoids, and steroids in the extracts of both *P. acidus* and *Z. aromaticum*. However, more intense color changes were noted in the *P. acidus* extract during the flavonoid test with 10% NaOH and the phenolic test with 5% FeCl₃, suggesting a greater relative quantity of these antioxidant compounds compared to *Z. aromaticum*. While quantitative standardization (e.g., LC–MS profiling) was not performed, the extraction was conducted under controlled conditions ensuring reproducible composition of key phytochemical groups.

The combined intake of a HFHF diet in rats for 12 weeks in this study successfully induced obesity and replicated the pathophysiological circumstances seen in human obesity [19]. This model exhibits notable alterations in visceral fat accumulation in rats, resulting in the enlargement of adipocytes, which play a role in weight gain [20]. The presence of fructose in the diet leads to the buildup of lipogenic triacylglycerol and cholesterol in the liver, which subsequently reduces insulin sensitivity and induces glucose intolerance, thus contributing to insulin resistance [18].

The HFHF diet also induces changes in inflammation and oxidative stress, which are indicative of obesity-related disorders [21]. In particular, excessive fat accumulation was accompanied by a marked elevation in circulating leptin levels, reflecting the development of leptin resistance. This phenomenon is commonly observed in diet-induced obesity, where hyperleptinemia fails to suppress appetite and energy storage, exacerbating adiposity and metabolic dysfunction [22].

This investigation assessed, for the first time, the comparative effects of PA and ZA extracts on body composition. The OB group, which did not receive any treatment, administered PA and ZA extracts, along with an HFHF diet, reduced fat accumulation and continued body weight loss (Figs. 1 and 2). Even the final BMI in the OB+PA group did not show any significant difference when compared with the ND and OB+O groups.

The current findings align with, yet extend, the earlier observations of Chongsa *et al.* [7], who reported that aqueous

P. acidus extracts reduced adiposity and improved lipid profiles in non-obese rats [7]. Our data demonstrate that ethanolic PA extract exerts broader metabolic regulation by improving insulin sensitivity, restoring leptin homeostasis, and reducing oxidative stress under diet-induced obesity conditions. This integrated response suggests that PA targets multiple nodes within the insulin–leptin–oxidative axis rather than lipid metabolism alone. The enhanced phenolic and flavonoid content in the ethanolic extract may underlie these mechanisms, offering a plausible molecular basis for its superior efficacy compared with *Z. aromaticum* and equivalence to orlistat.

The anti-obesity effect of *P. acidus* extract demonstrated in this study is also consistent with evidence from related species such as *P. emblica*. Polyphenol-rich extracts from *P. emblica* may restrict the differentiation of 3T3-L1 cells by diminishing the expression of PPAR γ and C/EBP α , and reducing intracellular lipid accumulation [23–25]. Specific evidence on the impact of PA extract on preadipocyte development is limited. However, the bioactive constituents of PA extracts, including flavonoids, phenolics, terpenoids, and alkaloids [4,26,27], enable these extracts to work via analogous mechanisms to other extracts that have been tested [28,29]. Flavonoids and phenolics, particularly quercetin, gallic acid, and other phenolic acids, have long been associated with anti-obesity activity through adipogenesis inhibition mechanisms [28,30,31]. This provides a strong biological foundation to clarify the *in vivo* observations of fat formation and weight reduction in the test subjects of this investigation.

In parallel, the OB+ZA group also showed the potential to significantly inhibit BMI improvement compared to the OB group, although it was less effective than the OB+PA and OB+O groups. The impact of *Z. aromaticum* on this investigation may be attributed to various molecular pathways. *Zingiber aromaticum* will likely share several bioactive compounds with *Z. officinale* and *Z. zerumbet*, including essential oils, polyphenols, and flavonoids [32,33]. The *Zingiber* species is characterized by these compounds' antioxidant, anti-inflammatory, and antimicrobial properties [34,35].

Consistent with alterations in body composition, the OB group presented elevated circulating free fatty acids (FFAs) and a detrimental lipid profile, which was characterized by increased total cholesterol, triglycerides, and LDL-C, as well as a decrease in HDL-C, in accordance with changes in body composition (Table 1). These changes are in accordance with the dyslipidemia commonly associated with metabolic syndrome and obesity [36]. Supplementing with PA and ZA significantly improved the lipid profile by lowering FFA, total cholesterol, triglycerides, and LDL-C levels, while increasing HDL-C levels.

PA extract's potential to prevent metabolic disorders and maintain lipid homeostasis has been supported by

additional studies demonstrating its capacity to modulate antioxidant enzymes and reduce lipid peroxidation [37]. Moreover, other species in the *Phyllanthus* genus, such as *P. emblica*, have been shown to inhibit adipogenesis, reduce triglyceride and cholesterol levels, and modulate the expression of genes associated with lipid metabolism [23,24,38]. These results indicate that *P. acidus* may exert its beneficial effects through analogous mechanisms, which could at least partly account for the results observed in this study. Concurrently, serum lipid parameters were also enhanced by ZA extract, although to a lesser extent than those of PA or orlistat. The precise mechanisms are not fully elucidated, yet its documented antioxidant and anti-inflammatory properties may enhance lipid management [39,40]. These findings suggest that ZA may serve as a supplementary therapeutic option for managing obesity. Nevertheless, further research is needed to elucidate its specific molecular mechanisms.

The HFHF diet in the OB group effectively elicited a series of metabolic abnormalities, marked by hyperglycemia, hyperinsulinemia, elevated HOMA-IR, increased serum leptin, and augmented oxidative stress (as indicated by MDA) (Tables 2 and 3). These findings highlight the impact of chronic food surplus on adipocyte hypertrophy, aberrant adipokine production, and heightened lipid peroxidation, all of which ultimately lead to the metabolic problems linked to obesity [41–43].

Among the interventions, *P. acidus* (PA) extract had the most significant ameliorative effects across many metabolic parameters. PA normalized fasting glucose, reduced hyperinsulinemia and HOMA-IR, and lowered leptin and MDA levels to near-normal values. These findings indicate that PA may operate through multiple complementary mechanisms. Previous reports support its glycemic potential; ethanolic seed extracts of *P. acidus* exerted significant hypoglycemic effects in both normoglycemic and streptozotocin-induced diabetic rats within 8–12 hours of treatment, associated with α -amylase and α -glucosidase inhibition and improved insulin sensitivity through antioxidant actions [44]. Similarly, ethanolic leaf extracts of *P. acidus* reduce blood glucose levels comparably to glibenclamide without inducing hypoglycemia in normal rats, suggesting its function as a safe metabolic modulator [45]. Beyond *P. acidus*, related species such as *P. amarus* have demonstrated improvements in glucose tolerance, insulin sensitivity, and lipid homeostasis in high-fructose-diet Wistar rats [46]. The results suggest that the therapeutic benefits of the *Phyllanthus* genus may be attributed to a range of bioactive compounds that regulate glucose metabolism, improve lipid homeostasis, and mitigate insulin resistance.

The stronger glucose and insulin effects observed in the present study compared with Chongsa *et al.* [7] likely reflect key methodological and chemical differences [7]. The use of a HFHF diet model introduced metabolic stress characterized by insulin resistance and oxidative imbalance, creating a pathophysiological context in which insulin-sensitizing compounds could act effectively. Furthermore, ethanolic extraction (96%) yielded a broader spectrum of bioactive compounds, particularly flavonoids and phenolic

acids, that may activate AMPK and IRS-1/Akt signaling, enhancing glucose uptake and restoring insulin sensitivity. These differences, combined with the longer treatment duration (12 weeks vs. 6 weeks in Chongsa's study), likely contributed to the more pronounced glycemic regulation observed here.

The current findings indicate that *P. acidus* (PA) significantly reduces leptin levels, aligning with other studies that emphasize the impact of polyphenol-rich plant extracts on enhancing adipokine equilibrium [47,48]. In obesity, increased leptin levels typically indicate excessive leptin synthesis and reduced leptin sensitivity; therefore, normalizing circulating leptin is crucial for reestablishing metabolic equilibrium.

In parallel, PA effectively reduced MDA, indicating its potent antioxidant activity. This result aligns with previous studies that demonstrate its capacity to restore natural antioxidant defenses, specifically superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). By enhancing these enzymatic systems, PA efficiently neutralizes free radicals and limits lipid peroxidation, thereby reducing circulating MDA level. These antioxidant effects are closely linked to leptin normalization, as oxidative stress and inflammation are key contributors to leptin resistance. Accordingly, *P. acidus* may facilitate leptin homeostasis through combined antioxidant and anti-inflammatory actions, a mechanism similarly suggested for related species such as *P. emblica*, which has shown promise in mitigating leptin resistance by reducing oxidative stress and inflammatory burden [49].

The observed concomitant reduction in leptin and MDA with PA treatment indicates that the extract not only enhances lipid metabolism but also restores redox and hormonal balance. This dual action suggests activation of antioxidant defenses alongside modulation of leptin sensitivity, thereby contributing to improved insulin responsiveness and attenuation of metabolic stress in diet-induced obesity.

Essential oils are important bioactive components in many medicinal plants, including *Phyllanthus* and *Zingiber* species, and are widely recognized for their antioxidant and anti-inflammatory activities. Recent reviews indicate that essential oils, as complex mixtures of volatile compounds, can scavenge reactive oxygen species, suppress pro-inflammatory mediators, and enhance endogenous antioxidant defense systems, thereby contributing to their broad biological effects [50,51]. In particular, essential oils rich in terpenoids and phenylpropanoids have been reported to influence metabolic pathways involved in glucose and lipid regulation. These activities may partly explain the reductions in MDA and leptin observed after PA and ZA administration in the present study. Therefore, the protective effects of PA and ZA are likely the result of synergistic actions between essential oils and other phytochemicals such as polyphenols and flavonoids.

Unlike PA, orlistat predominantly reduced leptin and MDA levels but did not completely normalize glucose and insulin parameters. This finding is consistent with its established mechanism as a gastrointestinal lipase inhibitor that reduces dietary fat absorption and limits lipid accumulation. Orlistat is widely used clinically as an anti-

obesity drug due to its efficacy in promoting weight loss and improving selected lipid parameters [52]. However, its influence on insulin resistance and systemic inflammation remains inconclusive. Some studies suggest that orlistat may exert modest or inconsistent effects on fasting glucose and HbA1c, particularly in individuals with type 2 diabetes [53], and may not sufficiently target the inflammatory and oxidative components of metabolic syndrome [54]. In addition, gastrointestinal adverse effects, including oily stools, diarrhea, abdominal discomfort, fecal urgency, and increased defecation, frequently reduce patient adherence, thereby limiting its overall therapeutic utility [55].

The administration of *Z. aromaticum* (ZA) extract in this trial showed a minor effect relative to PA or orlistat; however, it significantly suppressed insulin resistance, decreased leptin levels, and reduced oxidative stress, as evidenced by the decrease in MDA levels. These effects may be attributed to its bioactive constituents, including zerumbone, gingerol, and shogaol, which are well documented to possess antioxidant and anti-inflammatory properties [56]. While ZA may improve certain aspects of lipid metabolism, evidence regarding its direct modulation of glucose homeostasis remains limited and sometimes contradictory [57]. Indeed, although some ginger-derived compounds have been reported to enhance insulin sensitivity, others exhibit only partial or context-dependent efficacy, particularly in diet-induced obesity models [58].

Although the current work did not include biochemical safety panels, our observations showed no mortality or observable clinical signs of toxicity (such as changes in grooming, locomotor activity, or feeding behavior) were detected during the 12-week treatment period. Earlier toxicology work on *P. acidus* reported no significant hepatotoxicity or nephrotoxicity in acute/subacute protocols at doses in the range commonly used in rodent studies, and other reports demonstrate organ-protective activities of *P. acidus* extracts in preclinical models [6,45]. We therefore consider the applied doses to fall within an acceptable preclinical safety margin; however, comprehensive biochemical and histopathological safety evaluations remain warranted in future studies.

5. CONCLUSIONS

In conclusion, both ethanolic extract *P. acidus* and *Z. aromaticum* demonstrated beneficial effects in attenuating HFHF diet-induced metabolic disturbances, with *P. acidus* exhibiting more consistent improvements in adiposity, lipid profile, glucose control, and leptin levels. These findings underscore the preventive and modulatory potential of *P. acidus* against obesity-associated metabolic dysfunction. However, further research is necessary to elucidate its mechanistic pathways, particularly in relation to leptin resistance and inflammatory signaling. In addition, although leptin was selected as a primary adipokine marker in the present study, the absence of adiponectin measurement represents a limitation that should be addressed in future investigations.

Current research in our laboratory is investigating these aspects using purified *P. acidus* extract obtained via bioassay-guided fractionation and identification of specific active constituents, including the assessment of leptin signaling, adipokine profiling, and dose-response relationships, to more precisely delineate its therapeutic potential.

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7. DECLARATION OF GENERATIVE AI IN SCIENTIFIC WRITING

In analyzing scientific content, the authors did not employ generative AI technologies. AI-assisted tools, such as Scopus AI for literature exploration and Quillbot for language editing, were used solely to enhance readability and facilitate reference searching. The authors take full responsibility for the scientific accuracy and interpretation of the work.

8. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

9. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

10. ETHICAL APPROVALS

The study protocol was approved by the Health Research Ethics Committee, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta, Indonesia (Approval No.: 029/EC-HC-KEPK FKIK UMY/IV/2023).

11. DATA AVAILABILITY

All data generated and analyzed are included in this research article.

12. PUBLISHER'S NOTE

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13. SUPPLEMENTARY MATERIAL

The supplementary material can be accessed at the link here: https://japsonline.com/admin/php/uploadss/4786_pdf.pdf

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