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Oral Administration of Moringa (*Moringa oleifera*) Leaf Ethanol Extract Reduces Interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α) Levels of Obese Wistar Rats

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A B S T R A C T

Background: In obesity, low-grade chronic inflammation occurs, causing local and systemic increases in pro-inflammatory molecules, such as IL-6 and TNF-α. Moringa (Moringa oleifera) leaf has the potential to modulate several acute and chronic inflammatory conditions and diseases. The aim of this study was to prove whether the administration of ethanol extract of Moringa (Moringa oleifera) leaf orally can reduce levels of the inflammatory biomarkers IL-6 and TNF-α in obese Wistar rats.

Methods: This research is experimental research using a randomized pretest-posttest control group design. The experimental animal subjects were male white Wistar rats (Rattus norvegicus), aged 3.5-4.5 months, body weight 170-190 grams, a total of 15 rats were divided into three groups, namely the normal control group (P0), obesity control (P1), and extract (P2). All experimental animals were acclimatized for one week. For four weeks, obesity was induced by giving a high-fat diet to groups P1 and P2, while at P0 given standard food and drink ad libitum. In all groups, IL-6 and TNF-α levels were measured as pretest data. Afterward, for four weeks, at P1: rats were given a high-fat diet and distilled water 1 mL/time/day via orogastric tube, whereas in P2: rats were given a high-fat diet and ethanol extract of Moringa (Moringa oleifera) leaf 300 mg/kg BW/time/day via orogastric tube. After that, IL-6 and TNF-α levels were measured as posttest data. Statistical tests used paired t-test and One Way ANOVA.

Results: The results showed that giving ethanol extract of Moringa (Moringa oleifera) leaf orally 300 mg/kg BW can reduce IL-6 levels in obese Wistar rats, with IL-6 pretest compared to posttest (paired t-test p value) in groups P0, P1 , and P2 were 6.04±0.91 vs. 8.25±1.77 (p = 0.04), 5.77±1.93 vs. 12.64±3.88 (p = 0.04), 11.31±3.58 vs 8.74±2.98 (p = 0.02). Likewise, the administration of 300 mg/kg BW of ethanol extract of Moringa (Moringa oleifera) leaf orally can reduce TNF-α levels in obese Wistar rats. The TNF-α pretest compared to the posttest (paired t-test p value) in groups P0, P1, and P2 were 120.30 ± 24.27 vs. 120.81±10.68 (p = 0.95), 119.96±6.79 vs 125.82±17.65 (p = 0.47), 141.84±7.50 vs 122.07± 2.37 (p = 0.00).

Conclusion: From this study, it is found that administration of ethanol extract of Moringa (Moringa oleifera) leaf orally can reduce levels of IL-6 and TNF-α in obese Wistar rats

Keywords: Moringa (*Moringa oleifera*) leaf extract, IL-6, TNF-α, obesity

1. Introduction

Aging is a complex process that negatively affects body functions. Inflammaging is the term for chronic inflammation that characterizes the aging process (Frasca et al., 2017). A major relationship between aging, obesity, and age-related illnesses such as insulin resistance, cognitive decline, atherosclerosis, cancer, and autoimmune disorders is inflammation (Hotamisligil, 2017).

Obesity is characterized by excessive accumulation of adipose tissue in the body (Santos & Sinha, 2021). Every age group is impacted by the worldwide obesity pandemic. The increasing prevalence of obesity is a phenomenon that occurs worldwide (Frasca et al., 2017). In 2018, it was reported that the prevalence of obesity was 23.1% and central obesity was 28% in the adult Indonesian population (Harbuwono et al., 2018). Obesity is a serious problem for Indonesian public health and a poor predictor of clinical outcomes (Marseglia et al., 2014).

Obesity causes a decrease in organ function like the normal aging process. Being obese also means getting old prematurely (Pérez et al., 2016). Reduced insulin sensitivity is related to increases in pro-inflammatory cytokines. Insulin resistance, which develops because of low-grade (sterile) chronic inflammation, marks the change from physiologically normal obesity to metabolic syndrome. It is characterized by high levels of lipids, free fatty acids, glucose, and reactive oxygen species and is brought on by systemic inflammation and metaflammation (Hotamisligil, 2017), a process by which excessive feeding leads to low-grade chronic inflammation. Inflammation causes an increase in pro-inflammatory molecules locally and systemically, such as

Interleukin (IL)-6 and Tumor Necrosis Factor (TNF)-α (Grant & Dixit, 2015). The negative impact of inflammation caused by obesity can be mitigated by administering anti-inflammatories. One of the natural anti-inflammatories is Moringa (*Moringa oleifera*) leaf. Balusamy et al. have reported that Moringa (*Moringa oleifera*) leaf has an anti-obesity effect.

In a study by Martnez-González et al., the ethanol extract of Moringa (*Moringa oleifera*) leaf was administered orally at doses of 30, 100, and 300 mg/kg BW, and it was found to reduce inflammation in rat models of arthritis induced by subcutaneous collagen injection, leg edema caused by carrageenan, and formalin-testing-induced arthritis. The 300 mg/kg BW dose appeared to provide the strongest anti-inflammatory effects (Martínez-González et al., 2017). In a different study, male albino rats were given an ethanol extract of the Moringa (*Moringa oleifera*) leaf, which significantly reduced the liver damage caused by diclofenac sodium. The highest safe dose identified in this investigation was determined to be 300 mg/kg BW (El-Hadary & Ramadan, 2018). Moringa (*Moringa oleifera*) leaf contains several phytochemicals that are involved in anti-inflammatory responses, including flavonoids and isothiocyanates (Ray et al., 2017). Ethanol solvent can extract higher concentrations of flavonoids in Moringa (*Moringa oleifera*) leaf (Lin et al., 2018). Isothiocyanates were also detected in ethanol extract of Moringa (*Moringa oleifera*) leaf (Engsuwan et al., 2017).

Currently, there is no research to examine the benefits of oral Moringa (*Moringa oleifera*) leaf ethanol extract in reducing inflammation in obesity cases, even though obesity cases in Indonesia continue to increase. Meanwhile, Moringa (*Moringa oleifera*) is often found in Indonesia and is easy to grow, with little or no care at all (Roshetko et al., 2017). Moringa (*Moringa oleifera*) leaf is a suitable choice for developing countries, where people are looking for quality, inexpensive, and easily accessible treatments (Kashyap et al., 2022).

2. Material & Methods

This study employs an experimental randomized pretest-posttest control group design. The experimental animal subjects were white Wistar rats (*Rattus norvegicus*), aged 3.5-4.5 months, body weight 170-190 grams. The independent variable was Moringa (*Moringa oleifera*) leaf extract. Serum levels of IL-6 and TNF-α served as the dependent variables. The diet, rat strain, age, and body weight were the control variables. All experimental animals were acclimatized for one week. Total of 15 rats were divided into three groups, namely the normal control group (P0), obesity control (P1), and extract (P2). Groups P1 and P2 were provided with a high-fat diet for four weeks, while group P0 received free access to a conventional diet. IL-6 and TNF-α levels were assessed as pretest data in each group. Through the medial canthus of the orbital sinus, 1 cc of vein blood was drawn. The rats were previously given intramuscular injections of 10% ketamine at a dose of 50 mg/kg BW and 2% xylazine at a dose of 20 mg/kg BW to anesthetize them. Afterward, for four weeks, at P0: rats were given standard food and drink *ad libitum*, at P1: rats were given a high-fat diet and distilled water 1 mL/time/day via orogastric tube, whereas in P2: rats were given a high-fat diet and ethanol extract of Moringa (*Moringa oleifera*) leaf 300 mg/kg BW/time/day via orogastric tube. Following that, IL-6 and TNF-α levels were assessed as posttest data. 10% ketamine at a dose of 50 mg/kg BW and 2% xylazine at a dose of 20 mg/kg BW were intramuscularly injected into the thighs of rats to anesthetize them. To measure the levels of serum IL-6 and TNF-α, 1 cc of venous blood was drawn through the medial canthus of the orbital sinus. Then cervical dislocation was performed. Rats that have been used as research subjects were properly buried. Statistical tests used paired t-test and One Way ANOVA. Software SPSS Version 22 for Windows was used for data analysis.

3. Results

The results showed that giving 300 mg/kg BW ethanol extract of Moringa (*Moringa oleifera*) leaf orally can reduce IL-6 levels in obese Wistar rats, with IL-6 pretest compared to posttest (paired t-test p value) in groups P0, P1 , and P2 were 6.04±0.91 vs. 8.25±1.77 (p = 0.04), 5.77±1.93 vs. 12.64±3.88 (p = 0.04), 11.31±3.58 vs 8.74±2.98 (p = 0.02). Likewise, the administration of 300 mg/kg BW ethanol extract of Moringa (*Moringa oleifera*) leaf orally can reduce TNF-α levels in obese Wistar rats. The TNF-α pretest compared to the posttest (paired t-test p value) in groups P0, P1, and P2 were 120.30 ± 24.27 vs. 120.81±10.68 (p = 00.95) 119.96±6.79 vs 125.82±17.65 (p = 0.47), 141.84±7.50 vs 122.07± 2.37 (p = 0.00).

On the variables IL-6 and TNF-α, the descriptive analysis comprises the mean, standard deviation (SD), minimum, and maximum. Effect analysis was tested based on the average IL-6 and TNF-α between groups before and after being given treatment and its increase/decrease (delta). Table 1 displays the findings of the analysis. From the descriptive analysis it was found that in the P0 group (control group) which was not obese-induced and only given a standard diet, the mean IL-6 and TNF-α delta levels were 2,20 & 0,51, respectively, in the P1 group (obesity control group) which was obese-induced and given distilled water, the mean IL-6 and TNF-α delta levels were 6,87 & 5,86, respectively and in the P2 group (extract group) which was also obese-induced and given Moringa (*Moringa oleifera*) leaf extract, the mean IL-6 and TNF-α delta levels were -2,57 & -19,77, respectively. Furthermore, it was observed that the P2 group's IL-6 and TNF-α delta levels were lower than those of the P1 group after receiving Moringa (*Moringa oleifera*) leaf extract.

Table 1 - Descriptive Analysis Variables IL-6 and TNF- α Delta.

Variable	Group	n	Mean	SD	Min	Max
	P0	5	2,20	1,65	0,03	3,77
IL-6	P1	5	6,87	4,95	1,38	12,39
	P2	5	-2,57	1,41	-4,55	-0,60
	P0	5	0,51	16,20	-20,43	23,20
TNF- α	P1	5	5,86	16,30	-18,20	24,00
	P2	5	-19,77	6,24	-27,20	-12,80

Analysis of the treatment effect was tested based on the IL-6 and TNF-α delta between groups after being given treatment in the form of exposure to an obesity-induced diet and Moringa (*Moringa oleifera*) leaf extract. Interleukin-6 and TNF-α delta data were tested for normality using the Shapiro-Wilk test. The results show that the data are normally distributed ($p > 0.05$) and were tested for homogeneity using Levene's test. The findings demonstrate non-homogeneous data for IL-6 delta ($p < 0.05$) and homogenous data for TNF-α delta ($p > 0.05$). Significance analysis using the one-way ANOVA test for IL-6 and TNF-α delta shows that the value of $p = 0.00$ & $p = 0.03$, whereas this reduction was better in the P2 group (delta = -2,57±1,41 & -19,77±6,24). The test for differences in the mean IL-6 and TNF-α delta between groups was carried out using the Post Hoc Least Significant Difference (LSD) test. Based on the difference results on the mean IL-6 and TNF-α delta levels between groups, it can be concluded that there were statistically significant differences in IL-6 and TNF-α levels in all groups because they had a p value < 0.05.

4. Discussion

4.1 Obesity Increases IL-6 and TNF-α Levels in Wistar Rats

When compared to the P0 group, the P1 group's levels of IL-6 and TNF-α delta were considerably higher. High-fat diets can cause overweight and eventually obesity as well as low-grade chronic inflammation, which is closely linked to the etiology of metabolic syndrome and other chronic diseases. Low-level inflammatory conditions are generally associated with increased levels of certain biomarkers, especially pro-inflammatory cytokines, namely IL-6 and TNF-α **(**Cortez et al., 2012**)**. Obesity can produce large amounts of Reactive Oxygen Species (ROS) and mediate the inflammatory process followed by the release of pro-inflammatory cytokines such as IL-6 and TNF-α. Furthermore, ROS will stimulate the activation of transcription factors, one of which is NF-κB, which in the next stage will express proinflammatory genes. These pro-inflammatory genes will produce pro-inflammatory cytokines, including IL-6 and TNF-α, so that their levels will increase (McMurray et al., 2016).

4.2 The Effect of Moringa (Moringa oleifera) Leaf on IL-6 and TNF-α Levels in Obese Wistar Rats

The findings of this study suggested that oral administration of ethanol extract from Moringa (*Moringa oleifera*) leaf could lower IL-6 and TNF-α levels in obese Wistar rats because of a high-fat diet, as seen on IL-6 and TNF-α delta in the P2 group compared to the P1 group. If it is not inhibited, IL-6 and TNF-α levels in obese Wistar rats will continue to increase, whereas if it is inhibited, the levels will decrease. Moringa (*Moringa oleifera*) leaf as a source of anti-inflammatory is known to reduce IL-6 production by macrophages. In this study, ROS is formed due to obesity due to a high-fat diet. Reactive Oxygen Species can stimulate the phosphorylation process of IκB. To keep NF-κB inactive in the cytoplasm, IκB's role is to bind to it. If IκB is phosphorylated, the NF-κB and IκB bonds are released, so that NF-κB becomes active and moves to the nucleus. This process is called the NF-κB activation process. The phytochemicals found in Moringa (*Moringa oleifera*) leaf can prevent the production of ROS, which in turn prevents the activation of NF-κB. This inhibition of NF-κB activation will further inhibit the production of pro-inflammatory cytokines, including IL-6 and TNF-α (H & H, 2016).

Another study on the impact of Moringa (*Moringa oleifera*) leaf ethanol extract on inflammation caused by cobalt exposure in rat kidneys discovered that there was a reduction in IL-6 and NF-κB gene expression in the group of mice that received Moringa (*Moringa oleifera*) leaf ethanol extract, both prophylactically and therapeutically. Moringa (*Moringa oleifera*) leaf ethanol extract supplementation was associated with a significant reduction in the inflammatory response index. The ethanol extract of Moringa (*Moringa oleifera*) leaf repairs damage caused by inflammation by suppressing the mRNA expression patterns of genes encoding pro-inflammatory cytokines (Abdel-Daim et al., 2020).

Since oxidative stress and inflammation are converging at this point, ROS may serve as a secondary critical mediator that triggers the activation of NF-κB in response to diverse stimuli. Because it is involved in the development and differentiation of B and T cells, as well as the activation of acute phase proteins, IL-6 is the key mediator of inflammatory response (Abdel-Daim et al., 2020).

The inflammatory response is separated into at least two distinct pathways, namely the canonical pathway, stimulated by toll-like receptors, TNF-α, and IL-1, and the alternative pathway, stimulated by members of the TNF family such as lymphotoxin-ß, CD40, BAFF, and NF-κß ligand's receptor activator. Moringa (*Moringa oleifera*) and its bioactive components work in the canonical pathway (Ray et al., 2017), including the IL-6 signaling pathway. The anti-inflammatory mechanism of Moringa (*Moringa oleifera*) leaf overlaps between the canonical IL-6 and NF-κB signaling pathways. Consumption of Moringa (*Moringa oleifera*) leaf provides benefits because it contains bioactive compounds which collectively provide an anti-inflammatory effect by reducing IL-6 and TNF-α (Cuellar-Núñez et al., 2021).

Another study found that Moringa (*Moringa oleifera*) leaf extract inhibited the production of human macrophage cytokines induced by cigarette smoke. IL-6 and TNF-α levels are increased roughly tenfold by cigarette smoke. This research has shown that Moringa (*Moringa oleifera*) leaf lowered cytokine production caused by cigarette smoke to basal (control) level and could prevent cigarette smoke's potential to stimulate cell signaling. This study discovered that the inflammatory gene RelA, which is involved in the pathogenesis of NF-κB-mediated chronic inflammatory illness, was expressed less when Moringa (*Moringa oleifera*) leaf extract was used. It has been discovered that nuclear translocation in inflammatory response correlates with high levels of RelA gene expression. It is not unexpected that Moringa (*Moringa oleifera*) has been proven to be helpful in treating many inflammatory illnesses because macrophages and TNF are crucial in the pathophysiology of chronic inflammatory diseases (Kooltheat et al., 2014).

The content of flavonoids in Moringa (*Moringa oleifera*) leaf extract, such as quercetin and luteolin, can reduce the expression and secretion of cytokines. Nuclear Factor kappa B and AP-1 are important transcription factors in modulating pro-inflammatory mediators, such as cytokines (Leyva-López et al., 2016). Nuclear Factor kappa B regulates the expression of cytokines and other inflammatory mediators (Richmond & Yang, 2015), while AP-1 takes a

role in the production of effector molecules and cytokines during the innate immune response (Qiao et al., 2016). Because NF-κB and AP-1 play a significant role in inflammation, studies have been done to see how flavonoids affect the modulation of these to intranscription factors. In rat aortic endothelial cells, quercetin dramatically reduced by 43% and 69%, respectively, the rise in NF-κB and AP-1 activity brought on by glucose. Lutein dramatically reduced the production of IL-6 and TNF-a, blocked JNK and p38 activation, and decreased the activation of the transcription factors NF-κB and AP-1 in human synovial sarcoma cells that had been stimulated by IL-1β. These results demonstrate that luteolin flavonoids inhibit MAPKs (JNK and p38) and transcription factors (NF-κB and AP-1) to have anti-cytokine activity (Leyva-López et al., 2016).

4.3 Moringa (Moringa oleifera) Leaf Extract in Anti-Aging Medicine

In this study, administration of Moringa (*Moringa oleifera*) leaf extract was shown to reduce levels of IL-6 and TNF-α. Molecules that activate Nrf2 can suppress the NF-κB pathway, which is crucial to the inflammatory process. Under normal circumstances, Nrf2 interacts to Keap1, a cytoplasmic substrate adaptor protein for Cul3/Rbx1 ubiquitin ligase. If there is no stimulus such as oxidant, the Keap1-Nrf2 bond will experience ubiquitination followed by proteasomal degradation. If there is an oxidant stimulus such as ROS, Keap1 will be released from Nrf2. When Keap1 dissociates from Nrf2, Keap1 can interact with and regulate NF-κB transcription factors such as IκB. NF-κB binds to its inhibitor, IκB, in cytoplasm and NF-κB is activated by phosphorylation of IκB by the kinase enzyme, namely IKK, which dissociates the NF-κB-IκB complex so that NF-κB can move to the nucleus. In this situation, Keap1, which has separated from the Nrf2-Keap1 complex, can bind to IKK, increasing the ubiquitination and degradation of IKK in the process. As a result, Keap1 is crucial in suppressing the NF-κB pathway. Here, it can be explained that the decrease in IL-6 and TNF-α levels by consuming Moringa (*Moringa oleifera*) leaf extract is through the activation mechanism of the Nrf2-Keap1 complex and inhibiting the NF-κB pathway (Aguilar et al., 2016; Cuellar-Núñez et al., 2021). Quercetin, the most abundant flavonoid found in Moringa (*Moringa oleifera*) leaf (Rocchetti et al., 2019), is known to inhibit NF-κB activation and reduce IL-6 and TNF-α production (Saeedi-Boroujeni & Mahmoudian-Sani, 2021).

Moringa (*Moringa oleifera*) leaf's bioactive molecules play an important role in anti-aging interventions by protecting or modulating the immune system. An anti-inflammatory approach from Moringa (*Moringa oleifera*) leaf to control low-level chronic inflammation in obesity is expected to change the risk of disease in obesity, especially by treating and preventing metabolic diseases associated with aging. The results of this study indicate that administration of 300 mg/kg BW Moringa (*Moringa oleifera*) leaf extract orally can decrease IL-6 and TNF-α levels of male Wistar rats exposed to a high-fat diet.

5. Conclusion

From this study, it is known that feeding obese Wistar rats a high-fat diet can increase their levels of IL-6 and TNF-α, and that this can be decreased by giving them an oral ethanol extract of Moringa (*Moringa oleifera*) leaf. For assessing IL-6 and TNF-α levels in humans, additional study and clinical trials are required. Further study is required to compare the levels of IL-6 and TNF-α before obesity was induced as a normal reference value to the levels of IL-6 and TNF-α after obesity was induced, using a normal control population with a smaller Lee index, to increase the difference in the Lee index between the normal control and obese group. Also, more samples are needed so that the data's variation can be smaller.

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Not applicable.

Research Ethics

B/211/UN14.2.9/PT.01.04/2022 is the authorization number given by the Animal Ethics Committee of the Faculty of Veterinary Medicine at Udayana University for this study.

Author Contribution

From the stage of proposal development, data search, and data analysis to the interpretation of research data, and presentation of the final report, all authors have made the same contribution to writing the report on the findings of this study.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

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