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Bioactive Compounds, Pharmacological Activities, Toxicity Profiles, and Prospects for New Drug Discovery from *Rhodomyrtus tomentosa* (Aiton) Hassk.

Senyawa Bioaktif, Aktivitas Farmakologis, Profil Toksisitas, dan Prospek Penemuan Obat Baru dari *Rhodomyrtus tomentosa* (Aiton) Hassk.

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ABSTRACT

Rhodomyrtus tomentosa (Aiton) Hassk. (Karamunting) is an evergreen shrub of the Myrtaceae family traditionally used in South and Southeast Asia to treat diarrhea, dysentery, gynecological disorders, and wounds. A comprehensive review of 128 publications (2014–2024) demonstrates that its extracts and isolated metabolites exhibit diverse pharmacological properties, including antioxidant, antimicrobial, anti-inflammatory, and anticancer activities. Key bioactive compounds include rhodomyrtone, myricetin, gallic acid, ellagic acid, and piceatannol. Acute toxicity assays confirm safety up to 3000 mg/kg BW, though nanoformulations show heightened toxicity. Novel antibacterial mechanisms, such as membrane protein trapping and antibiofilm activity, highlight its prospective role against multidrug-resistant pathogens. Despite gaps in long-term toxicity and clinical data, *R. tomentosa* represents a valuable source for new drug discovery.

ABSTRAK

Rhodomyrtus tomentosa (Aiton) Hassk. (Karamunting) adalah semak hijau abadi dari famili Myrtaceae yang secara tradisional digunakan di Asia Selatan dan Tenggara untuk mengobati diare, disentri, gangguan ginekologis, dan luka. Tinjauan komprehensif terhadap 128 publikasi (2014–2024) menunjukkan bahwa ekstrak dan metabolit terisolasi memiliki aktivitas antioksidan, antimikroba, antiinflamasi, dan antikanker yang luas. Senyawa bioaktif utama meliputi rhodomyrtone, myricetin, asam galat, asam elagik, dan piceatannol. Uji toksisitas akut menunjukkan keamanan hingga 3000 mg/kg BB, meskipun nanoformulasi meningkatkan toksisitas. Mekanisme antibakteri baru seperti penjebakan protein membran dan aktivitas antibiofilm mendukung potensinya terhadap patogen resisten obat. Meskipun data toksisitas jangka panjang dan klinis masih terbatas, *R. tomentosa* berpotensi tinggi sebagai sumber penemuan obat baru.

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1. INTRODUCTION

Karamunting (*Rhodomyrtus tomentosa* (Aiton) Hassk.) is a flowering plant from the Myrtaceae family that is widely distributed across Southern and Southeastern Asia, including China, Taiwan, the Philippines, Malaysia, Indonesia, and Vietnam. This plant thrives in diverse environmental conditions, ranging from lowlands to elevations of 2400 m above sea level, even on poor-quality soils, demonstrating high resistance to pests and diseases (Abd Hamid et al., 2016; Vo & Ngo, 2019). In traditional medicine, *R. tomentosa* has been utilized in Vietnam, China, and Malaysia to treat diarrhea, dysentery, gynecological disorders, stomachaches, and uterine bleeding, as well as to accelerate wound healing. Additionally, its fruit serves as an immunostimulant and is processed into functional food products such as tea, wine, and jam (Vo & Ngo, 2019; Vo et al., 2020).

Phytochemical investigations have revealed that *R. tomentosa* contains diverse bioactive metabolites, including triterpenoids, flavonoids, phenolics, and acylphloroglucinols. Rhodomyrtone is the primary representative compound, exhibiting potent antibacterial activity against Gram-positive bacteria, particularly *Streptococcus pneumoniae* and *Staphylococcus aureus*, alongside marked anticancer, anti-inflammatory, and antioxidant properties (Liu et al., 2016; Mitsuwan et al., 2020; Saising et al., 2008). Furthermore, the identification of acylphloroglucinols and flavonol glycosides highlights the potential of this plant as a source of novel bioactive molecules for therapeutic development (Lai, 2013). The expanding global interest in natural products reinforces the necessity of exploring *R. tomentosa* to address modern health challenges, such as antimicrobial resistance, cancer, and inflammatory diseases (Hamed et al., 2024; Kinghorn & Balandrin, 1993).

Although several studies have documented its pharmacological activities and bioactive compounds, available information remains fragmented. Long-term toxicological data and complete molecular mechanisms of its active compounds are relatively limited (Chang & Kwon, 2016; Elgoud Said et al., 2021). Therefore, this review aims to comprehensively compile and critically analyze existing literature on *R. tomentosa*, including its reported pharmacological activities, isolated bioactive constituents, and safety profiles, while highlighting research gaps to guide future pharmaceutical research.

2. METHODS

2.1. Search Strategy

A systematic literature search was conducted using online scientific databases, including PubMed, ScienceDirect, and Google Scholar. Keywords utilized combinations of "*Rhodomyrtus tomentosa*", "Karamunting", "phytochemistry", "pharmacological activity", "antioxidant", "antimicrobial", "anticancer", and "toxicology" using Boolean operators (AND, OR). Search parameters were restricted to publications from 2014 to 2024 in English and Indonesian. Non-scientific literature, such as brief reports, editorials, and conference abstracts, were excluded, whereas primary research articles detailing compound isolation, biological assays, and ethnopharmacological studies were selected.

2.2. Study Selection Process

Initial screening evaluated titles and abstracts to remove duplicate entries, non-relevant literature, and records failing to meet the inclusion criteria. Full-text articles were independently evaluated by two researchers to assess eligibility based on study objectives. Discrepancies were resolved through consensus or consultation with a third researcher. Extracted parameters encompassed ethnopharmacological records, extraction techniques, phytochemical profiles, isolated constituents, pharmacological evaluations, and toxicity parameters.

2.3. Quality Assessment

Selected studies were critically appraised based on methodological transparency, outcome validity, and data reporting completeness. Preclinical in vitro and in vivo evaluations were assessed for appropriate control usage, replication, and analytical precision. Methodological risk of bias was appraised using a modified Cochrane Risk of Bias tool covering randomization, blinding, and analytical limitations. Studies presenting higher risk of bias were included qualitatively with appropriate qualification regarding their limitations.

2.4. Data Synthesis and Analysis

Extracted data were synthesized into structured tables detailing plant parts, extraction methods, bioactive constituents, and pharmacological activities. A qualitative narrative synthesis was conducted by categorizing findings into specific bioactivity domains (antioxidant, antimicrobial, anticancer, and anti-inflammatory). Descriptive statistics were applied where quantitative metrics were homogeneous (e.g., IC_{50} values or inhibition zones).

3. RESULTS AND DISCUSSION

3.1. Traditional Uses of Karamunting (*R. tomentosa*)

R. tomentosa, commonly known as rose myrtle, is an evergreen shrub belonging to the Myrtaceae family, widely distributed across South and Southeast Asia, including India, Southern China, Taiwan, the Philippines, Malaysia, Indonesia, and Vietnam (Lai et al., 2015). The plant thrives in coastal areas, natural forests, riparian zones, and wetlands at altitudes up to 2400 m above sea level. Morphologically, *R. tomentosa* reaches a height of 1–2 m, possessing gray tomentose branches, opposite elliptic-to-obovate leaves, flowers with five gray tomentose obovoid sepals, obovate petals, and red stamens. The fruit is a black urceolate berry, with flowering occurring from April to May and fruit maturation from July to August (Flora of China Editorial Committee, 2001).

Known locally as kemunting in Indonesia and Malaysia, *R. tomentosa* has a long history of empirical application. In Vietnamese traditional medicine, unripe fruits are prescribed for

diarrhea and dysentery, whereas ripe fruits serve as immunostimulants (Vo & Ngo, 2019). In Traditional Chinese Medicine (TCM), the species is utilized to nourish blood, relieve rheumatism, and manage hematemesis, diarrhea, and uterine bleeding (Lai, 2013). In Indonesia, roots and leaves are used to treat gastrointestinal distress and as postnatal tonics, whereas crushed leaves are applied topically to wounds (Zhao et al., 2020). Beyond medicinal uses, fruits are processed into wines, jams, jellies, and functional beverages (Lai, 2013). Modern pharmacological evaluations support these empirical applications, confirming antibacterial, antioxidant, anti-inflammatory, and antitumor activities (Vo & Ngo, 2019; Zhao et al., 2020).

3.2. Pharmacological Activities

a. Antioxidant Properties

The antioxidant potential of *R. tomentosa* has been validated across in vitro and in vivo models. In vitro evaluations demonstrate marked lipid peroxidation inhibition, ferric reducing antioxidant power (FRAP), and metal-chelating capacities (Lavanya et al., 2012). In Swiss Albino mice exposed to CCl_4, administration of *R. tomentosa* leaf extract at 0.8 g/kg body weight suppressed thiobarbituric acid reactive substances (TBARS) elevation while restoring reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) levels in liver, kidney, and blood tissues.

Phytochemically, *R. tomentosa* is rich in phenolic compounds, notably myricetin, gallic acid, and ellagic acid. Myricetin suppresses mast cell activation by decreasing β-hexosaminidase release, modulating intracellular calcium levels, and reducing interleukin-4 (IL-4) and tumor necrosis factor-alpha (TNF-α) production (Vo et al., 2020). Ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC–MS/MS) analysis of *R. tomentosa* fruit identified 29 phenolic compounds, with bound phenolic fractions demonstrating high concentrations of gallic acid (80.44 ± 8.74 mg/100 g) and ellagic acid (107.47 ± 7.28 mg/100 g) (Divya Priya & Martin, 2025).

b. Antimicrobial Effects

Rhodomyrtone exhibits potent antimicrobial activity against Gram-positive pathogens, notably *S. aureus* and *S. pneumoniae*, with minimum inhibitory concentrations (MIC) ranging from 0.125 to 1 μg/mL for *S. pneumoniae* and 0.25 to 2 μg/mL for *Staphylococcus* strains (Liu et al., 2016; Saising et al., 2008). Ethanolic leaf extracts show activity at higher concentrations, displaying MIC values of 16–32 μg/mL against *S. pneumoniae* and 32–512 μg/mL against *Staphylococcus* spp.

Sub-inhibitory concentrations (1/8 × MIC) of rhodomyrtone significantly suppress biofilm formation across clinical isolates ($p < 0.05$), whereas treatment at 16 × MIC reduces intra-biofilm cell viability by over 90% (Mitsuwan et al., 2020). Time-kill assays revealed that rhodomyrtone at 4 × MIC reduced *S. aureus* ATCC 25923 viability by 99.9% within 3 h. Furthermore, rhodomyrtone suppressed *S. pneumoniae* adherence and invasion into A549 alveolar epithelial cells by 40–90% while enhancing RAW264.7 macrophage phagocytosis by 90–99% at 1/2 × MIC (Mitsuwan et al., 2020). Phenolic constituents, including gallic acid and ellagic acid, demonstrate supplementary antimicrobial activity against *Bacillus cereus*, *S. aureus*, and *Escherichia coli*, with MIC values of 0.156, 0.625, and 1.25 mg/mL, respectively (Divya Priya & Martin, 2025).

c. Anti-inflammatory Activities

R. tomentosa extracts and isolated rhodomyrtone modulate pro-inflammatory gene expression. In lipopolysaccharide (LPS)-stimulated models, treatment downregulates the expression of pro-inflammatory cytokines, including il1b and tnfa (Na-Phatthalung et al., 2018). In head kidney macrophages from rainbow trout (*Oncorhynchus mykiss*), exposure to leaf extract and rhodomyrtone attenuated reactive oxygen species (ROS) generation and modulated cytokine expression profiles, demonstrating conserved immunomodulatory activity (Na-Phatthalung et al., 2018).

d. Anticancer Potential

Bioactive compounds from *R. tomentosa*, including phenolics (gallic acid, ellagic acid, myricetin) and terpenoids, contribute to anticancer effects by inhibiting initiation and progression pathways (Abd Hamid et al., 2016; Vo & Ngo, 2019). In a murine breast cancer model, administration of *R. tomentosa* extract at 300 mg/kg BW for 30 days restored serum malondialdehyde (MDA) levels and elevated SOD activity (Situmorang et al., 2024). Histopathological examination indicated structural normalization of ductal and lobular architecture. Furthermore, immunohistochemical profiling revealed downregulation of oncogenic biomarkers, including Her2, IL33, EGFR, and MUC1 (Situmorang et al., 2024).

e. Other Reported Pharmacological Activities

In the central nervous system, rhodomyrtone exhibits antidepressant-like effects in chronic unpredictable mild stress (CUMS) rodent models by restoring dendritic spine density, inhibiting glycogen synthase kinase-3beta (GSK-3β) hyperactivation, and upregulating brain-derived neurotrophic factor (BDNF) and postsynaptic density protein 95 (PSD-95) (Chai et al., 2019). Petroleum ether extracts of leaves and stems inhibited acetylcholinesterase (AChE) by 81% at 500 μg/mL, with isolated compounds demonstrating IC50 values ranging from 6.0 to 6.6 μM (Qin et al., 2019).

In digestive systems, 70% ethanol extracts conferred gastroprotection against experimental ulcers by maintaining endogenous SOD and catalase levels while suppressing lipid peroxidation (Geetha et al., 2010). For bone pathology, specific isolated metabolites enhanced alkaline phosphatase activity, elevated collagen synthesis, and promoted mineralization in *MC3T3-E1* osteoblasts (Nguyen et al., 2009). For dermatological applications, ethanolic extracts and piceatannol protected human keratinocytes against UV-induced cytotoxicity, reducing

cyclobutane pyrimidine dimer (CPD) formation and enhancing DNA repair machinery (Shiratake et al., 2015).

3.3. Isolated Compounds

Phytochemical investigations of *R. tomentosa* have led to the isolation and characterization of over 100 secondary metabolites encompassing triterpenoids, flavonoids, phenolics, and meroterpenoids (Lai, 2013; Lai et al., 2015), as summarized in **Table 1**. The triterpenoid fraction is predominantly composed of pentacyclic sapogenins with ursane, oleanane, and lupane skeletons, including betulin, lupeol, β-amyrin, friedelin, and oleanolic acid. Additionally, lanostane-type triterpenoids and glycosidic derivatives, such as laevigatanoside A, have been identified (Zhu et al., 2015).

Table 1. Chemical constituents isolated from *Rhodomyrtus tomentosa*

Compound Name	Chemical Class	Reference
23-Hydroxytormentic acid	Triterpenoid	(Zhu et al., 2015)
Laevigatanoside A	Triterpenoid	(Zhu et al., 2015)
β-Stigmasterol	Triterpenoid	(Zhu et al., 2015)
Hederagenin	Triterpenoid	(Zhang et al., 2016a; Zhang et al., 2016b)
Laricitrin	Flavonoids	(Zhu et al., 2015)
Kaempferol 3-arabinoside	Flavonoids	(Zhu et al., 2015)
Myricetin	Flavonoids	(Zhu et al., 2015)
Kaempferol	Flavonoids	(Wu et al., 2015)
Vitexin	Flavonoids	(Wu et al., 2015)
Dihydromyricetin	Flavonoids	(Wu et al., 2015)
Quercetin 7,4′-diglucoside	Flavonoids	(Wu et al., 2015)
Myricetin-3,7,3′-trimethyl ether-5′-O-β-glucopyranoside	Flavonoids	(Liu et al., 2016)
Naringenin	Flavonoids	(Liu et al., 2016)
Blumeatin A	Flavonoids	(Liu et al., 2016)
Myricetin-3,7,3′-trimethyl ether	Flavonoids	(Liu et al., 2016)
Trichocarpin	Phenol	(Liu et al., 2016)
Phloroglucinol	Phenol	(Hiranrat & Mahabusarakam, 2008)
Tomentodione S	Phenol	(Zhang et al., 2018)
Tomentodione T	Phenol	(Zhang et al., 2018)
Protocatechuic acid	Phenol	(Zhang et al., 2018)
Syringic acid	Phenol	(Zhang et al., 2018)
Ferulic acid	Phenol	(Zhang et al., 2018)
Rhodomyrtosone D	Meroterpenoids	(Hiranrat & Mahabusarakam, 2008)
Endoperoxide G3	Meroterpenoids	(Hiranrat & Mahabusarakam, 2008)
6R,9R-3-Oxo-α-ionol	Meroterpenoids	(Hiranrat & Mahabusarakam, 2008)
Rhodomentone A	Meroterpenoids	(Hiranrat & Mahabusarakam, 2008)
Tomentodione A	Meroterpenoids	(Hiranrat & Mahabusarakam, 2008)
Tomentodione B	Meroterpenoids	(Hiranrat & Mahabusarakam, 2008)
Tomentodione C	Meroterpenoids	(Hiranrat & Mahabusarakam, 2008)
Tomentodione D	Meroterpenoids	(Hiranrat & Mahabusarakam, 2008)
Watsonianone A	Meroterpenoids	(Liu et al., 2016)
Watsonianone C	Meroterpenoids	(Liu et al., 2016)
4R-Focifolidione	Meroterpenoids	(Liu et al., 2016)
4S-Focifolidione	Meroterpenoids	(Liu et al., 2016)
Tomentodione E	Meroterpenoids	(Zhang et al., 2017)
Tomentodione F	Meroterpenoids	(Zhang et al., 2017)
Tomentodione G	Meroterpenoids	(Zhang et al., 2017)
4,6(2H,5H)-Benzofurandione, 3,7-dihydro-2-hydroxy-5,5,7,7-tetramethyl-3-(1-methylethyl)-, (2R,3R)-	Meroterpenoids	(Zhang et al., 2018)
Tomentodione N	Meroterpenoids	(Zhang et al., 2018)
Tomentodione O	Meroterpenoids	(Zhang et al., 2018)
Tomentodione P	Meroterpenoids	(Zhang et al., 2018)
Tomentodione Q	Meroterpenoids	(Zhang et al., 2018)

Isolated flavonoids encompass myricetin, kaempferol, quercetin, and naringenin glycosides, along with anthocyanins such as cyanidin-3-O-glucoside and delphinidin-3-O-glucoside (Cui et al., 2013; Nguyen et al., 2009). Phenolic constituents consist of simple phenolic acids (gallic, protocatechuic, and syringic acids) and stilbenoids (resveratrol and piceatannol) (Lai, 2013). Rhodomyrtone, a specialized acylphloroglucinol possessing chiral centers at C2, C4, and C9, represents a primary driver of antimicrobial efficacy (Tan, 2017). Furthermore, meroterpenoids combining phloroglucinol and sesquiterpene units, such as rhodomyrtosones A–I and tomentodiones A–Q, demonstrate structurally diverse antimicrobial and cytotoxic profiles (Zhang et al., 2017; Zhang et al., 2018).

3.4. Toxicity Profiles

Toxicological evaluations indicate a favorable safety profile for crude *R. tomentosa* extracts. Acute administration of ethanolic leaf extracts in rodents up to 3000 mg/kg body weight for 14 days produced no mortality or overt toxicity, establishing a No-Observed-Adverse-Effect Level (NOAEL) of 2000 mg/kg body weight (Mordmuang et al., 2021). Purified rhodomyrtone demonstrated safety up to 5000 mg/kg body weight in vivo (Siriyong et al., 2020). In vitro cytotoxicity assays confirmed selective toxicity, displaying IC50 values of 476 µg/mL for crude extract and >200 µg/mL for rhodomyrtone—concentrations 15- to 400-fold higher than target antibacterial MIC values (Mordmuang et al., 2021; Saising et al., 2008).

Conversely, nanoherbal formulations exhibit elevated toxicity, displaying an acute LD50 of 10.4 mg/kg in rats alongside histological alterations in cardiac, renal, pulmonary, and cerebral tissues (Situmorang et al., 2020). Subacute evaluations (up to 2000 mg/kg body weight) revealed no systemic organ damage, though minor, reversible tubular changes were observed at 3000 mg/kg body weight (Mordmuang et al., 2021). Long-term toxicological evaluations (≥ 90 days) remain unrecorded in the literature.

3.5. Potential for New Drug Discovery

a. Promising Compounds for Further Investigation

Rhodomyrtone remains the primary drug candidate due to its potent activity against multidrug-resistant Gram-positive strains, including methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant Enterococcus (VRE) (Rani et al., 2024; Suwandecha et al., 2024). Pharmacokinetic evaluations in rodents (50–100 mg/kg oral) demonstrated linear profiles maintaining plasma concentrations above target MIC thresholds (Suwandecha et al., 2024). Additionally, piceatannol warrants development for dermatological photoprotection (Shiratake et al., 2015), whereas anthracene glycosides represent candidates for bone anabolic therapies (Nguyen et al., 2009).

b. Novel Mechanism of Action Identified

Rhodomyrtone operates via a distinct mechanism relative to conventional antibiotics. It disrupts bacterial cytoplasmic membranes by increasing lipid fluidity and inducing hyper-fluid domain formation that traps essential membrane proteins (Saeloh et al., 2018). This action induces membrane invagination, intracellular vesicle formation, and protein mislocalization, thereby impairing respiration, ATP synthesis, and cell wall assembly (Nwabor et al., 2021; Rani et al., 2024). Serial passage studies (45 passages) showed no detectable resistance development, indicating a high genetic barrier to resistance (Rani et al., 2024).

c. Gaps in Current Research and Future Directions

Key translational bottlenecks include: (i) absence of clinical trials evaluating purified compounds like rhodomyrtone or piceatannol; (ii) limited chronic toxicological profiles under long-term dosing regimens (Vo & Ngo, 2019); (iii) poor oral bioavailability and high lipophilicity (Biopharmaceutics Classification System Class II), necessitating lipid-based formulations, amorphous solid dispersions, or prodrug strategies (Suwandecha et al., 2024); and (iv) need for structure-activity relationship (SAR) studies to optimize pharmacokinetic parameters, along with standardized metabolite profiling to guarantee batch-to-batch consistency (Rani et al., 2024; Vo & Ngo, 2019).

4. CONCLUSION

Rhodomyrtus tomentosa (Aiton) Hassk. (Karamunting) represents a versatile natural source with therapeutic utility across infectious and non-infectious disease models. The specialized acylphloroglucinol rhodomyrtone exhibits a novel membrane-disruptive mechanism of action that addresses critical challenges in antibiotic resistance. Comprehensive preclinical evidence supports its continued development, provided future research addresses formulation limitations, chronic toxicological evaluation, and clinical validation.

AUTHOR CONTRIBUTIONS

Conceptualization, J.J.S. T.M.F and E.S.; methodology, J.J.S.; software, J.J.S.; validation, J.J.S. and E.S.; formal analysis, J.J.S.; investigation, J.J.S.; resources, E.S.; data curation, J.J.S.; writing—original draft preparation, J.J.S.; writing—review and editing, J.J.S. and E.S.; visualization, J.J.S.; supervision, E.S.; project administration, J.J.S.; funding acquisition, E.S. All authors have read and agreed to the published version of the manuscript.

INSTITUTIONAL REVIEW BOARD STATEMENT

Ethical review and approval were waived for this study because it is a comprehensive literature review and did not involve human participants or animal experimentation.

INFORMED CONSENT STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

No new empirical data were generated in this study. Data sharing is not applicable as this article synthesizes previously published literature.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) USE

The authors declare that no generative AI or AI-assisted technologies were used in the preparation or writing of this manuscript.

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