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Potency of Karamunting (*Rhodomyrtus tomentosa*) Leaf Extract as Antidiabetic for Type 2 Diabetes: A Systematic Review

Vivi Hendra Sutandar[1*], M. Irsan Saleh[2], Evi Lusiana[3], Nita Parisa[4], Nia Savitri Tamzil[5]

[1,2,3,4,5]Department of Pharmacology, Faculty of Medicine, Universitas Sriwijaya, Indonesia

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Corresponding author:
Vivi Hendra Sutandar

E-mail address:
vivihendras@unsri.ac.id

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ABSTRACT

Type 2 diabetes mellitus (T2D) is a chronic metabolic disorder characterized by reduced insulin sensitivity and inadequate insulin secretion, leading to elevated blood glucose levels. Standard treatment relies on synthetic drugs, which can cause adverse effects in some patients. *Rhodomyrtus tomentosa*, a plant native to Indonesia and widely used in traditional medicine, is being explored as a natural alternative for diabetes management due to its potential antidiabetic properties. This review compiles recent findings on its therapeutic potential. A systematic literature search was conducted in August 2024 in PubMed, Wiley Online Library, ScienceDirect, Cochrane Library, ProQuest, and Google Scholar using the keywords "*Rhodomyrtus tomentosa*" and "antidiabetic." Of 774 screened articles, five met the inclusion criteria (2014–2024). The studies employed in vitro, in vivo, and in silico approaches, focusing mainly on fruits and leaves. Results indicate that *R. tomentosa* may help control blood glucose by inhibiting α-glucosidase and α-amylase, enzymes critical in carbohydrate digestion. Bioactive compounds such as phloroglucinols and meroterpenes were frequently identified. However, most evidence comes from laboratory models, with limited animal research and no clinical trials. The risk of bias was moderate, often due to incomplete reporting. While findings suggest *R. tomentosa* is a promising natural candidate for diabetes treatment, its therapeutic value remains unconfirmed. More robust in vivo studies and human clinical trials are essential to clarify its mechanisms, safety, pharmacokinetics, and efficacy. This review serves as a basis for future research and highlights the need for rigorous studies to validate its clinical potential.

1. Introduction

Type 2 diabetes (T2D) is marked by impaired insulin action and insufficient insulin release from β-cells, frequently associated with insulin resistance. In some instances, diabetic ketoacidosis may occur, and the condition is more common among specific racial and ethnic populations.[1–3] T2D shows typical symptoms such as polyuria, polydipsia, polyphagia, and hyperglycemia. If undetected for a long time, some patients may experience severe weight loss.[4,5]

Type 2 diabetes (T2D) can be diagnosed based on several established criteria. A person is considered to have diabetes if they meet any of the following conditions: a hemoglobin A1C level of ≥ 6.5%, measured using a method certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT); a fasting plasma glucose level of ≥ 126 mg/dL (7.0 mmol/L) after at least eight hours without caloric intake; a two-hour plasma glucose level of ≥ 200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT) performed according to World Health Organization (WHO) guidelines; or the presence of classic symptoms of hyperglycemia accompanied by a random plasma glucose level of ≥ 200 mg/dL (11.1 mmol/L).[6]

Metformin is the standard initial oral treatment for T2D, frequently combined with agents like GLP-1 RAs or SGLT-2 inhibitors. Other medications may be prescribed depending on individual needs, with attention to efficacy, target organ effects, and side-effect profile.[7,8]

Despite its widespread use, medications prescribed for type 2 diabetes (T2D) can sometimes lead to adverse effects. Metformin, approved by the U.S. Food and Drug Administration (FDA) in 1994, remains a cornerstone in T2D management. It is available in both immediate-release and extended-release formulations and is frequently used with other antidiabetic agents. Although it is generally well-tolerated and considered safe, approximately 30% of patients may experience gastrointestinal side effects such as nausea, diarrhea, or indigestion shortly after beginning treatment.[9,10] Traditional medicine, particularly that derived from plant extracts, is increasingly viewed as a viable alternative.

Its appeal lies in affordability, ease of access, therapeutic potential, and a lower incidence of side effects relative to modern medications.[11,12]

2. Methods

The articles were collected from online platforms in August 2024 using six different platforms: PubMed, Wiley Online Library, ScienceDirect, Cochrane Online Library, ProQuest, and Google Scholar, using the Boolean search "Rhodomyrtus tomentosa" and "antidiabetic*". Both keywords are used to search all available selected databases. Relevant papers were then collected and selected based on their relevance to the topic, and predefined inclusion and exclusion criteria guided the literature search. To increase search sensitivity, Medical Subject Headings (MeSH) terms such as "Diabetes Mellitus" were utilized in databases like PubMed and the Cochrane Library. This paper synthesizes findings from the 2014–2024 period, focusing on the therapeutic potential of *R. tomentosa* leaves in the context of antidiabetic treatment. Medical Subject Headings (MeSH) terms were also used for databases supporting controlled vocabulary. No filters were applied except publication dates (2014–2024) and English language. The last search was completed on August 28, 2024. The flowchart of collecting articles is illustrated in Figure 1. Two reviewers independently screened all records for eligibility. Initial screening was conducted based on titles and abstracts, followed by a thorough review of the full texts. Any discrepancies during the selection process were addressed through discussion among reviewers. The overall methodology is illustrated in the PRISMA flow diagram. The PRISMA 2020 guidelines were used to carry out this systematic review.

The inclusion and exclusion criteria include all relevant English research articles, limited from 2014 to 2024, using *Rhodomyrtus tomentosa* with or without control groups as an antidiabetic. The collected articles were then filtered based on these criteria, and duplicate articles were removed from the selection. The selected articles were then analyzed.

The risk of bias in the included studies was evaluated using the SYRCLE tool. The evaluation showed that randomization procedures were often unclear or not reported, and blinding of outcome assessment was inconsistently described. Most studies had a low risk of selective reporting and attrition bias. Methodological differences excluded molecular docking studies from in vivo risk domains. A summary of the findings is presented in Table 2.

3. Results

Several papers were searched from six platforms, and 775 were obtained from the initial search. Seven papers were then selected based on inclusion and exclusion criteria. The papers are then checked for duplication and proceed to the final screening. The final five papers that matched the requirements were analyzed and shown in Table 3.

Four papers were collected from the five papers, using *Rhodomyrtus tomentosa's* different parts extract, and one paper used the ligand obtained from the database. The table below shows a summary of each research.

Table 1. Eligibility criteria for study selection

Criteria Type	Description
Inclusion	1. Articles in English
	2. Published in 2014–2024
	3. Evaluating *Rhodomyrtus tomentosa* for antidiabetic activity (with or without control groups)
Exclusion	1. Non-English articles,
	2. Conference abstracts, reviews, editorials, duplicate publications

Table 2. SYRCLE risk of bias summary table

Study Title	Random Sequence Generation	Baseline Characteristics	Random Housing	Blinding of Outcome Assessor	Incomplete Outcome Data	Selective Reporting
Hu et al., 2022 (China) [13]	Unclear	Low	Unclear	High	Low	Low
Mulyati & Panjaitan, 2021 (Indonesia) [14]	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Low
Idris et al., 2022 (Indonesia) [15]	Low	Low	Unclear	Unclear	Low	Low
Yu et al., 2022 (China) [16]	Unclear	Low	Unclear	High	Unclear	Low
Ma et al. 2018 (China)[17]	Unclear	Low	Unclear	Unclear	Low	Low

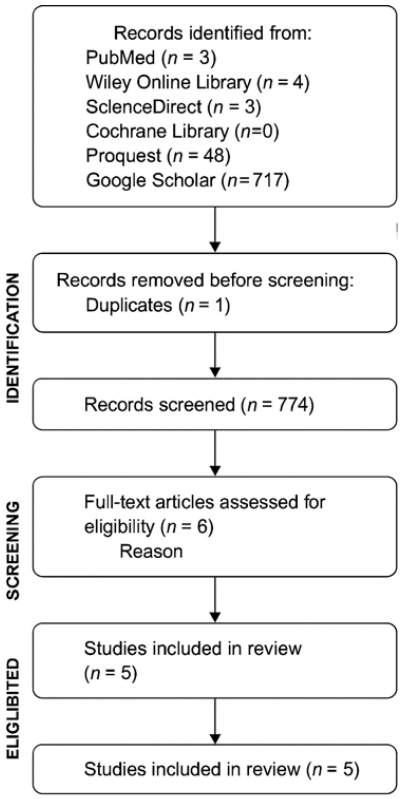

Figure 1. PRISMA 2020 flowchart illustrating the study selection process

Table 3. Summary of *Rhodomyrtus tomentosa* studies in T2D

Study	Samples	Extraction	Method	Compound(s)	Outcome
Hu et al., 2022 (China) [13]	*Rhodomyrtus tomentosa fruit (RTF) is categorized based on maturity level into two types:* • *Unripe fruit (UM-RTF)* • *Fully ripe fruit (FM-RTF)*	70% Ethanol/water was used to obtain free phenolic fraction. diethyl ether/ethyl acetate used to obtain bound phenolic fraction	Inhibitory activity, molecular docking analysis, HPLC	The following bioactive compounds have been identified: gallic acid, p-hydroxycinnamic acid, astragalin, ellagic acid, naringenin, and luteolin-7-O-glucoside	In *R. tomentosa* fruit, free phenolics showed stronger α-glucosidase inhibition, while bound phenolics exhibited greater α-amylase inhibition possibly due to their higher gallic acid content. Molecular Docking Analysis : Several bioactive compounds—including gallic acid, luteolin-7-O-glucoside, and astragalin—have demonstrated strong inhibitory effects on both α-glucosidase and α-amylase enzymes, which are critical in carbohydrate digestion. These inhibitory activities suggest their potential role in managing postprandial blood glucose levels. Acarbose, a known pharmaceutical α-

					glucosidase inhibitor, also showed excellent inhibition against this enzyme, serving as a benchmark for comparing natural alternatives. In addition, ellagic acid and p-hydroxycinnamic acid exhibited significant enzyme inhibitory properties, contributing to the observed antidiabetic effects of *Rhodomyrtus tomentosa*
Mulyati & Panjaitan, 2021 (Indonesia)[14]	Alkaloid derivate compound from the stem of *Rhodomyrtus tomentosa*	The selected compounds were evaluated using the Prediction of Activity Spectra for Substances (PASS) online tool. Ligand structures were prepared using Marvin Sketch software, version 5.2.5.1.	Molecular Docking Analysis	homolycorine, ismine, lycorine, maritidine, tazetine	In silico analysis revealed that alkaloid-derived compounds exhibited an average binding affinity of 83.84% to the α-glucosidase protein. These findings suggest that *Rhodomyrtus tomentosa* stem extracts hold promising potential as candidates for antidiabetic drug development
Idris et al., 2022 (Indonesia) [15]	Leaves of *Rhodomyrtus tomentosa*	Four solvents = n-hexane, dichloromethane, ethyl acetate, methanol	Inhibitory Activity (in vitro), Antidiabetic activity assay (in vivo), HPLC	Not mentioned	α-glucosidase and α-amylase inhibitory activities of the methanolic extract show higher activity than positive control (acarbose) using a dose of 400 mg/kg BW is the best dose to reduce blood glucose
Yu et al., 2022 (China) [16]	Leaves of *Rhodomyrtus tomentosa*	Dissolve in petroleum ether, the fraction with MeOH	Inhibitory Activity, Molecular Docking Analysis	phloroglucinol dimer and phloroglucinol meroterpenoids	Phloroglucinol dimer is possibly better as hAChE and α-glucosidase inhibitors, compared to phloroglucinol meroterpenoids
Ma et al. 2018 (China)[17]	*Rhodomyrtus tomentosa* not specified parts	Dissolve in paraformaldehyde	Inhibitory Activity, Semi HPLC	meroterpenoid-like compounds	Some compounds showed potential activities as α-glucosidase inhibitor

Abbreviation(s): HPLC: High Performance Liquid Chromatography, PASS: Prediction of Activity Spectra for Substances.

4. Discussion

Fruits of *Rhodomyrtus tomentosa* were used in the research of Hu *et al.* (2022) using two kinds of fruit, the unfully matured fruits (UM-RTF) and fully matured fruits (FM-RTF). Both unripe and fully ripe *Rhodomyrtus tomentosa* extracts demonstrated that the free phenolic fractions exhibited stronger α-glucosidase inhibitory activity compared to the bound phenolic fractions. In contrast, bound phenolic compounds showed greater inhibitory effects on α-amylase than their free counterparts. Molecular docking simulations further supported these findings, revealing that gallic acid, luteolin-7-O-glucoside, and astragalin possess strong binding affinities and potent inhibitory activity against both α-glucosidase and α-amylase.[13] Research Huang *et al.* (2024) Gallic acid has been identified as a promising natural inhibitor of α-amylase, primarily due to its ability to competitively bind to the enzyme's active site by forming four hydrogen bonds.[18] A combination of

gallic acid with acarbose, in a 3:1 ratio, had a synergistic inhibition of α-amylase; 100% gallic acid also shows antioxidant activity, whereas 100% acarbose shows higher radical scavenging ability.[19]

Alkaloid derivative compound from the stem of *Rhodomyrtus tomentosa* was investigated for its potency as an antidiabetic by Mulyati & Panjaitan (2021). The research used molecular docking to understand its ability as an α-Glucosidase inhibitor. The analysis revealed an average binding score of 83.84% between alkaloid-derived compounds and the α-glucosidase enzyme, indicating that the stem extracts of *Rhodomyrtus tomentosa* may serve as promising candidates for antidiabetic drug development.[14] Based on the results, lycorine had the highest affinity among other compounds; however, no study shows how the high affinity affects the hypoglycemic effect. One study reported that lycorine enhances autophagy in Schwann cells by activating the AMPK signaling pathway and promoting LC3-II transformation through MMP9 downregulation, indicating potential therapeutic effects in diabetic peripheral neuropathy.[20] Further research may be required to show how lycorine may be a promising antidiabetic agent.

The methanolic leaf extract of *Rhodomyrtus tomentosa* has demonstrated inhibitory activity against both α-glucosidase and α-amylase enzymes in research by Idris et al (2022). The methanolic extract of *Rhodomyrtus tomentosa* contained the highest concentrations of phenolic and flavonoid compounds when compared to extracts obtained using other solvents. Most of the flavonoids in the methanolic extract exist in the polar side, resulting in higher activity than the positive control (acarbose) and three other solvents used in the study, as analyzed by inhibitory activity in vitro. Then, an antidiabetic activity assay was also conducted in vivo based on blood glucose level; the optimum dose to reduce blood glucose was 400 mg/kg BW.[15] Studies have reported that the stem of *Bauhinia strychnifolia* craib contains both phenolic and flavonoid compounds, including quercetin. This flavonoid has shown significant biological activity by enhancing glucose uptake in 3T3-L1 adipocyte cells, suggesting its potential as an antidiabetic agent.[21]

Meanwhile, research from Yu et al. (2022), methanol-extracted fractions of *R. tomentosa* leaves revealed phloroglucinol dimers and meroterpenoids, with docking analysis indicating that phloroglucinol dimers have superior inhibitory potential against both α-glucosidase and hAChE enzymes.[16] The combination of phloroglucinol and procyanidin dimers from *Vitis vinifera* seed extract has been shown to reduce oxidative stress, with antioxidant activity (IC_{50} and SOD) comparable to ascorbic acid, suggesting ROS suppression as a key mechanism in its antidiabetic effect.[22]

Meroterpenoid-like compounds derived from *Rhodomyrtus tomentosa* were analyzed by Ma et al. (2018), following dissolution in paraformaldehyde, the compounds were assessed for α-glucosidase inhibition, and the results revealed that multiple candidates demonstrated notable inhibitory potential.[17] Due to their ability to selectively target specific biochemical sites, phloroglucinol meroterpenoids impact key metabolic functions, including lipid signaling, glycolytic regulation, and mitochondrial activity. This capacity may underlie their prospective role in antidiabetic therapy.[23]

While these findings support the potential of *R. tomentosa* in diabetes management mainly through its enzyme inhibitory effects, the current evidence base is still quite limited. Most of the available data come from lab-based or computer-simulated studies, which, while informative, don't yet tell us how the plant performs in living systems. For a clearer picture of its therapeutic promise, more thorough research, including animal testing and clinical trials, is needed to bridge the gap between early discovery and practical use.

5. Conclusion

In conclusion, *Rhodomyrtus tomentosa* shows considerable promise as a natural antidiabetic agent, with evidence pointing to its ability to regulate α-glucosidase and α-amylase activity and help reduce blood glucose levels. These effects have been observed in various plant parts, particularly the leaves and fruits, using computational modeling and controlled laboratory testing approaches. However, most current findings are based on early-stage experimental models offering critical mechanistic insights. Still, they do not yet confirm whether the findings can be translated into therapeutic use. To advance its potential toward clinical application, further rigorous studies, particularly animal models and clinical trials, must thoroughly assess its safety, pharmacokinetics, and clinical effectiveness. This review lays the groundwork for future research and emphasizes the importance of advancing to more comprehensive investigations.

6. Author Contribution

V. H. with support from M. I. conduct conceptualization, writing–original draft. V. H carried out methodology. V. H., M. I., E. L., N. P., and N. S. T. writing–review and editing manuscript

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