RESEARCH ARTICLE

Moringa oleifera Fruit Extract Improves Hypothalamic Superoxide Dismutase Activity and Reduces Glial Reactivity in Obese Wistar Rats

Dian Ayu Paramitha[1,*], Ria Maria Theresa[2], Maria Selvester Thadeus[2], Muttia Amalia[2], Tiwuk Susantiningsih[2]

[1]Postgraduate Biomedical Science Master's Program, Faculty of Medicine, Universitas Pembangunan Nasional "Veteran" Jakarta, Jl. RS. Fatmawati, Pondok Labu, Jakarta 12450, Indonesia
[2]Departement of Biomedical Science, Faculty of Medicine, Universitas Pembangunan Nasional "Veteran" Jakarta, Jl. RS. Fatmawati, Pondok Labu, Jakarta 12450, Indonesia

*Corresponding author. Email: athaparamitha@gmail.com

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Abstract

BACKGROUND: Obesity is linked to chronic low-grade inflammation and increased oxidative stress that may disrupt hypothalamic metabolic homeostasis. Excess nutrient intake activates inflammatory signaling and promotes glial reactivity, contributing to neuroinflammatory remodeling. Superoxide dismutase (SOD) is a key enzymatic antioxidant marker reflecting hypothalamic defense capacity. However, whether natural antioxidants can simultaneously restore SOD activity and attenuate obesity-induced glial reactivity remains unclear. Among many natural antioxidant, *Moringa oleifera* is rich in bioactive compounds with antioxidant properties that may attenuate neuroinflammation. Therefore, this study was conducted to evaluated the effect of *M. oleifera* fruit extract (MOFE) on hypothalamic total SOD activity and histopathological features of glial reactivity in obese Wistar rats.

METHODS: Male Wistar rats were divided into four groups: normal control, obese control, and two treatment groups. For obese control and treatment groups, obesity was induced for 8 weeks using a high-fat/high-sucrose diet. Fresh *M. oleifera* fruit pods were macerated to produce MOFE. Following the obesity-induction, the two treatment groups were treated with 500 and 1,000 mg/kgBW/day MOFE for 4 weeks. A hydroxylamine-based assay was employed to measure total SOD activity of hypothalamic tissue homogenate. Meanwhile, hematoxylin-eosin (HE) was used to stain hypothalamic sections for glial reactivity scoring.

RESULTS: After the obesity induction, the obesity-induced rats showed elevated Lee Index, but after the treatment with 500 and 1,000 mg/kgBW/day MOFE, the Lee Index decreased for 26.61±3.53% and 26.32±0.93%, respectively, which is greater compared to obese control. MOFE administration was also able to improve hypothalamic SOD activity (64.75±1.29 U/mL and 65.78±0.74 U/mL). MOFE groups also exhibited predominantly milder histopathological changes and glial reactivity than obese controls.

CONCLUSION: MOFE administration lowers Lee Index, improves hypothalamic SOD activity, reduces glial reactivity and improves neuroinflammation changes in obese rats, suggesting that MOFE might be potential agent for obesity-related oxidative-inflammatory brain injury.

KEYWORDS: *Moringa oleifera*, obesity, oxidative stress, superoxide dismutase, hypothalamus, gliosis, Wistar rat

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Introduction

Obesity is acknowledged as a chronic low-grade inflammatory and oxidative condition that impacts the central nervous system, specifically the hypothalamus, a critical regulator of energy homeostasis, in addition to peripheral metabolic tissues.(1-3) Excessive nutrients have been shown to induce hypothalamic inflammatory signaling, increased glial reactivity, and impaired metabolic signaling, all of which can contribute to dysregulated appetite and body-weight control.(3-6) In the arcuate nucleus and other hypothalamic regions, chronic exposure to energy-dense diets has been linked to innate immune activation at the cellular level. This is supported by the recruitment of macrophage-like cells, microglial activation, and reactive astrogliosis. Neuronal leptin and insulin responsiveness can be impaired by these glial-driven immune signals, which can lead to a feedback loop between overnutrition, neuroinflammation, and metabolic dysfunction.(1,5-8)

Oxidative stress is central to neuroinflammatory remodeling process. Redox imbalance is a common pathway that emerges in obesity models, where neuroinflammation and mitochondrial dysfunction are closely interconnected. The production of mitochondrial reactive oxygen species (ROS) and inflammatory mediators may be increased by excessive nutrient exposure, while endogenous antioxidant defenses may be insufficient to maintain tissue homeostasis.(2,8,9) Superoxide dismutase (SOD) is a critical enzymatic antioxidant that is essential for the redox defense of cells, including neural tissue.(9,10) Current evidence indicates that antioxidant interventions such as plant extracts or SOD mimetics, together with metabolic drugs, senolytics, and lifestyle/surgical approaches, might restore antioxidant capacity and dampen the obesity-related glial reactivity.(11,12)

Natural antioxidants, such as *Moringa oleifera*, *Acanthus mollis* L., *Olea europea* L. leaves, *Hybiscus sabdariffa* L., *Erythronium japonicum*, and *Juglans regia* L., are known to attenuate neuroinflammation by reducing oxidative stress and modulating redox-sensitive inflammatory pathways.(13,14) Among these natural antioxidant, *M. oleifera* is known to be rich in polyphenols, flavonoids, and other bioactive compounds with antioxidant and anti-inflammatory properties. Several preclinical and review literature have demonstrated its metabolic and anti-inflammatory effects.(15-18) However, evidence specifically examining the effects of *M. oleifera* fruit extract (MOFE) on hypothalamic oxidative status and neuroinflammation pathway in obesity remains limited. Most existing studies focus on peripheral metabolic outcomes or investigate other plant parts.(15,19) Therefore, this study was conducted to examine whether the administration of MOFE could enhances hypothalamic SOD activity and diminishes glial reactivity in obese Wistar rats.

Methods

Preparation of MOFE

M. oleifera fruits (pod) used in this study were purchased and identified at the Department of Chemistry, Faculty of Mathematics and Science, Universitas Indonesia. In order to preserve the heat-sensitive bioactive compounds, 8.0 kg of fresh *M. oleifera* fruit pods were washed, sliced in 1-2 cm, and dried in an oven at 40-50°C for 4 days until the moisture content was less than 10%. The desiccated material was then milled into coarse powder (simplicia), which produced an estimated 200 g (approximately 10% of the fresh weight). The material was immersed in 96% ethanol for 24 hours, filtered, and repeatedly macerated to optimize the extraction. The combined filtrates were concentrated at 40°C using a rotary evaporator to obtain a dense crude extract. The crude extract was subsequently reconstituted in 1% carboxymethyl cellulose (CMC-Na) solution as a suspending agent to obtain the desired concentrations for oral administration. Crude extract for treatment was prepared daily with dose calculation based on the individual body weight of experimental rats, with the final concentration of 500 or 1000 mg/kg BW/day of MOFE.

Animal Grouping

Male Wistar rats, weighed 150-200 g and aged 8-10 weeks, were included in this study. The animals were subjected to *ad libitum* access to food and water while being acclimatized for 1 week under controlled laboratory conditions (22-25°C; 12-hour light-dark cycle). The rats were then randomly assigned into four groups (n=6 for each group): 1) Healthy rats as normal control; 2) Obesity-induced rats receiving no treatment; 3) Obesity-induced rats receiving 500 mg/kgBW/day MOFE; and 4) Obesity-induced rats receiving 1000 mg/kgBW/day MOFE.

Obesity Induction and Animal Treatment

After a week of acclimatization, the normal control rats received standard food and water for 8 weeks. Meanwhile, the obesity-induced rats were given high-fat/high-sucrose

diet (HFHSD) for 8 weeks. The HFHSD regimen included 1 mL oral quail egg yolk feeding twice daily and an access to a 20%(w/v) sucrose in drinking water.(20,21) Rats were considered obese if they have Lee index of ≥300.(22,23) Hence, to confirm whether the obesity induction was successful, Lee index of each rat was measured based on following formula:

$$\text{Lee Index} = \frac{\sqrt[3]{\text{Body weight (g)}}}{\text{Naso-anal length (cm)}} \times 1000$$

After 8 weeks of obesity induction, the normal rats were given the same standard food and water for another 4 weeks. While the obesity-induced rats received 1 mL oral quail egg yolk feeding twice daily, but accompanied by standard drinking water (high fat, but not high sucrose diet) for 4 weeks. During these 4 weeks, the obesity-induced rats also received different treatment according to their group allocation daily via oral administration using gastric gavage (Figure 1). All procedures were conducted at the iRatco Laboratory, Bogor, in accordance with ARRIVE 2.0 recommendations and with prior ethical approval.

SOD Level Measurement

Following 4 weeks of treatment, all rats were euthanized under ketamine/xylazine anesthesia, and the hypothalamus was swiftly isolated. The hypothalamus was collected as a single block for homogenate preparation and histology; nucleus-level microdissection was not conducted. Around 0.1 g of hypothalamic tissue was homogenized in phosphate-buffered saline (pH 7.4) at a ratio of approximately 1:9 (w/v). The resulting supernatant was subsequently centrifuged at 10,000 × g. The hydroxylamine method was employed to measure the total SOD activity in hypothalamic homogenate supernatant using a commercial T-SOD assay kit with xanthine/xanthine oxidase system (Cat. No. E-BC-K019-M;

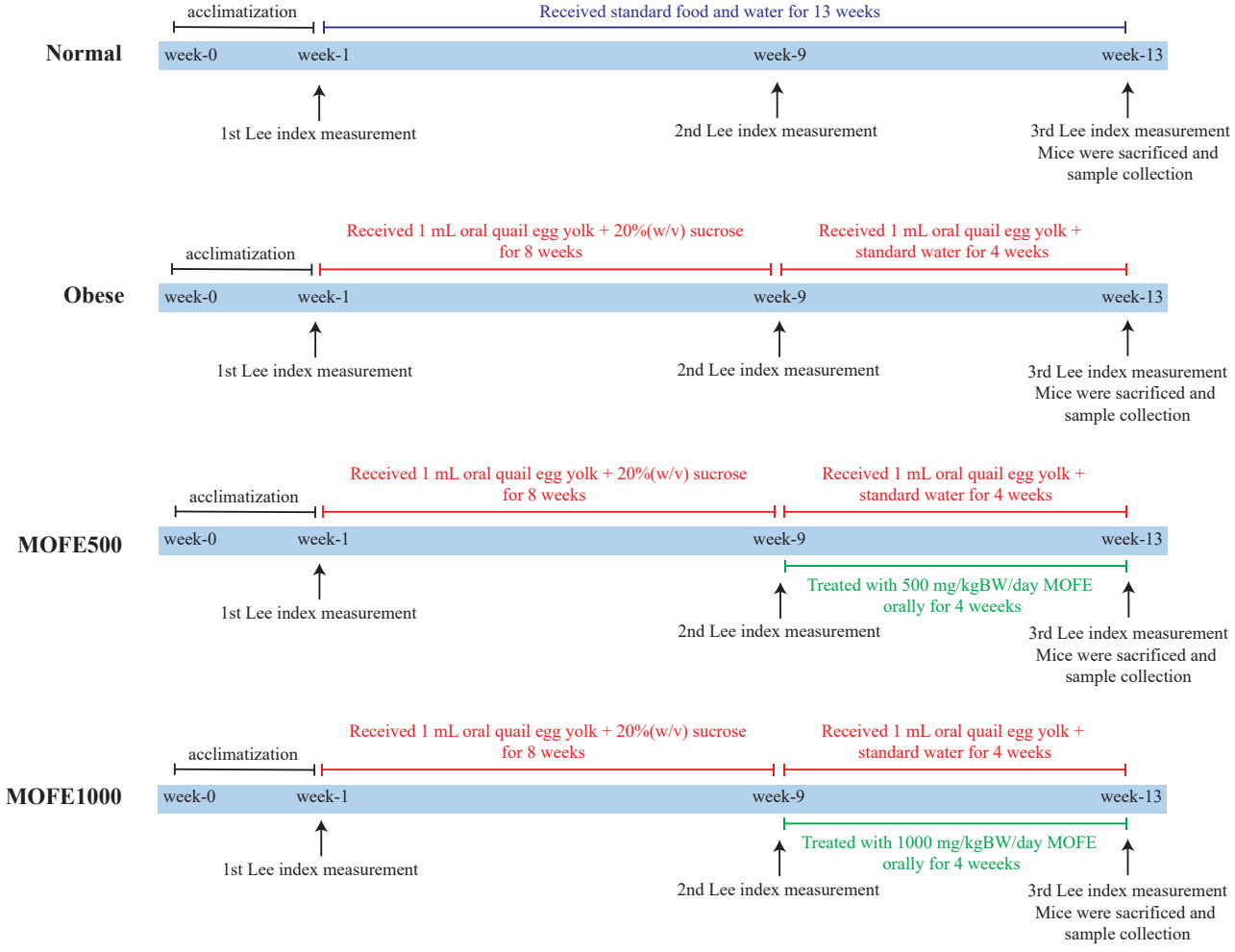

Figure 1. The study timeline and animal treatments. Normal: Healthy rats; Obese: Obesity-induced rats receiving no treatment; MOFE500: Obesity-induced rats receiving 500 mg/kgBW/day MOFE; MOFE1000: Obesity-induced rats receiving 1000 mg/kgBW/day MOFE. Lee Index was measured 3 times.

Elabscience, Wuhan, China). The reaction mixture was incubated at 37°C for 40 minutes, chromogenic reagents were introduced, the mixture was vortexed and allowed to stand for 10 minutes, and the absorbance was measured at 546 nm using spectrophotometry. The kit formula was used to calculate SOD activity (U/mL) by inhibiting the formation of chromogenic products.

Histopathological Analysis and Glial Reactivity Scoring

The hypothalamic tissue was fixed in 10% buffered formalin, paraffin-embedded, sectioned at a thickness of approximately 5 µm, and stained with hematoxylin and eosin (HE). The histopathological features of glial reactivity/neuroinflammatory change were semi-quantitatively assessed (score 0-3) based on its morphology by two blind anatomical pathologists. The parameters used were glial cellularity/reactivity (gliosis/microgliosis-like appearance), neuropil changes (edema/vacuolization), and neuronal injury. The scores of 0 (normal) and 1 (mild) indicated that the architecture was preserved without inflammatory changes, while score 1 (mild) indicated early edema/vacuolization with a slight increase in glial cells. Score 2 (moderate) indicated clearer gliosis and neuropil alteration without severe structural disorganization, and score 3 (severe) indicated dense/diffuse or multifocal gliosis with prominent neuropil disruption and visible neuronal injury. (24,25)

Statistical Analysis

Mean differences between groups and the post hoc analysis for each parameter, as well as the correlation between SOD activity and glial reactivity score were analyzed using SPSS version 25 (IBM Corporation, Armonk, NY, USA), with the statistical significance at $p<0.05$.

Results

Obesity was effectively induced after 8 weeks of high-fat/high-sucrose feeding. The obese, MOFE500, and MOFE1000 groups had Lee Index of 313.37±7.66, 310.65±8.70, and 310.34±9.26 respectively on the 2nd Lee Index measurement (Figure 2); showing that obesity-induction was able to elevate the Lee Index to >300 with mean comparisons of before and after the obesity-induction were $p<0.05$ for all three groups. Meanwhile, the Lee Index of the rats in normal group remains below 300 (282.64±7.27) on the 2nd Lee Index measurement; confirming that the obesity induction with HFHSD was successfully performed to the other 3 groups.

MOFE Administration Decreased Lee Index in Rats

After 4 weeks of treatment, all groups shown decreasing Lee Index, but on the 3rd Lee Index measurement, both groups that received MOFE exhibited greater decrease in Lee Index compared to the normal and obese groups (Figure 2, Table 1), with significancy of $p=0.013$ for MOFE500 and $p=0.002$ for MOFE1000.

Higher SOD Activity in MOFE-treated Groups

After 4 weeks of treatment with or without MOFE, there was significant difference of SOD activity among all groups ($p<0.001$). The hypothalamic SOD activity of obese group was lower than that of the normal group, showing that obesity caused decreases of SOD activity in the rats' hypothalamus. However, MOFE administration increased hypothalamic SOD activity, with the 1,000 mg/kgBW/day dose demonstrating a comparable increase (65.78±0.74 U/mL) with the normal control (65.87±0.68 U/mL) (Table 2),

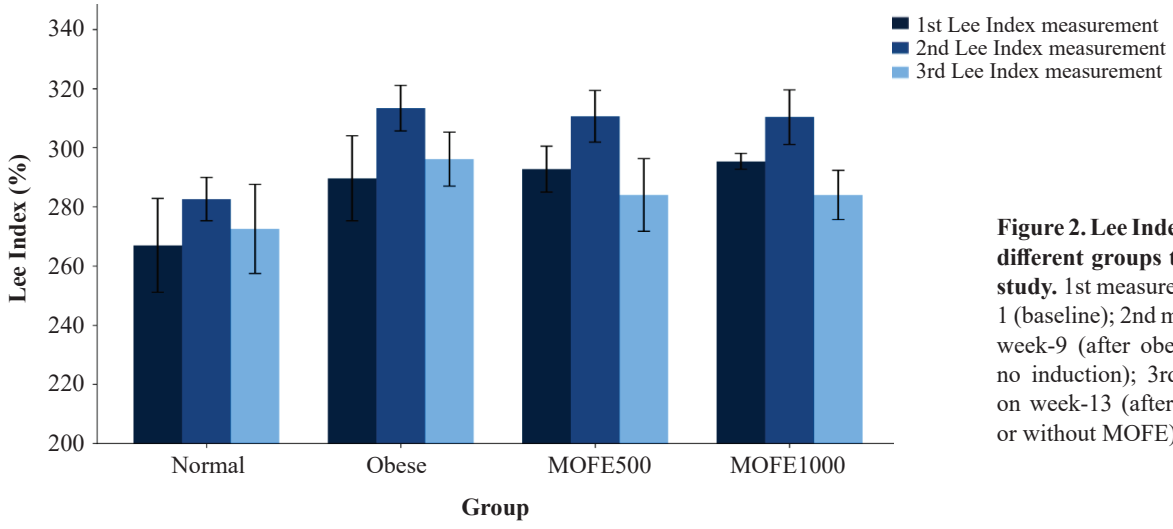

Figure 2. Lee Index of subjects in different groups throughout the study. 1st measurement: on week-1 (baseline); 2nd measurement: on week-9 (after obese-induction or no induction); 3rd measurement: on week-13 (after treatment with or without MOFE).

Table 1. The decrease in Lee Index before and after MOFE treatment.

Groups	Δ Lee Index (%)	*p*-value
Normal	10.06±7.84	0.037*
Obese	17.19±1.47	0.037*
MOFE500	26.61±3.53	0.013*
MOFE1000	26.32±0.93	0.022*

The decrease were measured between the period of the 2nd (week-9) and 3rd (week-13). Δ Lee Index = 2nd Lee Index measurement – 3rd Lee Index measurement. *p<0.05 is considered significant, Tested with Paired Sample T-Test

Table 2. Hypothalamic SOD activity after MOFE treatment (week-14).

Group	SOD (U/mL)
Normal	65.87±0.68
Obese	63.07±0.63
MOFE500	64.75±1.29
MOFE1000	65.78±0.74

suggesting that MOFE might be potential to restore SOD activity.

MOFE Administration Reduced Glial Reactivity and Neuroinflammation Score

In contrast to normal controls, obese controls exhibited more frequent hypothalamic histopathological abnormalities, such as increased glial cellularity and edema/vacuolization, which were consistent with reactive gliosis-like alterations. The MOFE-treated groups exhibited markedly milder lesions, with MOFE1000 group exhibiting a tissue appearance that was more reminiscent of the normal control pattern (Figure 3).

Based on the histopathological analysis of each subject, neuroinflammation scores were quantified. There were significant differences of glial reactivity distribution between all groups (p<0.05). The normal group showed quite low neuroinflammation score, with most of the rats had score of 0 (66.7%), while the obese group was the only group to exhibit moderate lesions (score 2). Both treatment groups exhibited primarily normal or modest changes, with most of the rats having neuroinflammation score of 1 (both 66.7%). No lesions with a score of 3 (severe) were detected in any of the groups (Table 3).

Correlation of Histopathological Glial Reactivity Score and Hypothalamic SOD Activity

Spearman analysis was further performed to evaluate the correlation between hypothalamic SOD activity and histopathological score, revealed a faint, non-significant inverse correlation (r=-0.227; p=0.287). Consequently, despite the consistent group-level tendencies, there was no linear association between higher hypothalamic SOD activity and a lower HE-based histopathological score of each the individual rats.

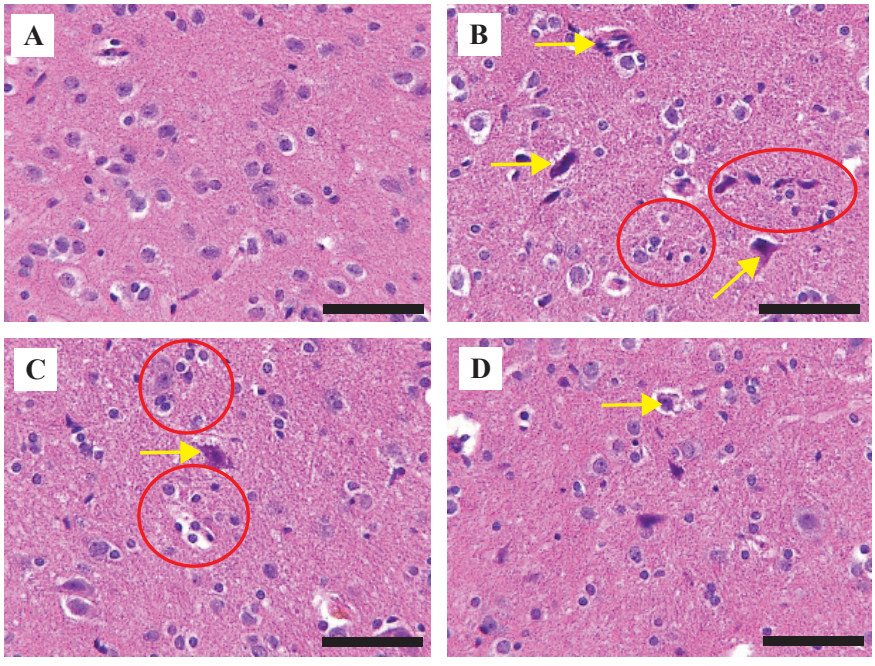

Figure 3. The representative histopathological analysis results of hypothalamic tissue in different experimental groups. A: Normal group; B: Obese group; C: MOFE500 group; D: MOFE1000 group. Red circle: reactive glial cells (gliosis); Yellow arrows: pericellular edema. Black bar: 50 µm.

Table 3. Distribution of hypothalamic neuroinflammation scores based on HE staining.

Group	Score 0	Score 1	Score 2	Score 3
Normal	4 (66.7%)	2 (33.3%)	0	0
Obese	0	4 (66.7%)	2 (33.3%)	0
MOFE500	2 (33.3%)	4 (66.7%)	0	0
MOFE1000	2 (33.3%)	4 (66.7%)	0	0

Discussion

Chronic nutrient excess can induce oxidative stress, inflammatory signaling, and glial reactivity in brain regions that regulate energy balance, this further leads to obesity-related hypothalamic injury.(1-3,6) Therefore, it is necessary to have natural agent that can manage the elevated oxidative stress and glial reactivity in hypothalamus. The results of this study shows that MOFE administration was able to lower Lee Index of obese rate after obesity induction, accompanied by restoration of hypothalamic SOD activity and more improve histopathological abnormalities. With rats given 500 mg/kgBW/day MOFE exhibited bigger decrease of Lee Index, indicating a stronger anti-obesity or weight-control effect. Meanwhile, rats given 1,000 mg/kgBW/day MOFE showed better SOD activity and reduced glial reactivity, suggesting that enhanced neuroprotective and antioxidative properties.

Both 500 and 1000 mg/kgBW/day MOFE administration was able to lower Lee Index of obese rats compared to the obese control. Though the fruit (pods) was used in this study, but it gives similar results with the root and leaf extract of *M. oleifera.* The *M. oleifera* root extract at the dose of 200 and 400 mg/kg BW was able to reduce rats body weight and Lee Index.(26) While 400 mg of *M. oleifera* leaf extract was also able to reduced Lee Index to for about 10.85±0.54% in obese rats.(27)

MOFE also exhibits endogenous antioxidant defenses, which is shown by the potential to restore hypothalamic SOD activity in obese rats. Previous study, similarly, show that *M. oleifera* leaf extract was able to improve SOD activity in obese rats, even though its combination with *H. sabdariffa* extract shows better results.(27) Meanwhile in diabetic rats, *M. oleifera* leaf methanol extract also exhibit the potency to increase SOD activity.(28,29) The restoration of local redox homeostasis may be evidenced by the recovery of hypothalamic SOD activity after treatment with *M. oleifera*, as SOD is responsible for detoxifying superoxide radicals.(9,10)

The metabolic and redox-modulating effects of *M. oleifera* preparations are supported by prior reviews and experimental studies, and *M. oleifera* fruit pods contain bioactive compounds with reported antioxidant and anti-inflammatory potential.(15-18) The findings of current study in an obesity model demonstrate an association between fruit extract treatment and enhanced hypothalamic SOD activity, thereby extending this rationale.

Due to the use of a HE-based histopathology score, the results of the current study indicate that the histopathological features might be consistent with glial reactivity/neuroinflammatory change, rather than as definitive immunophenotypic proof. Rats receiving either 500 or 1000 mg/kgBW/day MOFE had lower glial reactivity scores and fewer histopathological abnormalities compared to the obese rats. Another study using *M. oleifera* ethanol leaf extract showed that the extract was able to suppresses inflammatory activation of glial reactivity, demonstrating microglial-targeted anti inflammatory potential.(30)

Though MOFE administration improve SOD activity and suppress neuroinflammation scores, however there are no significant correlation between hypothalamic SOD activity and the histopathological score. It implies that the relationship between antioxidant enzyme activity and histopathological is not strictly linear in individual animals, despite the fact that both endpoints improved at the group level. This may be indicative of the coarse resolution of semi-quantitative HE scoring, temporal distinctions between biochemical and structural responses, or sample size limitations.

Since both 500 and 1000 mg/kgBW/day MOFE gave beneficial effects in obese rats, albeit on different aspects, further studies are needed to determine the optimal dosage. The data presented in this study are preclinical evidence in rats and do not establish definitive molecular targets, optimal human dosing, or human efficacy. Therefore, translational interpretation to human subjects should continue to exercise caution. Before clinical inference can be drawn, additional mechanistic research is also required to further elaborate the association between the fruit (pods) extracts of *M. oleifera*

and obesity-induced oxidative stress and neuroinflammation changes. This study evaluated neuroinflammatory change by employing a HE-based morphology score that did not involve automated image quantification or immunohistochemistry. Consequently, it was not possible to differentiate between specific glial phenotypes, such as astrocytic and microglial activation states. The biochemical evaluation was restricted to the total SOD activity in hypothalamic homogenate, and no additional oxidative/inflammatory mediators were measured. Future research should evaluate functional outcomes and incorporate immunophenotyping, quantitative image analysis, and broader redox and cytokine panels to more accurately delineate mechanisms and causal pathways.

Conclusion

The administration of MOFE lowers Lee Index, improve hypothalamic SOD activity, reduce glial reactivity and improves neuroinflammation changes in obese rats. These results suggest that MOFE might be potential agent for intervention in obesity-related oxidative-inflammatory brain injury models.

Acknowledgments

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Authors Contribution

DAP was involved in the conception and design, data acquisition, data analysis, drafting of the manuscript. RMT did primary supervision, methodological guidance, critical revision, and approved the final manuscript. MST performed co-supervision, methodological input, and critical revision. MA and TS were involved in the thesis examination, scientific critique, and recommendations for manuscript refinement.

Ethical Statement

The procedure of this study was conducted in accordance with the ARRIVE 2.0 recommendations, and the protocol was approved by The Health Research Ethics Committee, Faculty of Medicine and Health, Universitas Muhammadiyah Jakarta (No. 325/PE/KE/FKK-UMJ/VII/2025).

Conflict of Interest

Authors declare no conflict of interest.

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