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Research Paper

Potency of Leaf Water Extract Karamunting (*Rhodomyrtus tomentosa*) for Enhancing GLUT4 Translocation in Diabetic Rats

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Abstract
Insulin resistance and damage in the pancreas are associated with type 2 diabetes, which is a chronic disease affecting health, with 422 million people affected in 2016 and 1.5 million deaths related to diabetes in 2012. Several proinflammatory mediators, such as TNF-α and IL-6, may be involved in insulin resistance in T2DM. GLUT4 is one of the glucose transporters that help promote glucose uptake. GLUT4 activation is insulin-dependent in regulating glucose uptake. Karamunting (*Rhodomyrtus tomentosa* (Ait.) Hassk.) leaf water extract consists of alkaloids, flavonoids, triterpenoids, saponins, and tannins. This study proposes to investigate the potential of karamunting (*R. tomentosa*) leaf water extract to enhance glucose uptake by modulating GLUT4 translocation in the serum and skeletal muscle of diabetic rats. The dose variations used in this study were 100 mg/kgBW, 200 mg/kgBW, and 400 mg/kgBW. Based on the results, oral administration of karamunting water extract increases GLUT4 expression in serum. It increases GLUT4 mRNA levels in the skeletal muscle of the diabetic rat. It decreases TNF-α and IL-6 expression, with a 100 mg/kg BW dosage being the most effective. Meanwhile, 100 mg/KgBW is the most effective dosage for decreasing HOMA IR. These results indicate that karamunting (*R. tomentosa*) leaf water is antidiabetic by lowering TNF-α, IL-6, and HOMA IR in diabetic rats while increasing GLUT4.

Keywords
T2DM, TNF-α, IL-6, GLUT4, HOMA IR, *Rhodomyrtus tomentosa*

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1. INTRODUCTION

1.5 million deaths associated with diabetes were reported in 2012 by the WHO globally, and 422 million people were diagnosed with diabetes by 2016. Diabetes is a chronic metabolic disorder that occurs when the pancreas fails to produce sufficient insulin or when the body cannot effectively utilize the insulin that is produced (Roglic and Organization, 2016). Patients with diabetes must control their blood sugar levels by regularly taking diabetes medication, avoiding high-sugar or starchy foods, reducing stress, exercising regularly, and losing weight (NHS, 2022).

Type 2 diabetes mellitus (T2DM) is characterized by the presence of insulin resistance accompanied by pancreatic dysfunction. Insulin resistance may arise from several contributing factors, including elevated lipid concentrations, enhanced inflammatory signaling, and activation of endoplasmic reticulum stress pathways (Muoio and Newgard, 2008). Tumor necrosis factor α (TNF-α) plays a significant role as a proinflammatory mediator. TNF-α is produced mainly in adipocytes and/or peripheral tissue (Akash et al., 2018). Evidence indicates that obesity-associated insulin resistance has been observed, and TNF-α may be one of the factors, based on its α increased concentration in obese subjects. Although existing evidence is limited in its ability to prove the association, TNF-α is probably a contributing factor in insulin resistance and dyslipidemia incidents (Moller, 2000).

In addition to TNF-α, interleukin-6 (IL-6) is another proinflammatory mediator that contributes to the development of insulin resistance. IL-6 is a key inflammatory cytokine involved in inflammatory responses and plays an important role in regulating cellular processes such as differentiation, migration, proliferation, and apoptosis (Rehman et al., 2017). Proinflammatory mediator overexpression may induce insulin resistance, thus leading to T2DM (Akash et al., 2018). IL-6 has been proposed as a major contributor to insulin resistance at the cellular level in both primary hepatocytes and HepG2 cell lines. Therefore, this cytokine is considered to play an important role in the development of insulin resistance (Senn et al., 2002).

The condition of insulin resistance, shows increased in blood sugar levels due to the cells' inability to take up available sugar. Insulin resistance impairs glucose transporter activity; GLUT4 is a glucose transport protein predominantly expressed in skeletal muscle and adipose tissue. In T2DM condition, GLUT4 activity is decreased, thereby disrupting glucose uptake (Garvey et al., 1998).

Currently, T2DM medication commonly uses metformin and changes lifestyle. However, second and third-line medications are also widely used to treat T2DM. However, existing medications still have certain limitations and contraindications. Therefore, additional studies are needed to develop novel therapeutic strategies (He et al., 2015). Karamunting is a wild plant primarily found in some parts of Southeast Asia. Karamunting is found in Indonesia, typically on the islands of Sumatra and Kalimantan (Sinaga et al., 2019). Previous studies have identified phenolic compounds and terpenes from the leaves, roots, and fruits of *Rhodomyrtus tomentosa*, which demonstrate diverse biological activities such as antioxidant, antibacterial, anti-inflammatory, and anticancer effects (Vo and Ngo, 2019). Na-Phatthalung et al. (2018) Exposure to rhodomyrtone, one of the bioactive compounds isolated from the leaves, in combination with lipopolysaccharide (LPS), was shown to reduce the gene expression of inflammatory processes related to TNF-α, IL-8, IL-1β, iNOS, SAA, and hepcidin, along with the decrease in reactive oxygen species (ROS) levels (Na-Phatthalung et al., 2018). Winarsih et al. (2023) reported that ethanolic leaf extract of *R. tomentosa* significantly reduced circulating levels of TNF-α, IL-6, and IL-1β at a dose of 100 mg/kg body weight in diabetic mice (Winarsih et al., 2023). Febriyanto and Saleh (2021) reported that water leaf fractions of *R. tomentosa* effect in diabetic rats effectively decrease post-prandial blood sugar levels while increasing insulin levels using a dose of 200 mg/KgBW. Leaf water fraction compounds include alkaloids, flavonoids, triterpenoids, saponins, and tannins (Febriyanto and Saleh, 2021).

GLUT4 is activated through the PI3K and AMPK pathways. In the PI3K pathway, GLUT4 is stored in vesicles and is transported to the plasma membrane upon activation, thereby increasing glucose uptake (Wang et al., 2020). Recent evidence indicates that lipophilic extracts from *Wisteria sinensis* flowers enhance GLUT4 expression and activate Akt signaling in adipose and skeletal muscle tissues of diabetic mice. These effects are associated with improvements in hyperglycemia, insulin resistance, dyslipidemia, as well as attenuation of hepatic steatosis and pancreatic damage (Lv et al., 2020).

2. EXPERIMENTAL SECTION

2.1 Materials

2.1.1 Reagents

Rat GLUT4 ELISA Kit (Fine Test), Rat IL-6 ELISA Kit (Fine Test), Rat TNF-α ELISA Kit (Fine Test) were purchased from Wuhan Fine Biotech Co. Ltd. (Wuhan, China), HOMA IR ELISA Kit, RNAiso Plus, 5x RT Buffer (dNTP-dATP, dGTP, dTTP, dCTP), Oligo DT, Reverse transcriptase, DEPC-treated H_2O, Nuclease Free Water, All other reagents used were obtained according to the standard available.

2.1.2 Plant Preparation

Fresh karamunting leaves were collected, dried in an oven at 40-50 °C, macerated with 40 L of boiling water for 1 hour while stirred regularly, and then evaporated using a rotary evaporator to obtain a thick extract. The extract was divided into 100 mg/kgBW, 200 mg/kgBW, and 400 mg/kgBW.

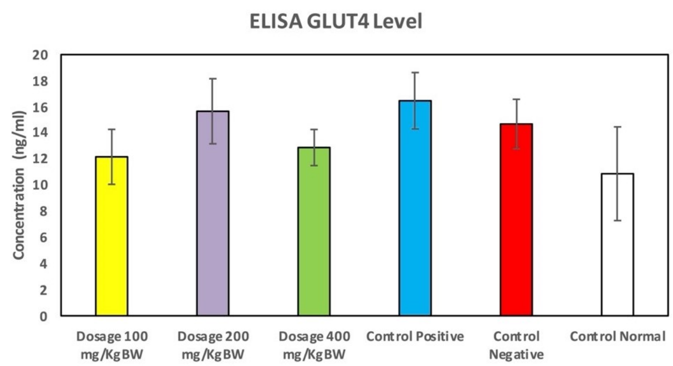

Figure 1. GLUT4 Protein Expression in the Serum of Rats was Measured by Using the ELISA in Comparison with Controls, and All Treatments were Not Significant ($p \geq 0.05$)

2.2 Methods

2.2.1 Identification of Chemical Compound

Phytochemical identification was conducted to determine the classes of compounds present in the aqueous extract of *Rhodomyrtus tomentosa* leaves. The analysis was performed using qualitative methods based on color changes observed after reaction with specific reagents corresponding to each compound class. Phytochemical screening was carried out using several standard reagents. This method was selected because it is simple, rapid, requires minimal equipment, is specific for particular compound groups, and is capable of detecting compounds even at low concentrations (Endarini, 2016).

2.2.2 Animals and Administration of Karamunting Leaf Water Extract

Thirty-three rats were prepared and acclimated for 7 days in controlled conditions at 22 °C, with 40-60% humidity, and fed ad libitum. The rats were weighed, and their fasting blood glucose (FBG) was measured. The rats were induced with a high fat and fructose diet for 6 weeks, followed by an injection of streptozotocin. The rats were then checked for their FBG and insulin levels. The rats were grouped into six groups: (1) diabetic rats fed with karamunting leaf water extract dose 1 (100 mg/kgBW), (2) diabetic rats fed with karamunting leaf water extract dose 2 (200 mg/kgBW), (3) diabetic rats fed with karamunting leaf water extract dose 3 (400 mg/kgBW), (4) diabetic rats positive control (pioglitazone), (5) diabetic rats

Table 1. Qualitative Phytochemical Screening of *Rhodomyrtus tomentosa* Leaf Water Extract

Phytochemical Test	Reagent	Color Change	Result
Alkaloids	Mayer, Dragendorff, Bouchardat	No precipitate observed	–
Flavonoids	Magnesium powder and concentrated HCl	Red coloration	+
Terpenoids	Liebermann–Burchard	Brownish/violet ring formation	+
Saponins	Froth test	Stable foam formation	+
Tannins	$FeCl_3$	Bluish-black coloration	+
Quinones	Borntrӓger test	Red coloration	+

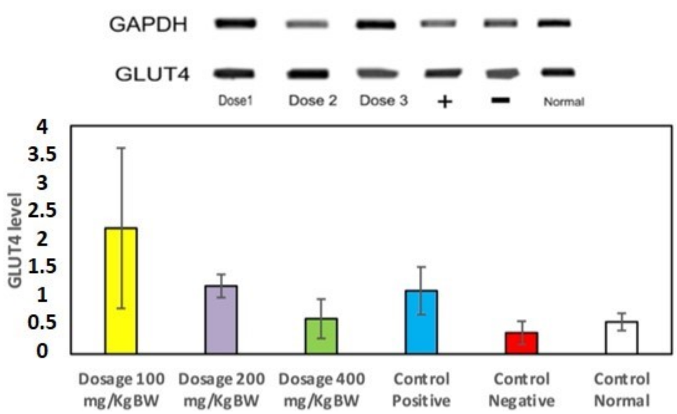

Figure 2. GLUT4 mRNA Expression in Rats' Skeletal Muscle was Measured Using RT-PCR Compared to Controls, and None of the Treatments were Significant ($p \geq 0.05$)

negative control, and (6) normal rats control. All groups were administered orally once daily for 2 weeks; on the 15^{th}, the rats measured their FBG and insulin levels.

2.2.3 Measurement of GLUT4, TNF-α, IL-6, Fasting Insulin, and Fasting Blood Glucose with ELISA

Rats serum from dose variations 100 mg/kgBW, 200 mg/kgBW, 400 mg/kg BW, and control were collected from the blood. The serum was then used to measure GLUT4, TNF-α, IL-6, fasting insulin, and fasting blood glucose using ELISA kits. HOMA-IR was then calculated using Equation 1.

$$\text{HOMA-IR} = \frac{\text{fasting blood glucose}\left(\frac{mg}{dL}\right) \times \text{fasting insulin}\left(\frac{mIU}{mL}\right)}{22.5} \quad (1)$$

2.2.4 RNA Extraction

RNA was extracted from rat skeletal muscle tissue in each treatment group using RNAiso Plus according to the manufacturer's instructions. RNA concentration determined by spectrophotometry. The extracted RNA was stored at -80 °C (Sari et al., 2021).

2.2.5 cDNA Synthesis

Extracted RNA was then denatured using OligoDT and DEPC-treated H_2O. After incubation, the cDNA buffer was added to the PCR (Polymerase Chain Reaction). The PCR was performed at 25 °C for 10 minutes, followed by 42 °C for 50 minutes, and finished at 85 °C for 5 minutes. cDNA was stored at -20 °C until use (Sari et al., 2021).

2.2.6 Reverse Transcriptase (RT) -PCR

cDNA was used to analyze GLUT4 using RT-PCR with GAPDH as an internal standard. Sense and antisense primers used were:
GLUT4
Sense primer: 5'-GGG CTG TGA GTG AGT GCT TTC-3'
Antisense primer: 5'-CAG CGA GGC AAG GCT AGA-3'
GAPDH
Sense primer: 5'-TGC TGG GGC TGG CAT TGC TC-3'
Antisense primer: 5'-TCC TTG CTG GGC TGG GTG GT-3'

RT-PCR was performed with the following thermal cycling conditions: an initial denaturation at 94°C for 3 min. Followed by 28 amplification cycles at 94°C for 30 s, at 61°C for 30 s, at 72°C for 30 s, at 72°C for 5 s, and hold at 4°C steps according to guidance (He et al., 2013).

2.2.7 Statistical Analysis

All results are presented as standard errors, and the analysis was performed using Microsoft Excel. Differences between groups were determined by one-way analysis of variance (ANOVA), with a post hoc test by Duncan analysis using SPSS 26.0 software. p-values < 0.05 were considered significant.

3. RESULT AND DISCUSSIONS

3.1 Compound Indentification

The aqueous extract of *Rhodomyrtus tomentosa* leaves was found to contain flavonoids, terpenoids, saponins, tannins, and quinones, while alkaloids were not detected in the present study. The absence of alkaloids in the aqueous extract contrasts with several findings reported that the aqueous fraction of *R. tomentosa* leaves contained alkaloids, flavonoids, triterpenoids, saponins, and tannins (Febriyanto and Saleh, 2021). However, another report shows that aqueous extracts of *R. tomentosa* leaves contained flavonoids, tannins, phenols, and terpenoids, which is more consistent with our findings. Variations in phytochemical composition within the same plant species may occur due to multiple factors (Hasibuan et al., 2015). Phytochemical production is influenced not only by species or variety but also

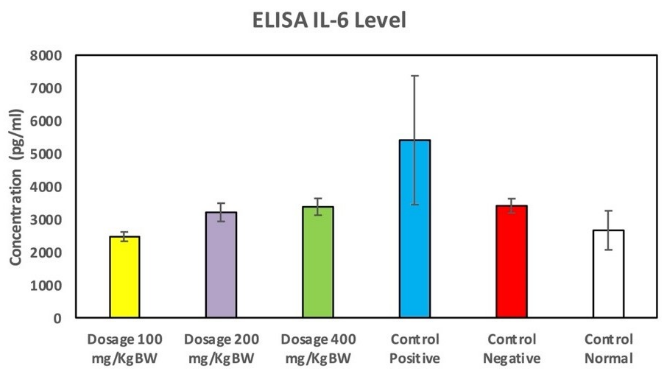

Figure 3. IL-6 Expression in Rat Serum was Measured by ELISA Compared with Controls, and None of the Treatments were Significant ($p \geq 0.05$)

by external factors such as environmental conditions, agricultural practices, and post-harvest handling (Ghasemzadeh et al., 2018). Therefore, the phytochemical profile of a plant species may vary depending on geographical region, soil composition, precipitation levels, light intensity, humidity, and other environmental variables.

3.2 GLUT4 Protein Expression in Rat's Serum

The research used two methods to examine the effect of extract administration on GLUT4 expression in 33 rats. In Figure 1. Show the ability of *R. tomentosa* to increase the GLUT4 expression in the serum of diabetic rats compared with controls. The three controls used were control positive, fed pioglitazone; control negative, fed Na CMC; and control normal, normal rats without supplementation.

Based on Figure 1, a dosage of 100 mg/kgBW is the most effective in increasing GLUT4 expression in serum, although slightly lower than the control-positive. The data were analyzed with one-way ANOVA with Duncan's multiple-comparison test, which showed no significant differences between groups. This may have happened because there was a lack of scientific evidence for the presence of GLUT4 in serum.

Leaf water extract from karamunting consists of several compounds, such as flavonoids, phenolics, tannins, and terpenes (Hasibuan et al., 2015). Reports show that the compounds generally increase GLUT4 activity; some increase GLUT4 activity directly in skeletal muscle, but no evidence indicates that karamunting-derived compounds affect GLUT4 activity (Brus et al., 2021; Feriotto et al., 2024; Wei et al., 2024; Zhou et al., 2023). GLUT4 is commonly found in heart tissue, skeletal muscle, adipose, and brain tissue (Bryant et al., 2002). However, research by Peng et al. (2020) found higher serum GLUT4 levels in critically ill children than in healthy children, suggesting the potential of GLUT4 serum screening to reflect disease severity.

The primary cellular pathway responsible for clearing an exogenous glucose load involves insulin-stimulated glucose uptake into skeletal muscle. Following cellular entry, glucose is either stored as glycogen or oxidized to generate energy. This process is predominantly mediated by GLUT4 (gene name: SLC2A4), belongs to the facilitative glucose transporter family and is characterized by the presence of 12 transmembrane domains. This transporter plays a crucial role in regulating blood glucose levels by facilitating the uptake of glucose from the circulation, thereby maintaining systemic glucose homeostasis. GLUT4 is highly expressed in skeletal muscle and adipose tissue, although other glucose transporter isoforms are also present in these tissues. Under basal conditions, GLUT4 is primarily located within intracellular compartments; however, in response to insulin stimulation or other signaling cues, it rapidly translocates to the plasma membrane, allowing enhanced glucose uptake (Huang and Czech, 2007).

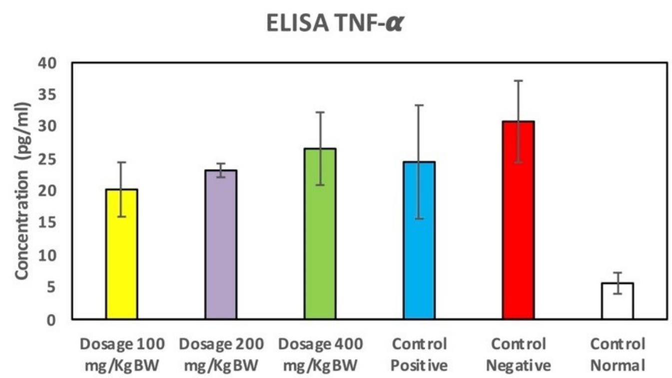

Figure 4. TNF-α Expression in Rat Serum was Measured by Using ELISA in Comparison with Controls; All Treatments were Insignificant ($p \geq 0.05$)

3.3 GLUT4 mRNA Expression in Rat's Skeletal Muscle

The mRNA (messenger ribonucleic acid) expression in skeletal muscle samples in rats was evaluated by RT-PCR. Based on the results shown (Figure 2), treatment using 100 mg/kgBW of extract shows the highest expression of GLUT4 in diabetic rats compared to the control positive. However, there is no significant difference ($p \geq 0.05$). The expression of GLUT4 is normalized to GAPDH to quantify expression accurately.

GLUT4 mRNA expression in skeletal muscle indicates that treatment with natural products may alter GLUT4 expression in diabetic rats. Recent research shows that oral administration of other natural products may affect GLUT4 mRNA expression (He et al., 2013; Nikzamir et al., 2014). Research stated that *R. tomentosa* can improve blood glucose levels in diabetic rats (Sari et al., 2021). Therefore, this study may conclude that administering *R. tomentosa* may improve blood glucose in diabetic rats by enhancing GLUT4 expression and thereby improving T2DM.

In skeletal muscle, insulin promotes glucose uptake primarily via activation of the phosphatidylinositol-3 kinase (PI3K)/Akt pathway, which induces the translocation of glucose transporter

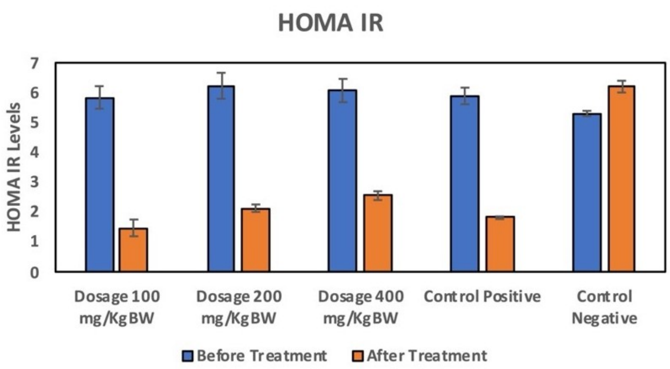

Figure 5. HOMA-IR in Rat Serum was Measured by ELISA, Compared with Controls; All Treatments were Significantly Different ($p < 0.05$)

4 (GLUT4) to the plasma membrane. Apart from this insulin-mediated pathway, AMP-activated protein kinase (AMPK) also regulates GLUT4 trafficking. AMPK is a heterotrimeric enzyme that functions as an energy sensor in mammalian cells and is activated when the cellular AMP/ATP ratio rises. Its activation, which may occur during exercise, muscle contraction, or through pharmacological agents such as metformin, facilitates GLUT4 translocation and enhances glucose uptake in skeletal muscle (Yagasaki, 2014).

3.4 IL-6 Expression in Rat's Serum

Water extract of karamunting can suppress IL-6 levels in diabetic rats (Figure 3). A 100 mg/kgBW dosage is the best among the other concentrations for decreasing IL-6 levels, better than pioglitazone and lower than the control group; however, the differences are insignificant. This result aligns with the research by Winarsih et al. (2023), who reported that a 100 mg/kgBW dose of the ethanolic extract from *R. tomentosa* lowered TNF-α and IL-6 levels in rats infected with *Escherichia coli*.

However, some papers reported that IL-6 is not associated with insulin resistance and may play a role in insulin metabolism (Kurauti et al., 2017; Pal et al., 2014). However, there is also research showing the role of IL-6 in inducing insulin resistance because of its nature as a proinflammatory cytokine (Senn et al., 2002).

Insulin resistance is a major pathological hallmark of type 2 diabetes mellitus (T2DM), characterized by decreased glucose uptake due to impaired GLUT4 function, which results in sustained hyperglycemia. GLUT4, abundantly expressed in skeletal muscle and adipose tissue, is essential for maintaining glucose homeostasis; however, its expression is often diminished in T2DM, leading to reduced peripheral glucose utilization. Elevated concentrations of the proinflammatory cytokine interleukin-6 (IL-6) also contribute to insulin resistance by disrupting insulin signaling pathways such as JAK/STAT activation. Poor glycemic control is frequently linked to increased IL-6 levels and decreased GLUT4 expression, indicating that chronic hyperglycemia triggers systemic inflammation and further aggravates metabolic dysfunction (Fatkhurrohman et al., 2025).

3.5 TNF-α Expression in Rat's Serum

In rat serum, TNF-α (Figure 4) showed the highest expression in the control negative, while the control normal had the lowest concentration compared to other samples. The 100 mg/Kg BW dosage had the lowest expression compared to the other dosages used in the research. And the highest TNF-α expression was at a dosage of 400 mg/Kg BW. Control positive shows no significant difference in the dosage used. Dosage 100 mg/Kg BW shows better potential in lowering TNF-α expression than control positive.

While suppressing IL-6 protein expression, using a dosage of 100 mg/kgBW of water extract karamunting is the best in decreasing TNF-α expression, although without any significance than the control positive. Dosages of 100 mg/kgBW can reduce the protein expression to less than 200 mg/kgBW and 400 mg/kgBW. Control negative produces the highest TNF-α concentration level compared to any other treatment. TNF-α is one of the pro-inflammatory cytokines that are associated with inflammation, obesity, and insulin resistance (Hotamisligil et al., 1995; Tilg and Moschen, 2008). Our results show that pioglitazone, used as a positive control, also decreases TNF-α expression better than the negative control. This may be because pioglitazone can ameliorate TNF-α-induced insulin resistance (Iwata et al., 2001).

Adipose tissue–derived proinflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), are associated with decreased GLUT4 expression, leading to impaired glucose uptake in skeletal muscle and the development of compensatory hyperinsulinemia. In addition to its metabolic role, insulin also possesses anti-inflammatory effects by reducing the production of cytokines such as TNF-α and IL-6 and by inhibiting activation of the transcription factor nuclear factor-κB (NF-κB) (Leguisamo et al., 2012).

In MSG-induced obese mice, research by Furuya et al. (2010) found that adipocyte hypertrophy promoted local inflammatory responses characterized by increased macrophage infiltration and elevated expression of TNF-α and IL-6, resulting in higher circulating cytokine levels. This inflammatory state was associated with reduced GLUT4 expression in white adipose tissue, an effect that was reversed following atorvastatin administration (Furuya et al., 2010).

3.6 HOMA-IR in Rat's Serum

Before and after treatment, changes in HOMA-IR measurements (Figure 5) were observed in all samples. Control negative shows an increase in HOMA-IR compared to before treatment. All dosages tested show a decrease in HOMA-IR. The 100 mg/Kg BW dose shows slightly lower HOMA-IR than the control positive.

HOMA IR shows that a water extract karamunting dosage of 100 mg/KgBW is the best dosage in lowering the HOMA IR

Table 2. Comparison of the Present Study with Previous Reports on *Rhodomyrtus tomentosa* and Other Plant-Based Antidiabetic Agents

Study	Plant / Extract	Model	Key Biomarkers	Main Findings	Novelty Aspect
(Febriyanto and Saleh, 2021)	*R. tomentosa* water fraction	Diabetic rats	Blood glucose, insulin	↓ glucose, ↑ insulin	Glycemic focus
(Winarsih et al., 2023)	*R. tomentosa* ethanolic extract	Diabetic mice	TNF-α, IL-6	↓ inflammatory markers	Cytokine focus
(Lv et al., 2020)	Other plant extract	Diabetic mice	GLUT4, Akt	↑ GLUT4, ↓ insulin resistance	Signaling pathway
Present study	*R. tomentosa* water extract	Diabetic rats	GLUT4 (mRNA & ELISA), TNF-α, IL-6, HOMA-IR	↑ insulin sensitivity, ↓ inflammation	Integrated GLUT4–inflammation–HOMA-IR analysis

value. This result indicates that the water extract of karamunting has the potential to improve insulin sensitivity in T2DM. Typically, T2DM is characterized by elevated blood glucose and excess fatty acids, leading to insulin resistance and deterioration of beta cell function (Leahy, 2005).

According to research by (Kouidhi et al., 2013), alterations in GLUT4 gene expression in adipose tissue are more closely associated with insulin resistance and type 2 diabetes than with obesity alone. Multivariate linear regression analysis identified a significant inverse correlation between adipose GLUT4 mRNA levels and the HOMA-IR index. Individuals with type 2 diabetes displayed markedly lower GLUT4 mRNA expression compared with obese and non-diabetic controls. Furthermore, reduced GLUT4 expression was strongly correlated with higher HOMA-IR values, indicating a close relationship between impaired GLUT4 regulation and the severity of insulin resistance. Consistently, previous studies have demonstrated that reduced glucose uptake in type 2 diabetes models is accompanied by decreased GLUT4 mRNA expression.

3.7 Summary Study

The present study demonstrates that oral administration of *Rhodomyrtus tomentosa* leaf water extract improves insulin sensitivity in diabetic rats, as reflected by reduced HOMA-IR values, accompanied by decreased proinflammatory cytokines (TNF-α and IL-6) and modulation of GLUT4 expression. Although the changes in GLUT4 expression did not reach statistical significance, the consistent trend observed at both the transcriptional (GLUT4 mRNA in skeletal muscle) and protein levels (quantitative GLUT4 ELISA) suggests a biologically relevant regulatory effect. TNF-α and IL-6 are well-recognized upstream mediators linking chronic inflammation to insulin resistance through disruption of insulin signaling and glucose transporter regulation. Elevated levels of these cytokines have been reported to impair GLUT4 translocation and reduce insulin-stimulated glucose uptake in skeletal muscle. Therefore, the observed reduction in TNF-α and IL-6 levels in the present study may contribute to improved insulin sensitivity and partially explain the concurrent improvement in HOMA-IR values. Compared with previous reports on *R. tomentosa* and other plant-based antidiabetic agents, this study provides a more integrated evaluation by combining metabolic, molecular, and inflammatory parameters (Table 2). These findings highlight the novelty of the present work, particularly in elucidating the relationship between GLUT4 modulation and systemic inflammatory markers in an insulin-resistant model.

4. CONCLUSIONS

In conclusion, our result demonstrated that *R. tomentosa* dosage of 100 mg/kgBW enhanced the expression of GLUT4 in serum while enhancing the highest levels of GLUT4 expression in mRNA of diabetic rats. A 100 mg/kgBW dosage is the best treatment for decreasing the expression of TNF-α and IL-6. A 100 mg/KgBW dosage is better in lowering HOMA IR levels. This result suggests the potency of *R. tomentosa* treatment in improving T2DM by increasing glucose uptake, enhancing GLUT4 expression, and lowering HOMA-IR, TNF-α, and IL-6 levels. However, the exact molecular mechanism of the respective indicator activity in *R. tomentosa* remains unknown, so further investigation may be needed. In addition to improving insulin sensitivity and inflammatory status, this study provides an integrated comparison with previous reports, highlighting the novelty of simultaneous GLUT4, inflammatory, and metabolic assessments in an *in vivo* model.

5. ACKNOWLEDGEMENT

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