Wild Stinging Nettle (*Urtica dioica*) Extract Suppresses Visceral Adipose Aromatase Levels and Improves Lipid Profile in Male Obese Rats

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ABSTRACT

Obesity can elevate estrogen levels through increased aromatase activity, adversely affecting male fertility. Although aromatase inhibitors are commonly used, they can disrupt lipid profiles and raise cardiovascular risks. This experimental study analyzed the effects of wild stinging nettle (Urtica dioica) extract on visceral adipose aromatase levels and serum lipid profiles in obese male rats. Twenty-five 7–8-week-old male Sprague Dawley rats were divided into five groups: normal control, obesity control, and three obesity groups receiving U. dioica extract at 125, 250, or 500 mg/kg body weight. After a 4-week intervention, blood samples were collected to measure lipid profiles, and visceral adipose tissue was harvested to assess aromatase levels. The U. dioica extract significantly reduced visceral adipose aromatase levels ($p < 0.01$) and improved lipid profiles in obese rats. Specifically, treated rats showed dose-dependent decreases in triglycerides, total cholesterol, and LDL-cholesterol, along with an increase in HDL-cholesterol ($p < 0.05$). These findings indicate that U. dioica extract can suppress adipose aromatase levels and ameliorate lipid disturbances in obesity.

Keywords: Aromatase, lipid profile, obesity, urtica dioica

ABSTRAK

Obesitas dapat meningkatkan kadar estrogen melalui peningkatan aktivitas aromatase, yang berdampak buruk pada kesuburan pria. Meskipun inhibitor aromatase umum digunakan, inhibitor ini dapat mengganggu profil lipid dan meningkatkan risiko kardiovaskular. Studi eksperimental ini menganalisis efek ekstrak jelatang liar (Urtica dioica) terhadap kadar aromatase adiposa viseral dan profil lipid serum pada tikus jantan obesitas. Dua puluh lima tikus Sprague Dawley jantan berusia 7–8 minggu dibagi menjadi lima kelompok: kontrol normal, kontrol obesitas, dan tiga kelompok obesitas yang menerima ekstrak U. dioica dengan dosis 125, 250, atau 500 mg/kg berat badan. Setelah intervensi selama 4 minggu, sampel darah dikumpulkan untuk mengukur profil lipid, dan jaringan adiposa viseral diambil untuk menilai kadar aromatase. Ekstrak U. dioica secara signifikan mengurangi kadar aromatase adiposa viseral ($p < 0,01$) dan memperbaiki profil lipid pada tikus obesitas. Secara spesifik, tikus yang diberi perlakuan menunjukkan penurunan trigliserida, kolesterol total, dan kolesterol LDL yang bergantung pada dosis, serta peningkatan kolesterol HDL ($p < 0,05$). Temuan ini menunjukkan bahwa ekstrak U. dioica dapat menekan kadar aromatase adiposa dan memperbaiki gangguan lipid pada obesitas.

Kata Kunci: *Aromatase, obesitas , profil lipid, urtica dioica*

1. Introduction

Obesity is a global problem affecting individuals of all ages and socioeconomic backgrounds (Lustig et al., 2022). It is a risk factor for various health disorders, including male infertility. This link is partly due to increased aromatase activity in obesity, since aromatase converts androgens to estrogens. In obese individuals, pro-inflammatory mediators such as prostaglandin E_2 (PGE_2), TNF-α, and IL-6, which are elevated in adipose tissue, can upregulate aromatase expression (Mair et al., 2020). Excess estrogen can disrupt the hypothalamic-pituitary-gonadal (HPG) axis by inhibiting the release of FSH and LH, leading to lower testosterone levels and impaired spermatogenesis (Xu et al., 2017). Moreover, high estrogen in males may activate testicular macrophages, causing them to phagocytize Leydig cells and further harm sperm production (Yuxin et al., 2021).

Aromatase inhibitors are often used to reduce estrogen in cases of male infertility. However, synthetic inhibitors can have serious side effects, such as adverse changes in lipid profiles and higher cardiovascular risk (Sund et al., 2021; Wang et al., 2020). In contrast, medicinal plants are widely used in traditional medicine and are gaining popularity due to their low cost and availability. Stinging nettle (*Urtica dioica*), for example, is used in food, cosmetics, and pharmaceuticals because of its rich bioactive compounds and high antioxidant capacity (Kregiel et al., 2018). Previous studies have shown that components of *Urtica dioica* can inhibit aromatase activity (Ganjer & Spiteller, 1995), and that its polyphenols have anti-inflammatory effects (Hajhashemi & Klooshani, 2013). By reducing inflammation, *Urtica dioica* extract may lower aromatase expression and decrease estrogen levels. In addition, stinging nettle has been reported to lower total cholesterol and LDL-cholesterol in hypercholesterolemic rats (Nassiri-asl, 2014). However, no study has yet examined its effects on triglycerides and HDL-cholesterol in an obese model. The multiple beneficial components of *Urtica dioica* suggest it could be an alternative therapy for obesity-related hormonal imbalances and lipid disturbances.

Research focusing on the comprehensive effects of *Urtica dioica* extract on aromatase levels and lipid profiles has not been previously explored. Therefore, this study aimed to investigate the impact of *Urtica dioica* on aromatase expression and lipid profiles, including serum triglycerides, total cholesterol, LDL, and HDL, in obese male rats.

2. Methods

2.1. Study Design

This experimental study employed a pretest-posttest control group design for lipid profile analysis and a posttest-only control group design for assessing visceral adipose aromatase levels.

2.2. Collection and Extraction of Wild Stinging Nettle (*Urtica dioica*)

Wild stinging nettle was collected from the Plemburan area, Sleman. Species identification was performed at the Plant Systematics Laboratory, Faculty of Biology, Universitas Gadjah Mada (UGM), with registration number 0172/S.Tb./XI/2022, confirming the material as *Urtica dioica*. The collected samples were washed, chopped, and dried in an oven at 50 °C for one day, then ground into a powder. Extraction was conducted by

maceration in 70% ethanol, following the method described by Fadilah & Susanti's research (2020). The powdered material was placed in a macerator and fully submerged in 70% ethanol solvent. Maceration was carried out at room temperature for 3×24 hours, with the solvent replaced every 24 hours. The resulting macerate was collected and evaporated using a rotary evaporator to obtain a concentrated extract.

2.3. Animal

Twenty-five male Sprague Dawley rats, aged 7–8 weeks and weighing 170–190 grams, were housed in the inter-university animal laboratory in individual standard cages. The animals were acclimatized for 7 days to monitor stable body weight and food intake. Room temperature was maintained at 23 °C, with a 12-hour light–dark cycle to support circadian rhythms, and conditions were kept free from noise stressors. During acclimatization and throughout the study, standard feed and water were provided ad libitum. The study commenced after ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, UGM (reference number KE/FK/0160/EC/2023).

2.4. Obesity Induction

Following acclimatization, four of the five experimental groups were induced to develop obesity by being fed a high-fat diet consisting of standard feed (50%), wheat starch (25%), lard (10%), pure cholesterol (2%), cholic acid (0.2%), and distilled water (12.8%) (Murwani, 2013). In addition, pure fructose at 1% of body weight was administered via gavage (Sunarti, 2021). This protocol was continued for 6 weeks until obesity was achieved, as indicated by a Lee index >300, a commonly used parameter to estimate adiposity in rodent models.

2.5. Experimental Design

The animals were randomly allocated into five groups: healthy control (K1), obesity control (K2), and three obesity groups receiving *Urtica dioica* extract at doses of 125, 250, and 500 mg/kg body weight (D1–D3). The extract was administered orally via gavage once daily for 4 weeks. At the end of the intervention, the animals were euthanized.

2.6. Blood Biochemical Measurements

Serum samples were collected twice: after the obesity induction phase and following the *Urtica dioica* intervention. Blood was drawn in the morning after the animals had fasted for approximately 10 hours. Lipid profiles, including triglycerides, total cholesterol, LDL, and HDL, were analyzed using a commercial kit (DyaSis®, Germany).

2.7. Aromatase Level Measurement

Aromatase levels in visceral adipose tissue were measured using a Rat CYP19A1 ELISA kit (Wuhan Fine Biotech), following the manufacturer's protocol. Tissue samples were homogenized and centrifuged, and the resulting supernatant was used for analysis. Briefly, samples were processed through sequential incubation steps with a biotin-labeled antibody, an HRP–streptavidin conjugate (SABC), and TMB substrate, followed by absorbance measurement at 450 nm. Aromatase concentrations were calculated using a standard curve.

2.8. Statistical Methods

Results were expressed as means ± standard deviation (SD). Statistical analyses were performed using SPSS for Windows, version 24. One-way ANOVA followed by post hoc LSD tests and paired t-tests were used to analyze the effects of *Urtica dioica* on lipid profiles. The effects on aromatase levels were analyzed using the Kruskal–Wallis test and independent-sample t-tests. Prior to conducting parametric tests, assumptions including normality were assessed using the Shapiro–Wilk test. A significance level of $p < 0.05$ was considered statistically significant.

3. Results and Discussion

3.1. The Effect of *Urtica dioica* Extract on Aromatase Levels

The visceral adipose aromatase levels in obese rats treated with *Urtica dioica* extract for 4 weeks were significantly lower compared to untreated obese rats ($p < 0.05$) (Figure 1). The average aromatase levels exhibited an inverse correlation with the administered dosage, indicating that higher doses resulted in lower average aromatase concentrations. Notably, the mean aromatase level in the D3 group approached that of the healthy control (K1), although the difference remained statistically significant.

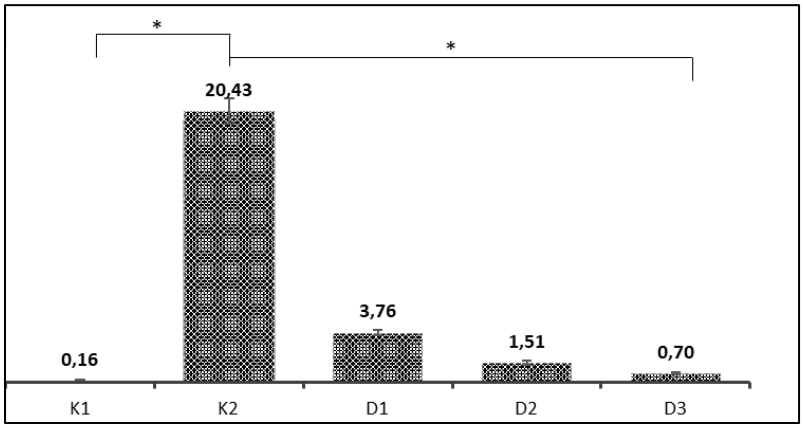

Figure 1. Visceral adipose aromatase levels after 4 weeks of *Urtica dioica* extract intervention (ng/mL).

3.2. The Effect of *Urtica dioica* Extract on Lipid Profile

Following successful obesity induction, lipid profile analysis demonstrated that all obese-induced rats developed dyslipidemia, characterized by elevated triglycerides, total cholesterol, and LDL levels, as well as reduced HDL levels, compared to the healthy control group. Intervention with *Urtica dioica* extract at various doses for 4 weeks improved the lipid profiles significantly, both relative to pre-intervention measurements and compared to the obese control group without treatment.

Triglyceride levels decreased following *Urtica dioica* extract administration, with all intervention groups exhibiting lower mean triglyceride values than the untreated obese controls. Remarkably, the D3 group showed an average triglyceride concentration that was not significantly different from the healthy control, as presented in Figure 2.

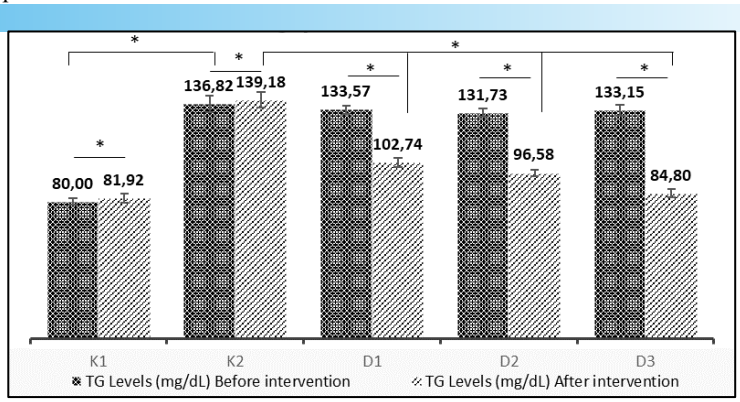

Figure 2. Triglyceride levels before and after 4 weeks of *Urtica dioica* extract intervention (mg/dL).

Total cholesterol levels, presented in Figure 3, increased after high-fat and fructose diet (HFFD) induction. Administration of *Urtica dioica* extract at all doses for 4 weeks significantly reduced total cholesterol concentrations.

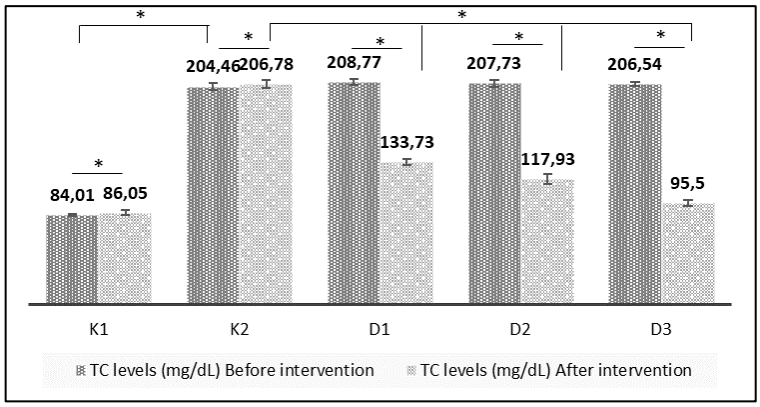

Figure 3. Total cholesterol levels before and after 4 weeks of *Urtica dioica* extract intervention (mg/dL).

Similarly, LDL levels rose following HFFD induction. *Urtica dioica* extract treatment significantly lowered LDL concentrations across all doses (Figure 4). Additionally, the D3 group's LDL levels were not significantly different from those of the healthy control.

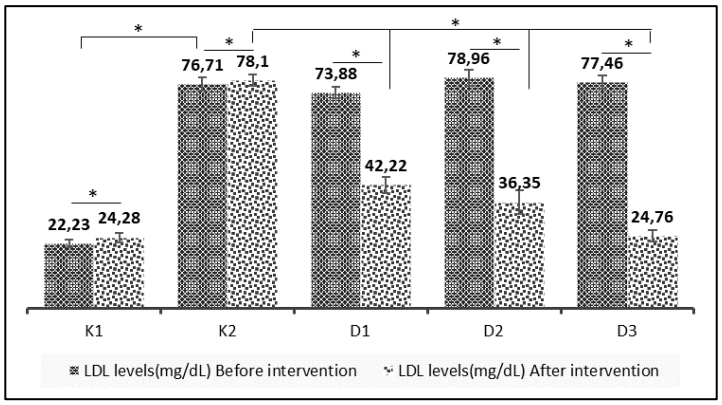

Figure 4. LDL levels before and after 4 weeks of *Urtica dioica* extract intervention (mg/dL).

Finally, HDL levels decreased after obesity induction with HFFD. Treatment with *Urtica dioica* extract at various doses for 4 weeks significantly increased HDL concentrations, as shown in Figure 5.

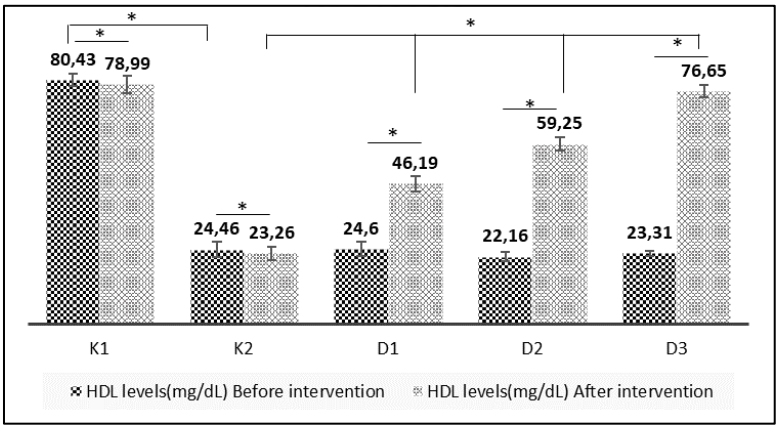

Figure 5. HDL levels before and after 4 weeks of *Urtica dioica* extract intervention (mg/dL).

Intervention with *Urtica dioica* extract in obese male rats resulted in a significant reduction in aromatase enzyme levels compared to the obese control group. The lowest aromatase levels were observed in Group 5, whose values approached those of the healthy group, although the difference remained statistically significant. These findings indicate that *Urtica dioica* extract is effective in reducing aromatase expression in visceral adipose tissue.

The results of this study are consistent with the findings of Rice et al. (2006), who investigated the effects of plant bioactive compounds, also known as phytoestrogens, on aromatase expression and activity in human granulosa-luteal (GL) primary cell cultures stimulated with phytoestrogens for 48 hours. The tested compounds included flavones (apigenin, quercetin) and isoflavones (genistein, biochanin A, daidzein). Their study demonstrated that all tested compounds suppressed aromatase expression, with apigenin showing the most potent inhibitory effect on aromatase mRNA. Additionally, Lephart (2015) described how phytoestrogens suppress CYP19A1 gene expression by inhibiting the use of promoters 1.3 and II of the CYP19A1 gene, resulting in decreased aromatase production and, consequently, reduced estrogen biosynthesis, proliferation, inflammation, and carcinogenesis.

The expansion of visceral adipose tissue represents a fat deposition pattern associated with metabolic disorders. As visceral adipose tissue expands, the production of adipocyte-related products such as aromatase and leptin increases (Van Gaal et al., 1999). Persistent expansion of visceral adipose tissue becomes a risk factor for additional health problems, including metabolic dysfunction and impaired fertility. Elevated visceral fat stores, as seen in obesity, lead to increased aromatase levels and activity, resulting in further testosterone reduction.

Treatment with *Urtica dioica* extract lowered aromatase enzyme levels in obese subjects compared to untreated obese controls. This effect can be attributed in part to the well-documented anti-inflammatory properties of *Urtica dioica*. Johnson et al. (2013) explored and compared extracts from various parts of the *Urtica dioica* plant (root, stem, leaves, and

flowers) using different solvents (water, methanol, hexane, and dichloromethane) for anti-inflammatory activity on lipopolysaccharide-stimulated murine macrophage cell lines. Their results showed that extracts from the root, stem, and leaves demonstrated anti-inflammatory effects in NF-κB luciferase assays. Supporting this, in vivo research by Rahmati et al. (2021), reported significant reductions in pro-inflammatory cytokine expression in the hippocampal tissue of streptozotocin-induced diabetic Wistar rats after six weeks of *Urtica dioica* treatment compared to controls. Chronic low-grade inflammation in obesity is one of the key factors that drives increased aromatase expression. Various pro-inflammatory mediators, including PGE_2, TNF-α, IL-1, IL-6, and COX-2, are elevated in obese individuals and are known to regulate estrogen production in adipose tissue by upregulating aromatase expression.

In addition to its anti-inflammatory effects, *Urtica dioica* also acts as an antioxidant, both by directly scavenging free radicals and by enhancing the expression of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). The antioxidant activity of *Urtica dioica* hydroalcoholic extract was investigated by Güder & Korkmaz (2012), who compared extracts from different plant parts (seeds, roots, flowers, and leaves) using the FTC method. Their results indicated that *Urtica dioica* exhibited strong antioxidant potential in inhibiting lipid peroxidation, achieving inhibition levels exceeding 75%, which were reported to be superior to those of standard antioxidants such as BHA, BHT, and α-tocopherol. Moreover, Ahmadipour & Khajali (2019) found increased SOD1 and CAT enzyme activity in the liver and lungs, along with significant reductions in lipid peroxidation, in subjects fed an *Urtica dioica* supplement. The vicious cycle of oxidative stress and inflammation in metabolic disorders such as obesity can be disrupted by breaking oxidative stress pathways, thereby reducing inflammation and aromatase expression.

The lower aromatase levels in the intervention group did not worsen the lipid profile, in contrast to the use of aromatase inhibitors, which some studies have reported to negatively affect lipid metabolism. *Urtica dioica* intervention improved the lipid profiles of obese subjects with dyslipidemic characteristics (elevated triglycerides, total cholesterol, and LDL levels, along with decreased HDL levels), restoring them to a healthier state. This improvement was evident when comparing pre- and post-intervention measurements as well as comparisons with the obese control group without treatment. Several mechanisms may explain this effect.

Metabolic dyslipidemia and insulin resistance occur concurrently with adiposopathy in obese patients. These processes are mediated by chronic inflammation, oxidative stress, and insulin resistance. Obanda et al. (2016) reported that *Urtica dioica* extract reduces insulin resistance by inhibiting protein phosphatase-2A (PP2A) activity through post-translational modification, accompanied by decreased Akt dephosphorylation. This leads to improved glucose homeostasis and increased insulin sensitivity. Enhanced insulin sensitivity and glucose regulation can potentially prevent metabolic dyslipidemia by reducing lipolysis, thereby decreasing circulating free fatty acids and lowering the hepatic synthesis of triglyceride-rich lipoproteins. Metabolic dyslipidemia and insulin resistance occur concurrently with adiposopathy in obese patients. These processes are mediated by chronic

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In addition to the roles of inflammation and insulin resistance, changes in lipid profiles, such as reductions in triglycerides and total cholesterol, can also be attributed to polyphenols in *Urtica dioica*, primarily hydroxycinnamic acids, which inhibit HMG-CoA reductase and ACAT in the liver Lee et al. (2007). HMG-CoA reductase is a key enzyme responsible for cholesterol biogenesis and is a primary target in the treatment of lipid disorders. Unlike HMG-CoA reductase, ACAT enhances the utilization of fatty acids for cholesterol esterification (Alam et al. 2016). Wu et al. (2021) demonstrated that cinnamic acid administration prevents hepatic lipogenesis and promotes fatty acid oxidation. Cinnamic acid suppresses lipogenic transcription factors such as ChREBP and SREBP-1c and lipogenic enzymes including ACLY, ACC, FAS, and SCD1. Furthermore, cinnamic acid increases fatty acid oxidation by upregulating CPT1A, PPAR-α, and PGC1-α expression, all of which play crucial roles in β-oxidation.

In addition to the hydroxycinnamic acid group, the most abundant polyphenol group in *Urtica dioica* is the flavonoid group, particularly flavonols. Flavonol compounds such as kaempferol, quercetin, and myricetin also contribute to improving lipid metabolism. According to da-Silva et al. (2007), kaempferol activates metabolic pathways in skeletal muscle myoblasts, resulting in a 30% increase in oxygen consumption, mainly through activation of PGC1-α, CPT1-α, mitochondrial transcription factor 1 (mtTF1), citrate synthase, and UCP-3, all of which are involved in cellular energy utilization. Moreover, kaempferol regulates enzymes responsible for thyroid hormone (T3) activation.

Inhibiting lipogenic enzymes, as described above, is not the only mechanism by which polyphenols improve lipid profiles. Another important effect of *Urtica dioica* polyphenols is the upregulation of LDL receptor (LDL-R) expression, which increases LDL-c clearance from circulation. This is supported by Li et al. (2021), who demonstrated that quercetin, also a flavonol, enhances LDL-R expression while suppressing HMG-CoA reductase.

The reduction in total cholesterol levels following *Urtica dioica* intervention, in addition to decreased synthesis and increased excretion, also involves the role of HDL as a key component of reverse cholesterol transport. HDL also exerts a range of biological activities, including antioxidant, anti-inflammatory, anti-apoptotic, antithrombotic, and vasorelaxant effects (Millar et al., 2017). In this study, all rats with diet-induced obesity exhibited low HDL levels. Chronic inflammation in obese subjects is thought to remodel HDL into pro-inflammatory particles, leading to impaired antioxidant function and altered composition, including increased serum amyloid A (SAA) and acute-phase proteins, along with decreased paraoxonase (PON1) (Kappelle et al., 2011). Obese individuals also tend to have more intense lipid peroxidation, lower antioxidant levels, and reduced LCAT and PON activity. Paraoxonase 1 (PON1), an enzyme associated with HDL, contributes to preventing oxidation

of both HDL and LDL (Mackness & Mackness, 2015). Lecithin–cholesterol acyltransferase (LCAT) facilitates the uptake of cholesterol from peripheral tissues into HDL particles, maintaining a concentration gradient that depletes free cholesterol (Fielding, 1984). LCAT dysfunction results in decreased formation of mature HDL.

The increase in HDL levels after *Urtica dioica* intervention for 4 weeks is thought to result from the antioxidant and anti-inflammatory actions of its bioactive compounds, which inhibit lipid peroxidation within HDL. Moreover, research by Zagayko et al. (2013), administering grape polyphenols to obese rats, detailed the increase in HDL enzyme activities such as PON-1 and LCAT, which were directly proportional to improvements in functional HDL levels. As HDL levels return to normal, the mechanism of reverse cholesterol transport from peripheral tissues to the liver can be restored, facilitating cholesterol catabolism and excretion.

The improvements in lipid profiles and reductions in aromatase levels observed in this study are biologically meaningful, particularly in the context of male obesity, where increased adiposity is associated with metabolic dysfunction and hormonal imbalance due to elevated estrogen synthesis. Lowering aromatase levels may help restore the androgen–estrogen ratio, which is essential for reproductive and metabolic health in obese males.

Nevertheless, this study has several limitations. The relatively small sample size and short duration of the intervention may limit the generalizability of the findings. Inter-individual variability and the absence of molecular validation (e.g., gene or protein expression) also highlight the need for further mechanistic investigations.

The findings of the study indicate that *Urtica dioica* extract holds significant potential as a functional ingredient for health-oriented food products. For both the food service and manufacturing sectors, this creates opportunities to develop innovative nutraceutical beverages, dietary supplements, or enriched menu items designed to aid in lipid regulation and prevent obesity. Integrating wild stinging nettle extract into functional foods may attract health-conscious consumers who prefer natural solutions for improving metabolic health. This approach also gives businesses a strategic advantage by merging scientific validation with creative food innovation.

4. Conclusion

This study demonstrates that *Urtica dioica* extract can suppress visceral adipose aromatase levels while simultaneously improving the lipid profile, as evidenced by reduced triglycerides, total cholesterol, and LDL levels, as well as increased serum HDL levels. Based on these findings, *Urtica dioica* extract offers therapeutic potential for individuals with dyslipidemia and estrogen excess, particularly in obese male subjects. Thus, *Urtica dioica* extract can be utilized as a therapeutic agent for suppressing aromatase levels and improving lipid metabolism. These findings indicates the potential of *Urtica dioica* extract as a functional ingredient for developing healthier food products to improving lipid metabolism and supporting obesity management.

5. Acknowledgments

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