



Pharmacological potential of ten indigenous medicinal plants from North Sumatra: A systematic review

[Potencial farmacológico de diez plantas medicinales indígenas del norte de Sumatra: Una revisión sistemática]

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Abstract

Context: Herbal medicine is an integral part of traditional healthcare practices in North Sumatra, Indonesia, particularly among the Batak and Deli Malay communities. Despite their widespread use, many medicinal plants lack systematic pharmacological evaluation.

Aims: To review systematically synthesizes evidence on the pharmacological activities and therapeutic potential of ten indigenous medicinal plants traditionally used in North Sumatra: *Arenga pinnata*, *Rhodomyrtus tomentosa*, *Cananga odorata*, *Phyllanthus emblica*, *Gynura procumbens*, *Premna serratifolia*, *Styrax sumatranus*, *Saurauia vulcani*, *Vitis gracilis*, and *Zanthoxylum acanthopodium*.

Methods: A systematic literature review was conducted following PRISMA 2020 guidelines. Searches were performed across PubMed, Scopus, and Google Scholar using MeSH terms and Boolean operators. From 750 retrieved records, 166 studies were included based on predefined eligibility criteria. Only experimental studies reporting bioactive compounds and pharmacological outcomes were considered.

Results: The included studies reported diverse bioactivities, including antioxidant, anti-inflammatory, antimicrobial, anticancer, and immunomodulatory effects. *Phyllanthus emblica* and *Gynura procumbens* consistently demonstrated strong antioxidant activity via DPPH and ABTS assays, while *Zanthoxylum acanthopodium* exhibited potent antimicrobial properties. However, substantial heterogeneity in experimental designs, assay conditions, and compound quantification limited data comparability.

Conclusions: The reviewed species show strong potential for therapeutic application and support their ethnomedical use. Further *in vivo* and clinical investigations are required to validate efficacy, standardize formulations, and support integration into evidence-based medicine.

Keywords: *Arenga pinnata*; herbal medicine; traditional medicine; medicinal plants; *Saurauia vulcani*; *Styrax sumatranus*.

Resumen

Contexto: La medicina herbaria es parte integral de las prácticas tradicionales de salud en el norte de Sumatra, Indonesia, particularmente entre las comunidades malayas Batak y Deli. A pesar de su uso generalizado, muchas plantas medicinales carecen de una evaluación farmacológica sistemática.

Objetivos: Revisar sistemáticamente la evidencia sobre las actividades farmacológicas y el potencial terapéutico de diez plantas medicinales indígenas utilizadas tradicionalmente en el norte de Sumatra: *Arenga pinnata*, *Rhodomyrtus tomentosa*, *Cananga odorata*, *Phyllanthus emblica*, *Gynura procumbens*, *Premna serratifolia*, *Styrax sumatranus*, *Saurauia vulcani*, *Vitis gracilis* y *Zanthoxylum acanthopodium*.

Métodos: Se realizó una revisión sistemática de la literatura siguiendo las directrices PRISMA 2020. Se realizaron búsquedas en PubMed, Scopus y Google Académico utilizando términos MeSH y operadores booleanos. De los 750 registros recuperados, se incluyeron 166 estudios según criterios de elegibilidad predefinidos. Solo se consideraron estudios experimentales que reportaron compuestos bioactivos y resultados farmacológicos.

Resultados: Los estudios incluidos reportaron diversas bioactividades, incluyendo efectos antioxidantes, antiinflamatorios, antimicrobianos, anticancerígenos e inmunomoduladores. *Phyllanthus emblica* y *Gynura procumbens* demostraron consistentemente una fuerte actividad antioxidante mediante ensayos DPPH y ABTS, mientras que *Zanthoxylum acanthopodium* exhibió potentes propiedades antimicrobianas. Sin embargo, la heterogeneidad sustancial en los diseños experimentales, las condiciones de ensayo y la cuantificación de compuestos limitó la comparabilidad de los datos.

Conclusiones: Las especies revisadas muestran un gran potencial para la aplicación terapéutica y respaldan su uso etnomédico. Se requieren más investigaciones *in vivo* y clínicas para validar la eficacia, estandarizar las formulaciones y respaldar su integración en la medicina basada en la evidencia.

Palabras Clave: *Arenga pinnata*; medicina herbaria; medicina tradicional; plantas medicinales; *Saurauia vulcani*; *Styrax sumatranus*.

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Abbreviations: CAT: Catalase; COX-1: Cyclooxygenase 1; COX-2: Cyclooxygenase 2; CXCR4: C-X-C chemokine receptor type 4; GPx: Glutathione peroxidase; HepG2: Hepatoblastoma cell line; HIV: Human immunodeficiency virus; HSV-1: Herpes simplex virus type 1; HSV-2: Herpes simplex virus type 2; IC₅₀: 50% inhibitory concentration; IL-1 β : Interleukin 1 β ; IL-6: Interleukin 6; iNOS: Inducible nitric oxide synthase; LPS: Lipopolysaccharide; MCF-7: Michigan Cancer Foundation-7; MMP-9: Matrix metalloproteinase-9; PGE₂: Prostaglandin E₂; SOD: Superoxide dismutase; TGF- β : Transforming growth factor- β ; TNF- α : Tumor necrosis factor α ; UV: Ultraviolet; VEGF: Vascular endothelial growth factor; VEGFR1: Vascular endothelial growth factor receptor 1.

INTRODUCTION

Herbal medicine represents a critical component of traditional healthcare in Indonesia, valued for its accessibility, cultural relevance, and perceived safety, particularly in areas with limited access to conventional pharmaceuticals (Ghosh et al, 2022). The World Health Organization encourages the integration of traditional medicine into national healthcare frameworks, especially in countries with abundant biodiversity. Indonesia is among the world’s most biodiverse nations, hosting more than 20,000 plant species, approximately 40% of which are endemic (Bahtiar et al., 2017). A significant portion of these species is used in *jamu*, a traditional polyherbal remedy.

In North Sumatra, extensive ethnomedicinal knowledge persists among communities such as the Batak and Deli Malay. Indigenous flora has long been utilized to treat ailments ranging from fevers and infections to chronic inflammatory conditions (Fatmah et al., 2022). However, despite this rich tradition, most scientific investigations remain limited to ethnobotanical documentation or preliminary phytochemical studies (Andadari et al., 2022; Jadid et al., 2020), with few systematic evaluations of pharmacological mechanisms or therapeutic outcomes.

While previous reviews have discussed Indonesian herbal medicine, none have comprehensively synthesized experimental data on North Sumatran plants across bioactivity categories such as antioxidant, anti-inflammatory, antimicrobial, and anticancer. Moreover, earlier syntheses often lack stand-

ardized reporting and do not reflect the breadth of recent findings.

To address these gaps, this review focuses on ten widely used medicinal plants from North Sumatra. These species were selected based on their high ethnopharmacological relevance and preliminary pharmacological evidence. The objective is to evaluate the current experimental literature on their pharmacological effects, including mechanisms of action where available. Table 1 outlines the guiding research question based on the PICO (Population, Intervention, Comparison, Outcome) framework.

This synthesis aims to inform future pharmacological development, encourage clinical validation, and support the integration of these herbal resources into evidence-based therapeutic strategies.

MATERIAL AND METHODS

Summary of study type

This study is a systematic review of experimental research assessing the pharmacological activities of ten traditional medicinal plants from North Sumatra, Indonesia. The included studies comprised *in vitro*, *in vivo*, and *in silico* models investigating antioxidant, anti-inflammatory, antimicrobial, and anticancer effects. The review was conducted in accordance with the PRISMA 2020 guidelines (Page et al., 2021), and the protocol was developed based on PRISMA-P and BMJ evidence synthesis standards. The research question was framed using the PICO strategy (Table 1).

Table 1. PICO framework guiding the research question.

Component	Description
P (Population)	Medicinal plants traditionally used in North Sumatra
I (Intervention)	Experimental evaluation of pharmacological activities and bioactive compounds
C (Comparison)	Control groups, untreated conditions, or synthetic drug comparators
O (Outcome)	Antioxidant, anti-inflammatory, antimicrobial, and anticancer effects

Studies were considered eligible if they:

1. Investigated one or more of the following plants: *Arenga pinnata*, *Rhodymyrtus tomentosa*, *Cananga odorata*, *Phyllanthus emblica*, *Gynura procumbens*, *Premna serratifolia*, *Styrax sumatranus*, *Saurauia vulcani*, *Vitis gracilis*, or *Zanthoxylum acanthopodium*.
2. Reported original experimental findings (including *in vitro*, *in vivo*, or *in silico* data).
3. Evaluated pharmacological activities, specifically antioxidant, anti-inflammatory, antimicrobial, or anticancer effects.
4. Were published between 2000 and 2024 in peer-reviewed journals, in English or Bahasa Indonesia.

Studies were excluded if they:

1. Were review articles, book chapters, conference abstracts, or editorials without primary data.
2. Focused solely on taxonomy, ecology, or cultivation without pharmacological evaluation.
3. Provided insufficient data or lacked methodological transparency.
4. Were duplicate entries.

Information sources

Three electronic databases, PubMed, Scopus, and Google Scholar, were systematically searched. Additional relevant articles were identified through manual searches of reference lists. To enhance the interpretive depth of the included literature, we utilized ResearchRabbit, a visual research discovery platform, to map relationships among the 166 included studies. The tool facilitated identification of thematic clusters based on pharmacological focus (e.g., antioxidant, anti-inflammatory, anticancer), citation interlinkages, and co-authorship networks. This helped reveal research densities and underexplored areas across the ten reviewed herbal species.

Search strategy

A combination of Medical Subject Headings (MeSH) and free-text keywords was used, applying Boolean operators (AND, OR). Sample queries included "*Arenga pinnata*" AND "pharmacological activity" OR "bioactive compound" or "*Gynura procumbens*" AND "anticancer" OR "antioxidant". The search period ranged from database inception through April 2024.

Study selection

All retrieved citations were imported into Rayyan QCRI, where duplicates were automatically removed. Two independent reviewers screened titles and abstracts against the eligibility criteria. Full texts were assessed for inclusion. Discrepancies were resolved through discussion or consultation with a third reviewer.

Data extraction

A standardized data extraction form was used. Two reviewers independently extracted and cross-validated the following items from each included study: First author and publication year; plant species studied; type of study (*in vitro*, *in vivo*, *in silico*); pharmacological activity evaluated; identified bioactive compound(s); mechanisms of action (if available); outcome metrics (e.g., IC₅₀, inhibition zones, % inhibition); and reported limitations.

Study risk of bias assessment

The AXIS tool was used to assess the quality of observational studies, while CAMARADES criteria were applied to preclinical experimental studies. Two reviewers independently evaluated the risk of bias based on sample selection methods, presence or absence of randomization and controls and transparency in outcome reporting and statistical analysis. Disagreements were resolved through consensus or third-party adjudication.

Effect measures

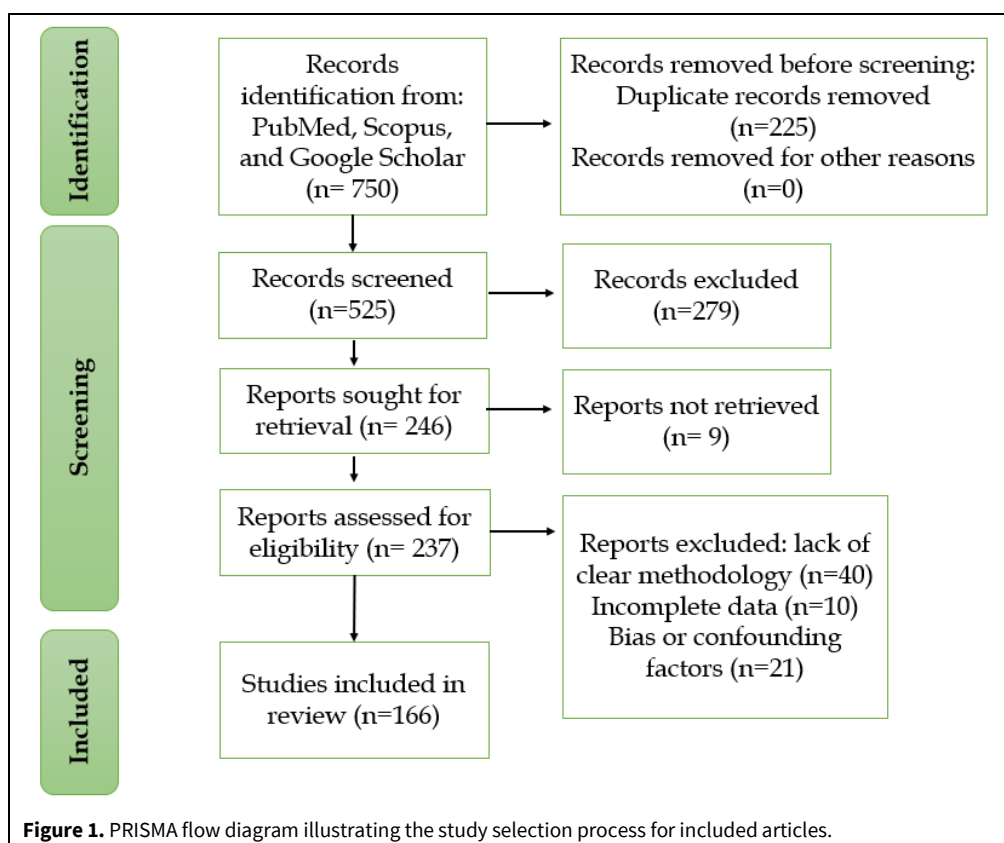
Quantitative data (e.g., IC₅₀ values, inhibition zones) were extracted and tabulated. Where available, effect sizes were recorded. Due to high methodological heterogeneity, a meta-analysis was not feasible.

Synthesis methods

Given the variation in study design, assay protocols, and outcome measures, a narrative synthesis approach was employed. Studies were grouped by plant species and pharmacological category. Quantitative outcomes were summarized in tabular format where applicable. Results were described with reference to pharmacological mechanism and bioactive composition.

Reporting bias assessment

Only peer-reviewed, full-text articles were included to minimize publication bias. Both positive and non-significant findings were considered. Funnel plot analysis was not conducted due to the narrative nature of the synthesis.



Certainty assessment

The GRADE principles were used to qualitatively assess the strength of evidence, based on study limitations, inconsistency, indirectness, imprecision, and publication bias. Certainty levels were assigned to each pharmacological category (e.g., antioxidant, anti-inflammatory),

RESULTS

Selected and excluded studies

A total of 750 records were initially identified through PubMed, Scopus, and Google Scholar. Following the removal of 225 duplicates using the Rayyan QCRI software, 525 records remained for screening. Based on title and abstract review, 279 articles were excluded due to irrelevance, lack of pharmacological focus, or ineligible study design. Subsequently, 246 full-text articles were assessed for eligibility, resulting in the exclusion of 80 studies due to incomplete data, absence of experimental findings, or insufficient methodological detail. Ultimately, 166 studies met the inclusion criteria and were retained for analysis. The study selection process is depicted in Fig. 1 in accordance with the PRISMA 2020 flowchart.

Of the included studies, eight were used for background and methodological referencing, while 158 directly supported pharmacological analysis of the

selected herbal species. Categorically, 38 studies focused on antioxidant activity, 30 on anti-inflammatory effects, 28 on anticancer activity, and 20 on antimicrobial mechanisms. A number of studies overlapped across multiple bioactivity domains.

Study quality analysis

To ensure methodological rigor, eight representative studies, covering a diversity of plant species and study types, were selected and evaluated using the AXIS quality assessment tool (Table S1). These included three cohort studies, one case-control study, and four observational studies involving either *in vitro* or *in vivo* models.

Quality scores ranged from 13 to 16 out of 20. Four studies, comprising the three cohort and one case-control designs, were rated as high quality (15–16 points). The remaining observational studies received medium-quality ratings (13–14 points). Frequent methodological limitations included lack of sample size justification, absence of proper control groups, non-blinded protocols, and incomplete or insufficient statistical analysis.

All assessments were independently conducted by two reviewers, with any discrepancies resolved through discussion or by involving a third reviewer. Overall, the selected studies were deemed methodologically sufficient to support inclusion in this review.

Results of individual studies

A total of 166 studies were included in this review, each contributing evidence related to one or more pharmacological activities of the selected herbal plants. The majority of findings clustered around four major bioactivities: antioxidant, anti-inflammatory, anticancer, and antimicrobial properties. Antioxidant activity was the most frequently reported (109 studies), commonly evaluated through DPPH and ABTS radical scavenging assays. *Phyllanthus emblica* and *Gynura procumbens* consistently exhibited strong antioxidant capacity, with several studies reporting low IC₅₀ values and high total phenolic content (Ahmad Nazri et al., 2019; Asmilia et al., 2020). Anti-inflammatory effects were identified in 78 studies, typically demonstrated by COX-2 inhibition, nitric oxide suppression, and downregulation of pro-inflammatory mediators such as TNF- α and IL-6. Extracts of *Premna serratifolia* and *Styrax sumatranus* showed significant inhibition of inflammatory pathways in both *in vitro* and *in vivo* models (Dianita and Jantan, 2017; Elfiati et al., 2022). Anticancer properties were reported in 56 studies, primarily using cytotoxicity assays on human cancer cell lines including HeLa, MCF-7, and HCT116. Notably, *Zanthoxylum acanthopodium* and *Cananga odorata* extracts exhibited selective cytotoxicity, with some studies highlighting apoptosis induction and cell cycle arrest mechanisms (Adrian et al., 2023; Situmorang et al., 2021). Antimicrobial activity was examined in 45 studies, employing methods such as MIC determination, disc diffusion, and agar well diffusion. *Rhodomyrtus tomentosa* and *Saurauia vulcani* demonstrated notable inhibitory effects against common bacterial and fungal pathogens, including *Staphylococcus aureus* and *Candida albicans* (Chen et al., 2021; Elfiati et al., 2022).

To explore the landscape of the supporting literature, a cross-study visualization was performed using the ResearchRabbit platform. Rather than dissecting each species in isolation, this analysis mapped the thematic and methodological relationships among the included studies. The resulting network (Fig. 2) illustrated clusters of research focusing on similar bioactivities, such as antioxidant or antimicrobial studies, while also identifying sparsely connected nodes that may represent underexplored areas. This visualization not only offers a macroscopic view of the evidence landscape but also facilitates recognition of gaps, redundancies, and opportunities for future investigation within the domain of North Sumatran ethnopharmacology. Although a wide range of pharmacological effects was observed across the reviewed plants, several shared mechanisms emerged, including reactive oxygen species (ROS) modulation, inhibition of inflammatory mediators, and NF- κ B pathway

suppression. In multiple studies, synergistic effects were suggested, particularly combinations of flavonoids, terpenoids, and saponins, enhancing the overall therapeutic outcome.

However, substantial methodological heterogeneity was noted across studies, especially in dosage forms, extraction protocols, and assay conditions. This variation limited the feasibility of conducting a quantitative meta-analysis. Consequently, a narrative synthesis approach was adopted to allow meaningful integration of diverse data. To minimize reporting bias, only peer-reviewed, full-text studies were included, and both positive and negative findings were considered. Funnel plot analysis was not feasible due to heterogeneity in outcomes and study designs. Based on the GRADE criteria, the certainty of evidence was considered moderate for antioxidant and anti-inflammatory activities. In contrast, anticancer and antimicrobial results were supported by fewer studies and inconsistent models, leading to lower certainty. Studies relying solely on *in silico* predictions, without experimental validation, were rated as having very low certainty.

DISCUSSION

The present review consolidates current scientific evidence on selected medicinal plants traditionally utilized across North Sumatra. These species demonstrate a broad spectrum of pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial, and anticancer effects, that align with their ethnomedicinal uses. Each species is presented separately to enhance clarity, while also highlighting specific mechanisms of action, bioactive constituents, and research gaps.

To contextualize their ethnopharmacological significance, it is important to recognize the geographical distribution of these plants across the province. North Sumatra encompasses diverse ecological zones ranging from coastal lowlands to volcanic highlands, where traditional plant-based medicine remains a key component of community healthcare, particularly among the Batak and Malay ethnic groups. Table 2 provides a summary of regency-level distributions for each of the ten reviewed species, underscoring their ecological prevalence and cultural relevance.

Arenga pinnata (Wurmb) Merr. (Areacaceae)

Arenga pinnata, widely referred to as sugar palm, is extensively used within North Sumatran communities for both nutritional and medicinal purposes. Traditional applications include treatment of kidney stones, digestive disorders, and inflammatory conditions (Fazil and Nikhat, 2022).

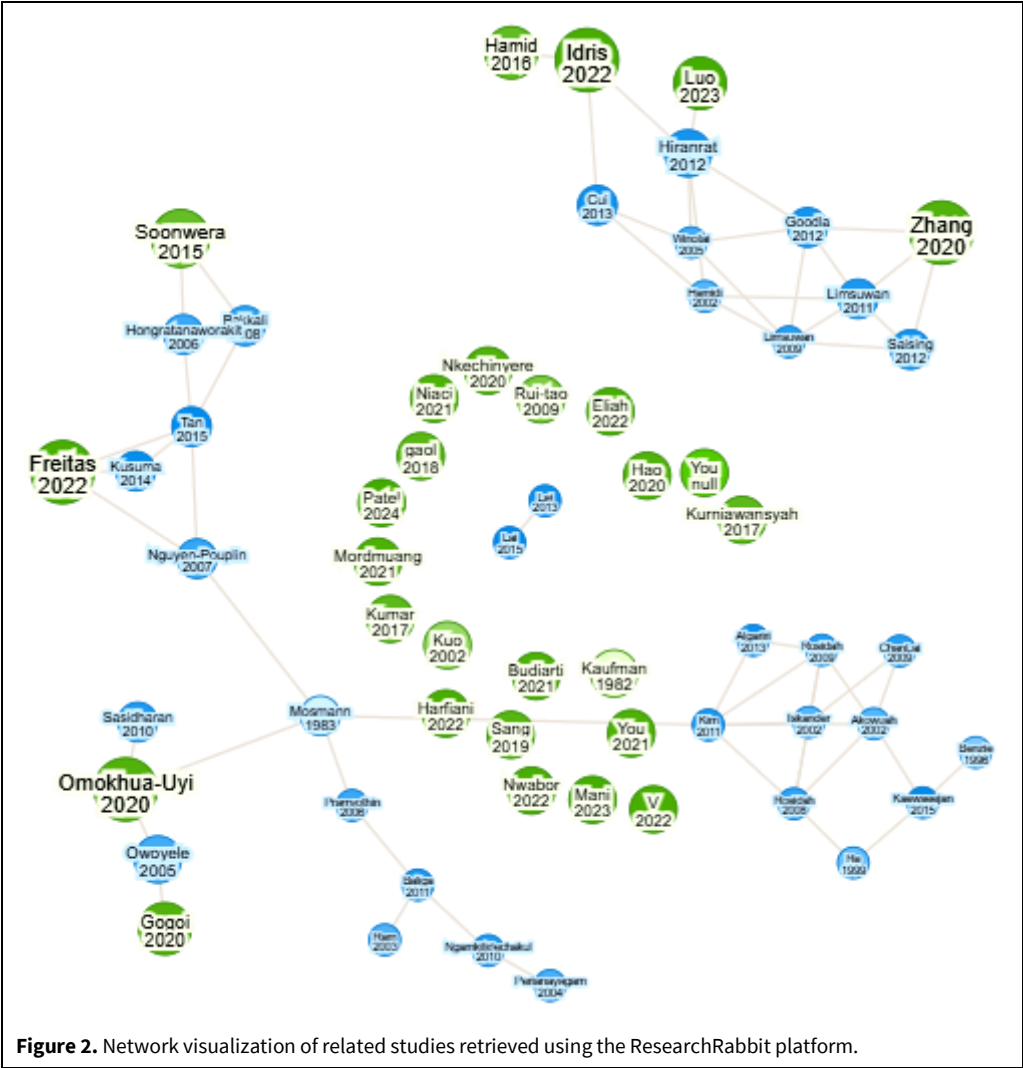


Figure 2. Network visualization of related studies retrieved using the ResearchRabbit platform.

Table 2. Geographic distribution of the ten selected herbal plants across regencies in North Sumatra, Indonesia.

No	Herb	Regency
1	<i>Arenga pinnata</i>	Nias, Mandailing Natal, Toba Samosir, Sipirok, Serdang Bedagai, Karo.
2	<i>Rhodomyrtus tomentosa</i>	South Labuhan Batu, Padanglawas, North Padanglawas, and South Tapanuli District.
3	<i>Cananga odorata</i>	Asahan, Labuhanbatu, Labuhanbatu Selatan, Serdang Bedagai, Langkat.
4	<i>Phyllanthus emblica</i>	South Labuhanbatu, North Padang Lawas, Padang Lawas, South Tapanuli, Padangsidimpuan City, and Mandailing Natal.
5	<i>Gynura procumbens</i>	Nias, Karo, Toba Samosir, Dairi, Langkat.
6	<i>Premna serratifolia</i>	Mandailing Natal, Karo, Langkat.
7	<i>Styrax sumatera</i>	North Tapanuli, Dairi, Toba Samosir, and Central Tapanuli.
8	<i>Saurauia vulcani</i>	Lumban Julu, Sipangan Bolon, Merek, and Sipiso-piso.
9	<i>Vitis gracilis</i>	Karo, Mandailing Natal, Langkat.
10	<i>Zanthoxylum acanthopodium</i>	Samosir (Desa Salaon Dolok), Dairi (Desa Parbuluan V), Humbang Hasundutan (Pollung), Toba (Lumban Julu, Silaen, Aek Unsim) dan Simalungan (Jandi Raya and Batu Mardinding).

Phytochemical studies have identified diverse bioactive compounds such as phenolic acids, quinones, alkaloids, and diterpenoids, including the lignan li-

quiritin (Djeni et al., 2020; Jdaini et al., 2023). The plant's antioxidant capacity is supported by a high

total phenolic content ($2432 \pm 32 \mu\text{g/g}$ GAE) and low IC_{50} values in DPPH assays.

Anti-inflammatory effects have been demonstrated in xylene-induced and carrageenan-induced edema models, with reductions in swelling and suppression of pro-inflammatory cytokines such as $\text{TNF-}\alpha$, $\text{IL-1}\beta$, IL-6 , and PGE_2 (Akhtar, 2022). Anticancer activity has also been observed, particularly through the inhibition of cell proliferation in multiple tumor cell lines (P-388, H-22, A549, CNE-2), which may involve both redox modulation and cytokine inhibition (Calvaruso et al., 2019).

Despite these findings, most evidence is derived from *in vitro* and rodent studies. Standardized dosages, clinical validation, and pharmacokinetic evaluations remain absent. Future investigations should focus on safety profiling, chronic toxicity, and *in vivo* efficacy models. Fig. 3 presents a schematic of the plant's pharmacological mechanisms, and Table 3 provides details of identified bioactive compounds.

***Rhodomyrtus tomentosa* (Aiton) Hassk. (Myrtaceae)**

Rhodomyrtus tomentosa, locally known as *haramonting*, is traditionally applied in the treatment of infections, wounds, and diabetes in North Sumatra (Rumahorbo et al., 2023). Its primary active constituent is rhodomyrtone, an acylphloroglucinol, supported by terpenoids, anthocyanins, and ellagic acid derivatives (Abd Hamid et al., 2017; Vo and Ngo et al., 2019).

Strong antibacterial activity has been demonstrated *in vitro* against *Staphylococcus aureus*, *Streptococcus agalactiae*, *Escherichia coli*, and *Candida albicans* (Gonelimali et al., 2018; Limsuwan et al., 2009). Rhodomyrtone is known to compromise microbial cell walls and suppress virulence gene expression (Nwabor et al., 2021).

Anti-inflammatory properties have been attributed to the inhibition of nitric oxide and prostaglandin E_2 in LPS-activated macrophages (Vo and Ngo et al., 2019). Moreover, the plant exhibits significant antioxidant effects by preserving enzymatic activities (SOD, CAT, GPx) and reducing lipid peroxidation (Lavanya et al., 2012).

The plant's cytotoxic effects have been validated on HepG2, MCF-7, and HT29 cells, with IC_{50} values ranging from 0.28 to $16.18 \mu\text{g/mL}$. Notably, several newly isolated meroterpenoids have been shown to reverse multidrug resistance in leukemia and breast cancer models (Greenwell and Rahman, 2015; Vo and Ngo, 2019).

Nevertheless, current studies lack robust clinical

or toxicological validation. Recommendations for future research include nanoformulation development, dose-response modeling, and preclinical testing of isolated compounds. Fig. 4 illustrates its pharmacological targets, and Table 4 compiles its principal bioactives.

***Cananga odorata* (Lam.) Hook.f. & Thomson (Annonaceae)**

Cananga odorata (*kenanga*), widely referred to as *ylang-ylang*, holds cultural significance across North Sumatra, where it is employed in traditional rituals, aromatherapy, and herbal medicine for conditions such as fever, asthma, postpartum recovery, and malaria (Asazawa et al., 2017; Jin et al., 2015; Soares et al., 2021).

The plant contains a rich profile of volatile oils and secondary metabolites. The flowers are particularly abundant in β -caryophyllene, α -cadinol, α -pinene, limonene, and 1,8-cineole, while the roots and bark yield alkaloids, glycosides, and lignans (Caloprisco et al., 2002; Mustaqim and Hartiningtias, 2021).

Extracts exhibit broad pharmacological activity, including antimicrobial, anti-inflammatory, antioxidant, neuroprotective, and hypoglycemic effects (de Freitas Junior et al., 2022). Essential oils inhibit a range of bacteria, including *Bacillus cereus*, *B. subtilis*, and β -hemolytic *Streptococcus* (Zhang et al., 2018), while *in vitro* studies support its utility against biofilm formation and fungal growth (Sedky et al., 2023).

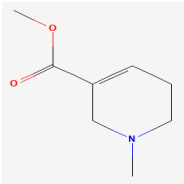
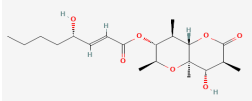
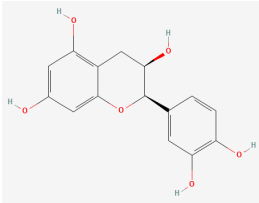
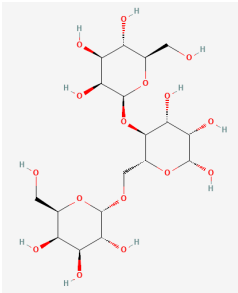
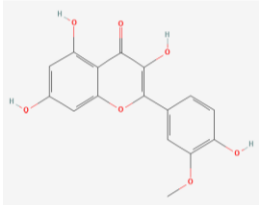
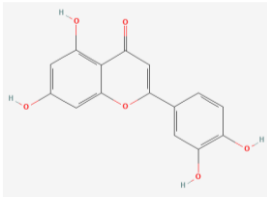
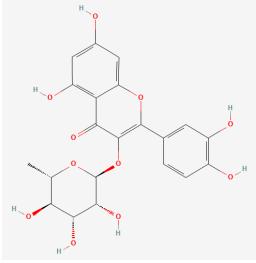
Despite its promise, limitations include variability in oil composition, extraction methods, and dosage data. Standardized protocols, safety evaluations, and clinical data remain lacking. Future studies should focus on bioactivity-guided isolation and formulation of standardized aromatherapeutic or antimicrobial products. Fig. 5 depicts its therapeutic pathways, with constituent data listed in Table 5.

***Phyllanthus emblica* L. (Phyllanthaceae)**

Known locally as *malaka*, widely referred to as Indian gooseberry, *Phyllanthus emblica* is widely distributed in regions such as Mandailing Natal, Labuhanbatu, and Tapanuli. Cultural significance is reflected in its association with the name of the Malacca Strait (Prananda et al., 2023).

The plant is rich in vitamin C, polyphenols, flavonoids, tannins, alkaloids, and unique compounds such as emblicanin A and B (Asmilia et al., 2020; Quranayati et al., 2022). The synergy between polyphenols and vitamin C contributes to its potent antioxidant effects (Chaikul et al., 2021).

Table 3. Bioactive compounds and their pharmacological mechanisms in *Arenga pinnata*.

Compound	Chemical structure	Pharmacological benefit	Molecular activity	Reference
Arecoline		Anti- inflammation	This drug inhibits IL-1 β , TNF- α , PGE2, and IL-6 production in leg tissue in response to edema.	(Hu et al., 2022)
Botcinin F		Anti-tumor effects	Its fruit has outstanding <i>in vivo</i> and <i>in vitro</i> anti-tumor effects. The total diterpenes inhibited P-388, H- 22, Lewis B-16, A-549, and CNE-2 tumor cells.	(Fantini et al., 2015)
Epicatechin		Anti- inflammation	Increases articular cartilage structure and chondrocyte cellularity by reducing nitric oxide generation and tissue degradation by proteases.	(Grogan and D'Lima, 2010)
Galactomannan		Cosmetic potential for brightening effects	Inhibition of tyrosinase, antioxidant action by chelating Fe 2+ ions, and anti-photaging activity by inhibiting MMP-1 and MMP-13 gene expression.	(Oliveira Amorim et al., 2013)
Isorhamnetin		Anti- inflammation	Suppresses NO, PGE2, iNOS, COX-2, COMP, CTX-II, and osteopontin production.	(Sartinah et al., 2022)
Luteolin		Cytoprotective against oxidative injury	Activates AMPK/Nrf2 and AMPK signaling pathways to protect primary murine chondrocytes from oxidative damage, inflammation, and disintegration.	(Saha and Rebouh, 2023)
Quercetin		Protects and prevents osteoarthritis.	It inhibits IL-1 β and TNF production via the TLR-4/NF- κ B pathway, suppressing matrix-degrading proteases and inflammatory mediators in joints and bones.	(Mukherjee and Das, 2024)

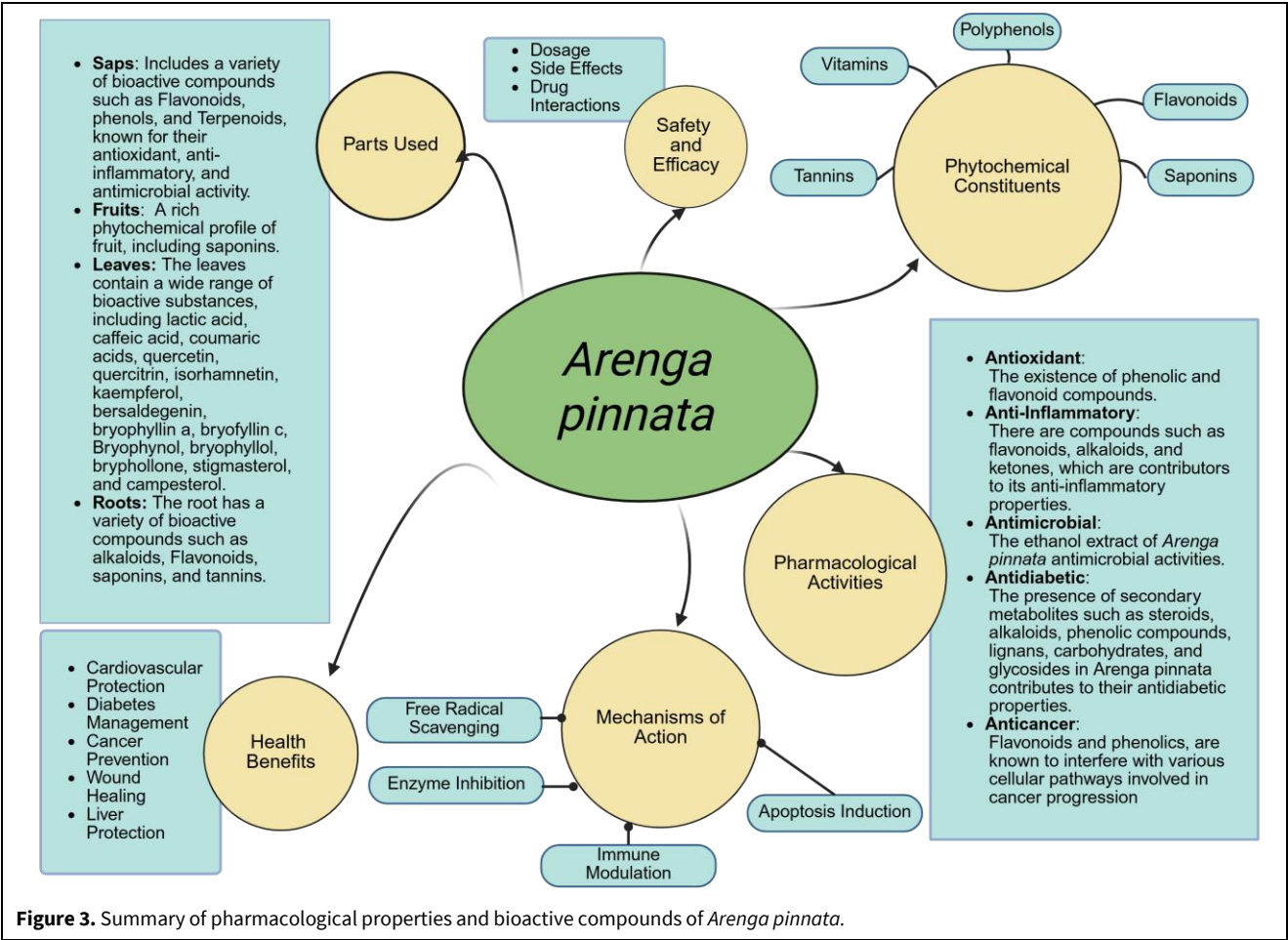


Figure 3. Summary of pharmacological properties and bioactive compounds of *Arenga pinnata*.

Table 4. Identified phytochemicals and pharmacological actions of *Rhodomyrtus tomentosa*.

Compound	Chemical structure	Pharmacological benefit	Molecular activity	Reference
β-Amyrin		Antidiabetic, anticancer, cytotoxic, and antioxidant activities	α-Amyrin component inhibits α-glucosidase and α-amylase and is cytotoxic against MCF-7 cancer cells.	(Phuong et al., 2023)
α-Tocopherol		Anti- hypertension	In hypertensive rats, treatment with this plant increases HSP27, HSP70, and HSP90 levels. In placental histology, it inhibits Fas synthesis, thereby preventing trophoblast cell apoptosis.	(Situmorang et al., 2021)
Betuline		Antioxidant activity	Betuline is effective at healing stomach ulcers and reducing lipid peroxidation by increasing CAT and SOD.	(Vo and Ngo, 2019)
Kaempferol		Anti-cancer effects	As cancer biomarkers, PDGF- and IL-18 levels can be reduced through the use of <i>R. tomentosa</i> supplementation	(Simanullang et al., 2022)

Table 4. Identified phytochemicals and pharmacological actions of *Rhodomyrtus tomentosa* (continued...)

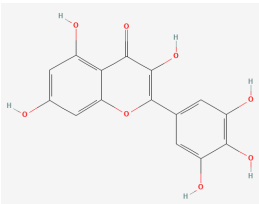
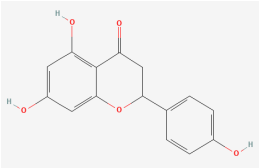
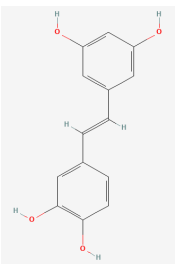
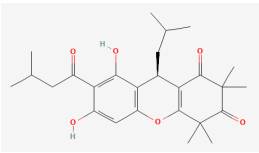
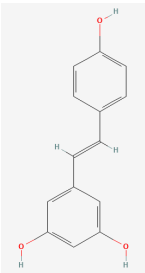
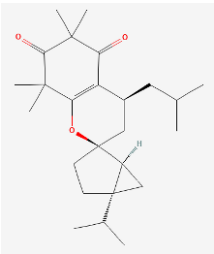
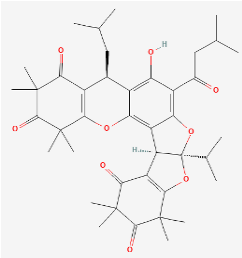
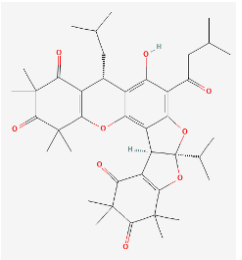
Compound	Chemical structure	Pharmacological benefit	Molecular activity	Reference
Myricetin		Apoptosis activity	Suppress G2/M phase cell cycle progression via the ATM-Chk2-p53-p21 signaling pathway. The induction of ER stress and inhibition of STAT3 induce apoptosis	(Zhanget al., 2020)
Naringenin		Anti- inflammation	<i>R. tomentosa</i> exhibits promise as a potential anticancer, antidiabetic, and antioxidant agent against several human cancer cell lines, including MCF-7, HeLa, A549, and B16. The range of IC ₅₀ values observed for this extract is 28.28 to 168.88 µg/mL.	(Idris et al., 2022)
Piceatannol		Anti-cancer effects	Apoptosis and cell cycle arrest in human melanoma and hepatoma cells.	(Pan et al., 2019)
Rhodomyrtone		Anti-cancer effects	Blocking A431 cancer cell metastasis by lowering cell movement, adhesion, and invasion.	(Laomethakorn et al., 2023)
Resveratrol		Anti-cancer effects	<i>R. tomentosa</i> in cervical tissue resulted in enhanced histological improvement, reduced tumor distance, inhibited carcinoma growth, and lowered production of MMP9, GLUT-1, and IL-1β.	(Situmoranget al., 2024)
Tomentodione M		Anti-cancer effects	Reverse MDR in cancer cells by decreasing P-gp expression via p38 MAPK inhibition	(Han et al., 2022)

Table 4. Identified phytochemicals and pharmacological actions of *Rhodomirtus tomentosa* (continued...)

Compound	Chemical structure	Pharmacological benefit	Molecular activity	Reference
Tomentosone A		Anti-cancer effects	Increase chemotherapeutic drug cytotoxicity in human breast cancer and immortalize myelogenous leukemia cells with reversed multidrug resistance.	(Labbozzetta et al., 2022)
Tomentosone B		Anti-malarial activity	Tomentosone B decreased sensitive and resistant strain growth of malaria parasite	(Hiranrat et al., 2012)

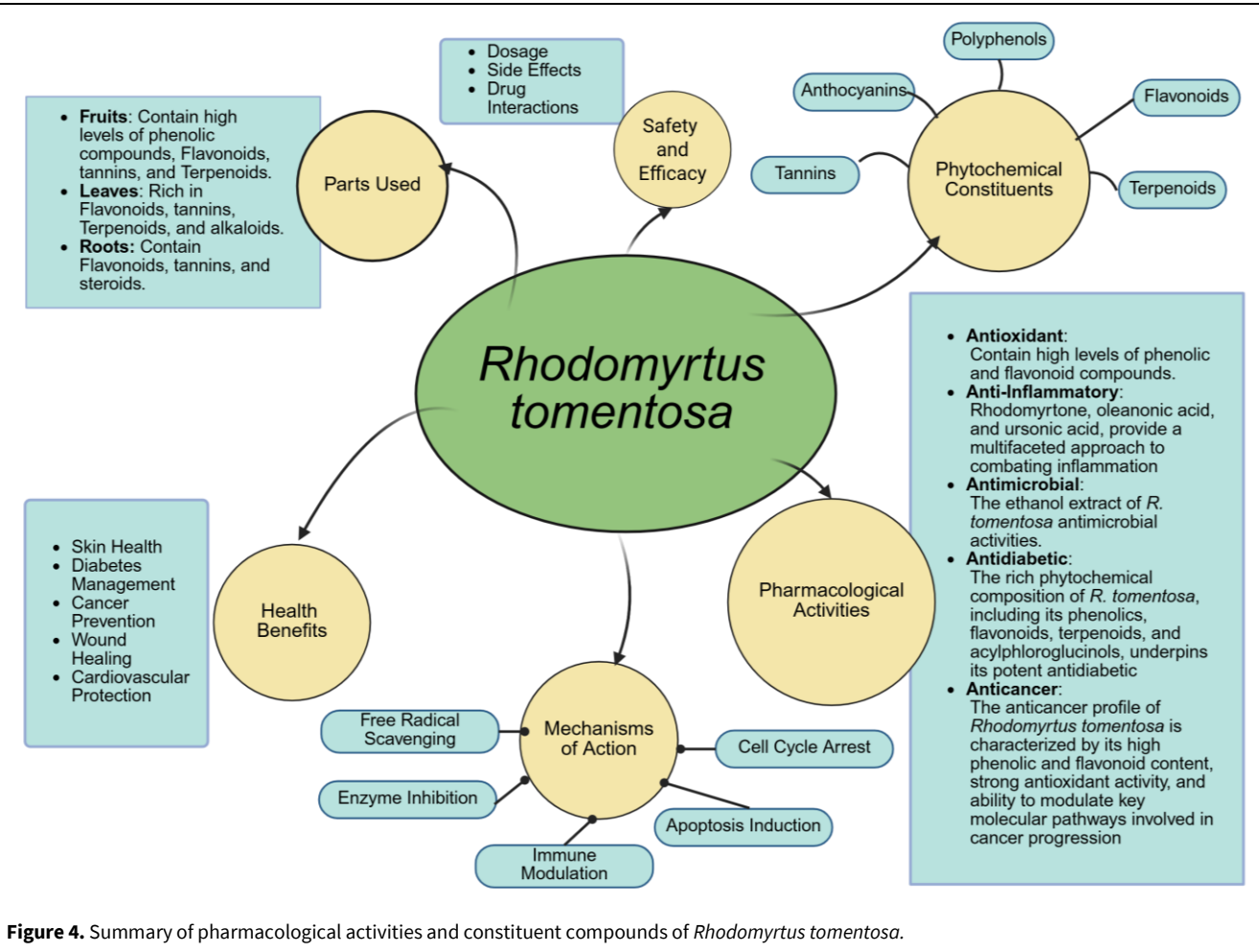
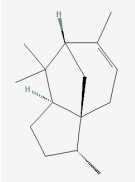
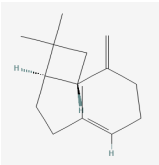
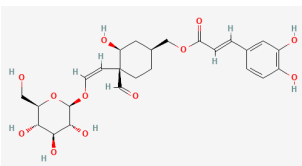
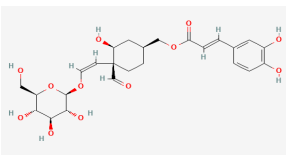
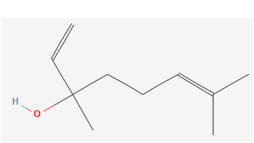
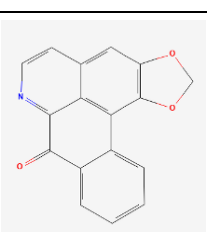


Figure 4. Summary of pharmacological activities and constituent compounds of *Rhodomirtus tomentosa*.

Table 5. Key chemical constituents and biological activities of *Cananga odorata*.

Compound	Chemical structure	Pharmacological benefit	Molecular activity	Reference
α -cedrene		Antihyperglycemic	Inhibit porcine pancreatic α -amylase. However, it did not block the α -glucosidase enzyme.	(Li et al., 2018)
β -caryophyllene		Anxiolytic effect	This plant's anxiolytic effect is linked to the ERK1/2/CREB pathway in the hippocampus and the serotonin system.	(Zhang et al., 2018)
Canangafruticoside E		Antihyperglycemic	<i>C. odorata</i> extracts may be effective α - α -amylase inhibitors for treating postprandial hyperglycemia and contain terpenoid derivatives and flavonoids that inhibited aldose reductase.	(Fattaheian-Dehkordiet al., 2021)
Canangaterpenes I		Anti- melanogenesis	Inhibition of mouse B16 4A5 melanoma cell melanin synthesis and tyrosinase protein expression	(Changet al., 2012)
Linalool		Anti-inflammation activity	In a 15-lipoxygenase inhibitor screening experiment, linalool catalyzed arachidonic acid metabolism to produce inflammatory response-regulating metabolites.	(Tan et al., 2022)
liriodenine (24)		insecticidal	bioactive compounds with antibacterial properties and insecticidal.	(Patil et al., 2023)

Extensive pharmacological activities have been reported, including anti-inflammatory, cytoprotective, antibacterial, antifungal, hypoglycemic, and immunomodulatory effects (Khairunnisa and Angio, 2023). Cytostatic effects against A549, HepG2, MCF-7, and SK-OV3 cell lines have been documented *in vitro* at 50–100 $\mu\text{g/mL}$ (Saqban et al., 2022). Antiviral activity was demonstrated by 1,2,4,6-tetra-O-galloyl- β -D-glucose, which inhibited herpes simplex virus (HSV) type HSV-1 and HSV-2 replication (Díaz-Herrera et al., 2024).

Vector control activity was observed in larvicidal and pupicidal assays against *Anopheles stephensi* (Yousefbeyk et al., 2018), while leaf extracts exhibited spasmolytic and antidiarrheal effects in rodent models (Mehmood et al., 2011). However, most studies remain at the preclinical stage. Future efforts should

aim to validate compound-specific mechanisms, improve extract standardization, and initiate human trials. Fig. 6 outlines major pharmacological pathways, and Table 6 lists associated bioactive constituents.

***Gynura procumbens* (Lour.) Merr. (Asteraceae)**

Gynura procumbens, locally known as *sambung nyawa*, is commonly cultivated across tropical and subtropical areas of Indonesia, including North Sumatra. The plant adapts well to diverse environments, thriving in both outdoor and indoor settings such as gardens, parks, and household plots (Nguyen et al., 2021; Tan et al., 2016). It has long been employed in traditional medicine to manage conditions such as fever, hypertension, diabetes, inflammation, and malignancies (Mou Dash, 2016).

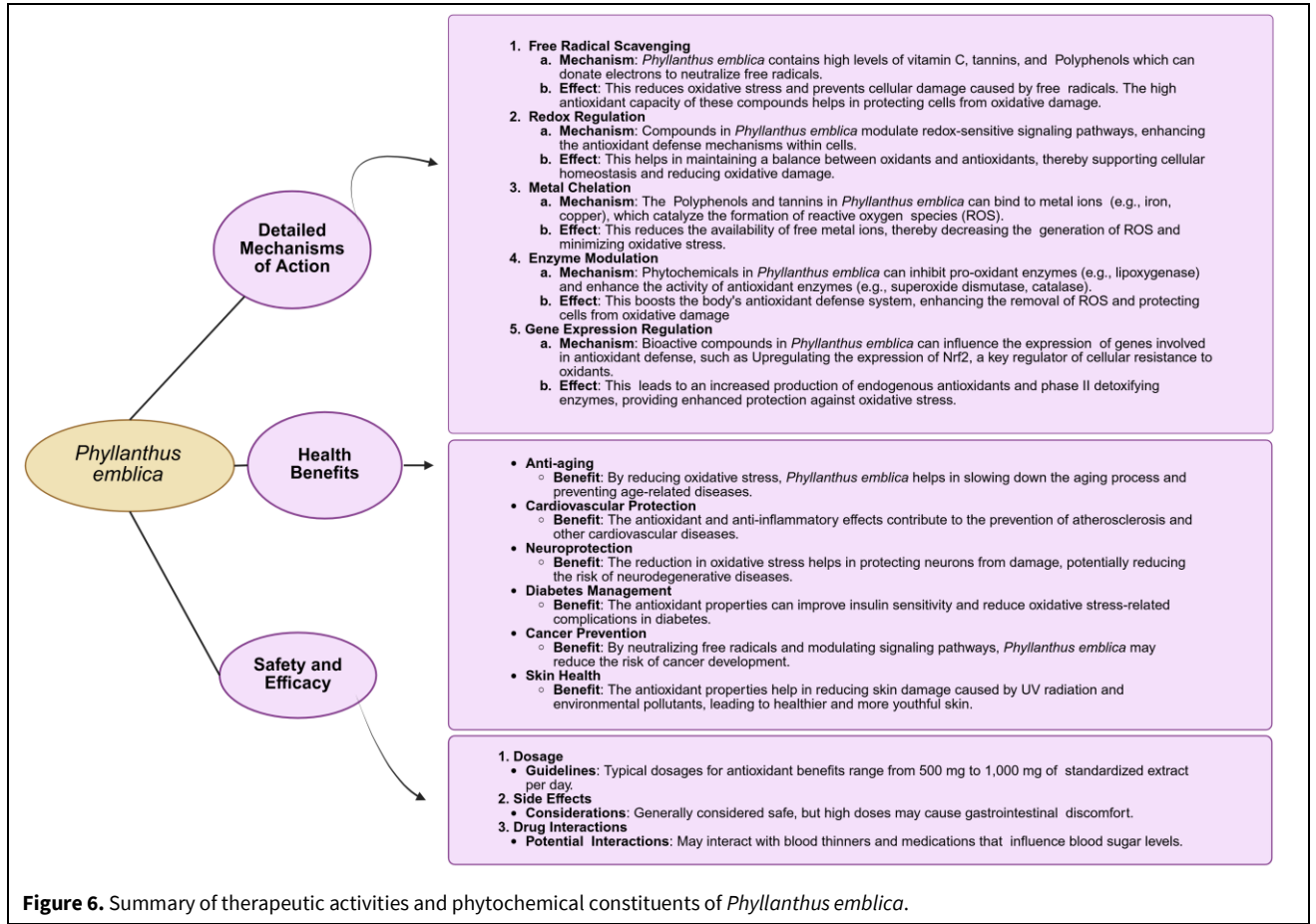
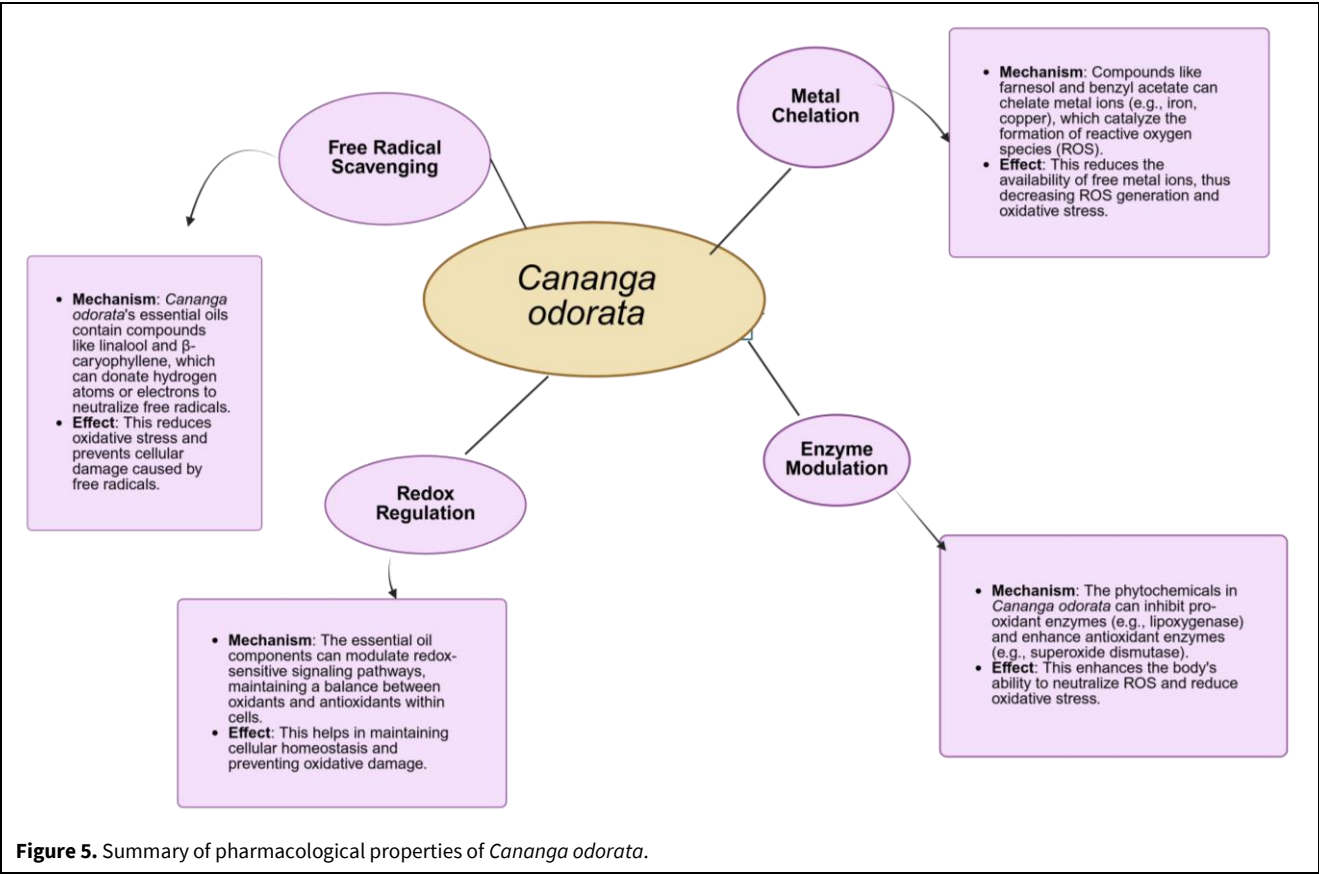


Table 6. Pharmacologically active compounds identified in *Phyllanthus emblica* and their molecular mechanisms.

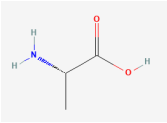
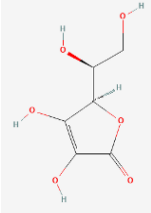
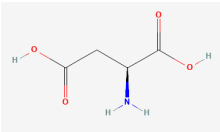
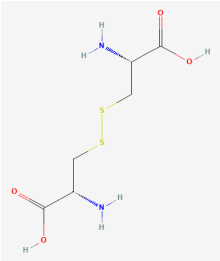
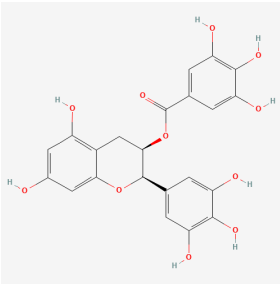
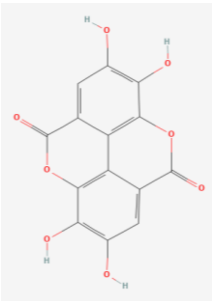
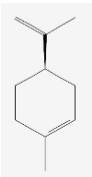
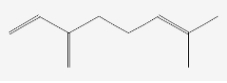
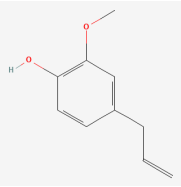
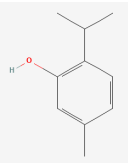
Compound	Chemical structure	Pharmacological benefit	Molecular activity	Reference
Alanine		Analgesic, antipyretic, and anti-inflammatory activities	The dorsal root ganglia (DRG) of a rat model with spared nerve injury exhibited reduced levels of IL-1 β , IL-2, IL-6, and IL-12, while displaying elevated levels of IL-10.	(Wu et al., 2021)
Ascorbic acid		Protection against diabetes	The results demonstrated a decrease in oxidative stress, nitrite concentrations, and various inflammatory cytokines, including TNF- α , IL-1, and TGF- α , in both the blood and sciatic nerve homogenate.	(Kitwetcharo en et al., 2024)
Aspartic acid		Antioxidant activity	The aqueous extract from this compound greatly increased antioxidant activity by increasing GSH and antioxidant system enzymes such as superoxide dismutase, catalase, GSH peroxidase, GSH reductase, and GSH S-transferase.	(Cecerska-Heryć et al., 2022)
Cystine		Oncolytic activity	The L-cysteine derivative acts as an L-glutamine antagonist, preferentially targeting purine nucleotide biosynthesis enzymes.	(Yoo et al., 2020)
Epigallocatechin-3-O-gallate		anti-proliferative and anti-diabetic activity	In comparison to 5-fluorouracil, it exhibited significant anti-proliferative efficacy against HeLa and MK-1 cell lines.	(Benassi et al., 2020)
ellagic acid		Protection against diabetes	Inhibit α -amylase and β -glucosidase. The increased levels of ellagic acid were found to be responsible for the antidiabetic action.	(Xu et al., 2021)
Limonene		Nephroprotective activity	Research on cisplatin-induced nephrotoxicity in rats revealed that the fruit extract enhanced kidney function, antioxidant status, and histological changes via inducing apoptosis and suppressing MAPK-induced inflammation.	(Iskander and Yan, 2022)

Table 6. Pharmacologically active compounds identified in *Phyllanthus emblica* and their molecular mechanisms (continued ...)

Compound	Chemical structure	Pharmacological benefit	Molecular activity	Reference
Myrcene		Analgesic activity	Myrcene's low affinity for opioid receptors suggests α -2-adrenoceptor-stimulated opiate release.	(Richter et al., 2021)
Methyl eugenol		Anti- inflammation	Reducing proinflammatory cytokines, including TNF- α , NF- κ B signaling pathway, and macrophage infiltration, improved lung function and structure by reducing inflammation.	(Mehdi et al., 2023)
Tetracosane		Antioxidant activity	The essential oil and its primary constituents demonstrated a strong ability to scavenge nitric oxide (NO) and suppressed the activity of inducible NO synthase.	(El Amir et al., 2014)
Thymol		Anti- inflammation	Thymol can reduce inflammation by decreasing T cell immunological response and increasing the ratio of T-helper cells-1 (Th1) to IL-2 and IFN- γ /Th2 (IL-4, IL-5, and IL-10), in mouse primary splenocytes.	(Nagoor Meeran et al., 2017)

Phytochemical analyses have confirmed the presence of multiple secondary metabolites in the leaves, including flavonoids, tannins, saponins, terpenoids, and steryl glycosides. Among these, kaempferol-3-O-rutinoside and astragalin have been identified as dominant antioxidant constituents, exhibiting potent free radical scavenging properties. The ethyl acetate fraction, in particular, demonstrated the highest antioxidant activity across various assays due to its high phenolic content (Jobaer et al., 2023; Tan et al., 2020).

Antihypertensive effects have been substantiated through both *in vivo* and *in vitro* studies, primarily via inhibition of angiotensin-converting enzyme (ACE) and promotion of vasorelaxation through prostaglandin pathways (Ahmad Nazri et al., 2019; da Silva et al., 2022). Extracts also exhibited hypoglycemic effects in diabetic rodent models, evidenced by improved glucose tolerance and reductions in fasting blood glucose, without inducing hypoglycemia in non-diabetic controls (Jobaer et al., 2023).

The plant's anticancer activity has been documented in various cellular models, with observed inhibition of proliferation, migration, and invasion. These effects are thought to be mediated through cell cycle arrest and apoptosis induction (Jermnak et al., 2022). Antiplasmodial activity has also been reported, with extracts demonstrating chemosuppressive effects against *Plasmodium falciparum* and *Plasmodium berghei*, potentially involving glycogen synthase kinase-3 (GSK3) inhibition and modulation of the PI3K/Akt signaling pathway (Saha et al., 2023).

Antiviral efficacy has been shown against herpes simplex virus types 1 and 2, while immunomodulatory properties have been evidenced in murine lymphocyte models, suggesting dual immunostimulatory and anti-inflammatory roles (Moon et al., 2021). Additionally, gastroprotective effects have been validated in ethanol-induced ulcer models, where the extract attenuated mucosal damage, reduced leukocyte infiltration, and minimized submucosal edema (Jabbar et al., 2023).

Despite the breadth of pharmacological activity reported, limitations remain regarding dosage standardization, clinical applicability, and long-term safety data. No clinical trials have yet been conducted, and pharmacokinetic evaluations are lacking. Future directions should prioritize formulation development, chronic toxicity assessments, and translational validation in human populations. A concise summary of pharmacological mechanisms is presented in Fig. 7, and a comprehensive list of bioactive constituents and their associated activities is provided in Table 7.

***Premna serratifolia* L. (Lamiaceae)**

Premna serratifolia, locally referred to as *buas-buas*, is widely recognized in North Sumatra for its dual function as both a traditional vegetable and medicinal herb. It is frequently used among Malay communities to address ailments such as fever, halitosis, postpartum disorders, rheumatism, and microbial infections (Dianita and Jantan, 2017).

Table 7. Major bioactive constituents and therapeutic effects of *Gynura procumbens*.

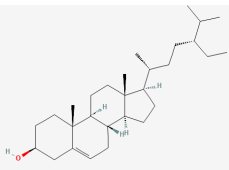
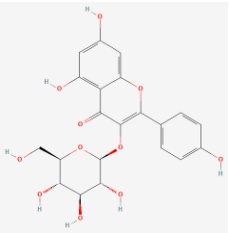
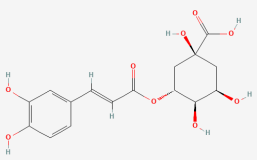
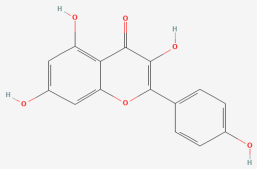
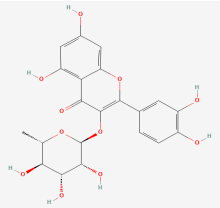
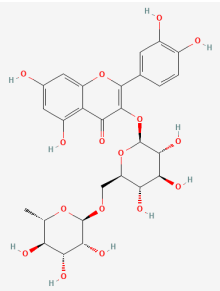
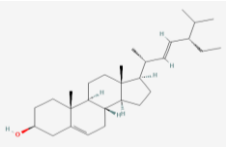
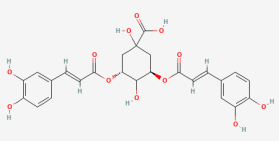
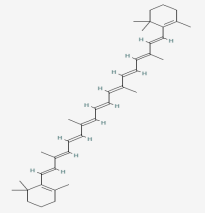
Compound	Chemical structure	Pharmacological benefit	Molecular activity	Reference
β-sitosterol		Anti-cancer	The modification of the cell cycle, including arrests in the G1 and S phases, as well as the activation of apoptosis.	(Qi and Calvi, 2016)
Astragalin		Anti-diabetic	Reduced fasting blood glucose levels in diabetic rats.	(Alfheeaaid et al., 2023)
Chlorogenic acid		Anti-diabetic	Fasting blood glucose levels decreased in diabetic rats, with metformin-like effects enhancing hepatic gluconeogenesis and insulin sensitivity.	(Hu et al., 2021)
Kaempferol		Anti-diabetic	The fasting blood glucose levels of diabetic mice are reduced through the inactivation of GSK-3β.	(Sampath et al., 2020)
Quercetin		Anti-diabetic and anti-inflammatory	UV inhibits MMP-1, MMP-9, IL-6, IL-8 expression, ROS production, and pro-inflammatory cytokines.	(Jang et al., 2023)
Rutin		Anti-diabetic	Glucose metabolism occurs via glycolysis, while hepatic glucose production is inhibited by gluconeogenesis.	(Rui, 2014)
Stigmasterol		Anti-cancer	WiDr colon cancer growth is suppressed, with 5-FU efficacy enhanced but counteracted by cisplatin.	(Hong et al., 2020)
3,5-dicaffeoylquinic acid		Anti-cancer	The compound inhibited MCF-7 cell proliferation by inducing apoptosis and downregulating Bcl2.	(Lee et al., 2019)

Table 7. Major bioactive constituents and therapeutic effects of *Gynura procumbens* (continued ...)

Compound	Chemical structure	Pharmacological benefit	Molecular activity	Reference
β-carotene		Anti-inflammation	Anti-inflammatory protection occurs by reducing IL-6, TNF-κ, PGE2 production, and COX-2 activity.	(Ju et al., 2022)

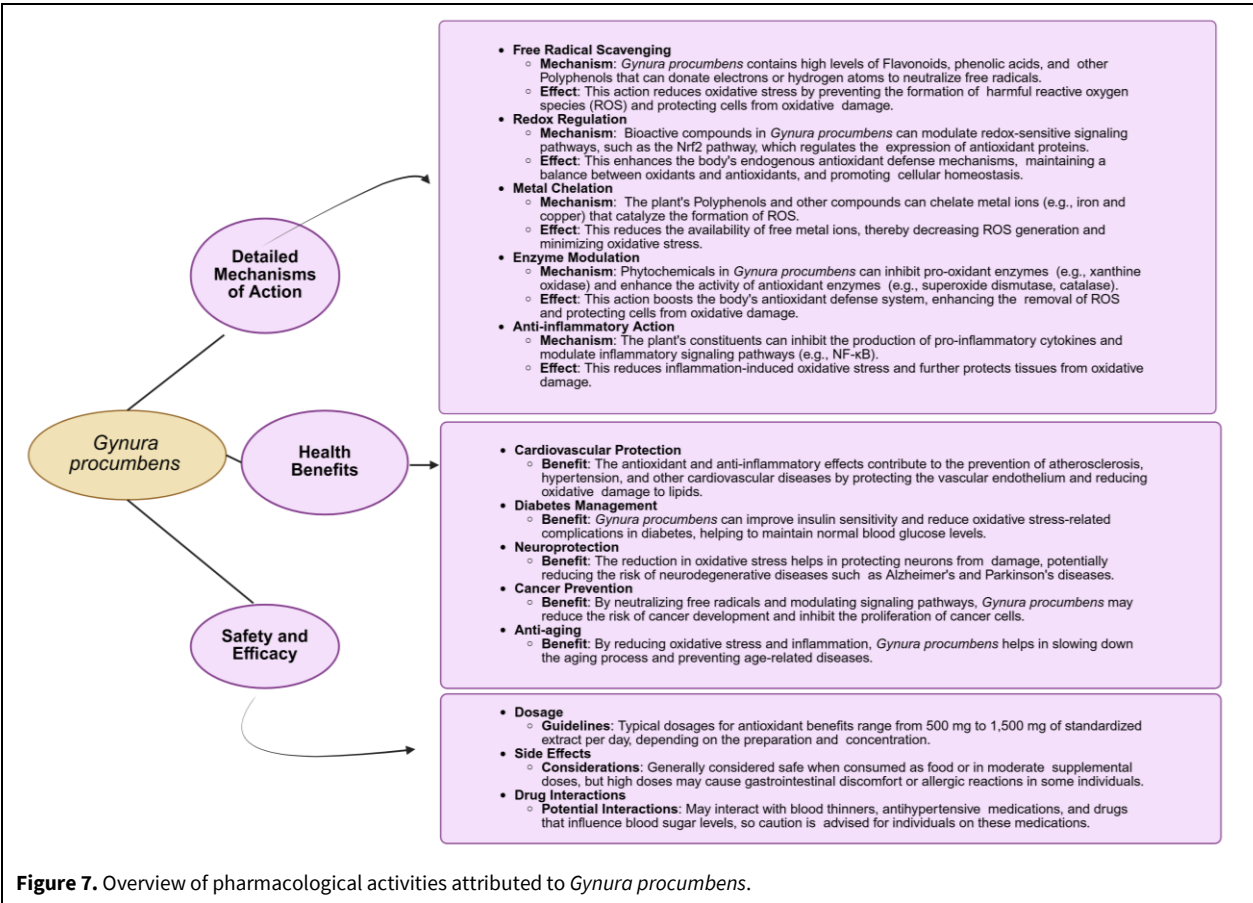


Figure 7. Overview of pharmacological activities attributed to *Gynura procumbens*.

Phytochemical investigations have revealed a broad spectrum of secondary metabolites, including flavonoids, saponins, polyphenols, terpenoids, steroids, and amino acids. These compounds are distributed across various extract fractions, with antioxidant activity confirmed by IC₅₀ values ranging between 10.3 and 53.8 mg/L depending on the solvent used (Mali, 2016; Selvam et al., 2012).

The analgesic potential of *P. serratifolia* has been validated through ethanol extract studies, which demonstrated significant inhibition of acetic acid-induced writhing in murine models. The observed effects were comparable to those of standard analgesics such as diclofenac (Barbosa et al., 2023; Lalrinzuali et al., 2016). Anti-inflammatory effects have also

been documented in carrageenan-induced paw edema and histamine-induced wheal models, where suppression of inflammation was attributed to cyclooxygenase-1 (COX-1) inhibition and membrane stabilization mechanisms (Kalam et al., 2022; Mansouri et al., 2015).

Antimicrobial and larvicidal activities are primarily associated with the plant's essential oils, particularly those rich in sesquiterpene hydrocarbons and oxygenated derivatives. These extracts have shown efficacy against *Aedes aegypti* and other pathogenic vectors (Silvério et al., 2020). Additionally, in adjuvant-induced arthritis models, ethanol extracts of *P. serratifolia* significantly attenuated paw edema, suggesting

promising anti-rheumatic properties (Rajendran and Krishnakumar, 2010).

Emerging studies have further explored the plant's therapeutic versatility through nanotechnology. Silver nanoparticles biosynthesized from *P. serratifolia* leaf extracts exhibited inhibitory effects on carbon tetrachloride-induced tumor formation in murine models, highlighting potential antitumor applications (Jo et al., 2021). Broader pharmacological actions reported in the literature include hepatoprotective, antidiabetic, antimicrobial, neuroprotective, and immunomodulatory activities (Arega et al., 2023).

Despite this wide pharmacological profile, research on *P. serratifolia* is constrained by several limitations. Variability in phytochemical composition across extracts, lack of standardization in dosage and administration, and absence of clinical trial data restrict the translation of findings into medical applications. Future research should emphasize pharmacokinetic evaluation, formulation development, chronic toxicity testing, and validation in human subjects. A visual synthesis of *P. serratifolia*'s pharmacological mechanisms is provided in Fig. 8, and a detailed list of its active compounds and associated bioactivities is presented in Table 8.

Styrax sumatranus J.J.Sm. (Styracaceae)

Styrax sumatranus (synonym of *Styrax paralleloneurus* Perkins), commonly referred to as *kemenyan toba*,

is endemic to the highland regions of North Sumatra and serves as the principal source of benzoin resin in Indonesia. Major production areas include North Tapanuli, Dairi, Toba Samosir, and Central Tapanuli Regencies, where the species grows in montane forest ecosystems (Rahmawaty et al., 2023). The resin exudate of *S. sumatranus* has long been valued for its aromatic, medicinal, and ritual significance.

Phytochemical analyses of the resin have identified various cinnamic acid derivatives, including cinnamyl cinnamate, benzyl benzoate, and styrene. These constituents have been implicated in its antioxidant and anti-inflammatory activity. *In vitro* assays demonstrated notable antioxidant effects, with IC₅₀ values below 16 mg/L for the *n*-hexane extract. Additionally, essential oils derived from this species contain fatty acid methyl esters such as methyl palmitate, methyl stearate, methyl oleate, and methyl-13,16-octadecadienoate, contributing to its therapeutic profile (Xia et al., 2023).

In silico docking studies identified cinnamyl cinnamate as a promising anti-inflammatory agent due to its favorable binding affinity (ΔG) with the chemokine receptor CXCR4, a molecular target implicated in inflammatory signaling (Elfiati et al., 2022). While such computational findings are encouraging, they remain hypothetical without corroborating *in vitro* or *in vivo* data.

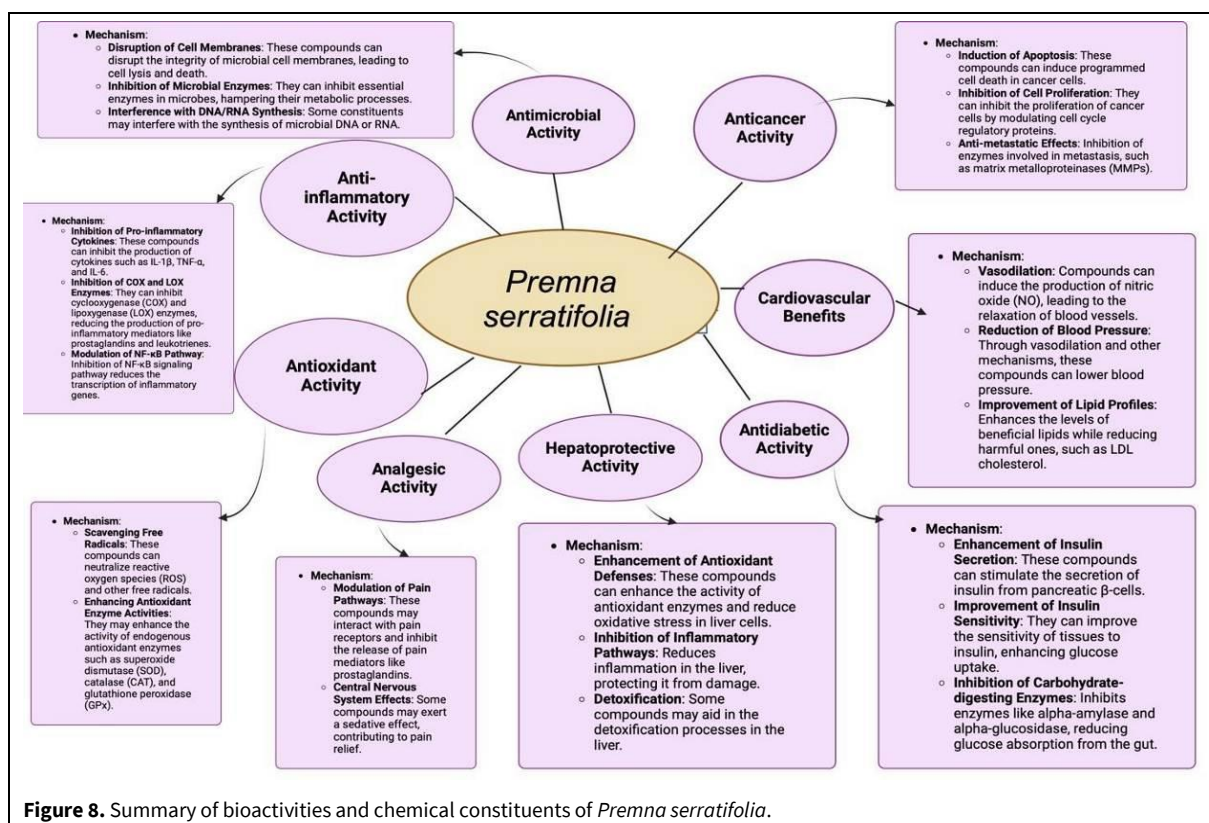
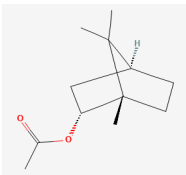
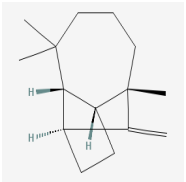
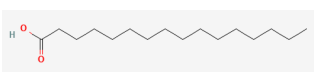
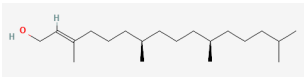
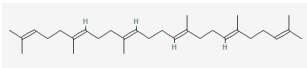
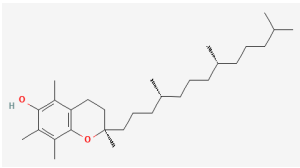


Table 8. Active phytoconstituents and pharmacological benefits of *Premna serratifolia*.

Compound	Chemical structure	Pharmacological benefit	Molecular activity	Reference
Bornyl acetate		Hypotensive effect	Systolic blood pressure decreases dose-dependently, with minimal effect on heart rate.	(Reule and Drawz, 2012)
Longifolene- (V4)		Anti-fungal activity	Some target compounds exhibited excellent <i>in vitro</i> antifungal activity.	(Zhao et al., 2021)
n- Hexadecanoic acid		Anti-inflammation	N-hexadecanoic acid inhibits phospholipase A2 <i>in silico</i> , showing anti-inflammatory potential.	(Aparna et al., 2012)
Phytol		Anti-tumor activity	N-hexadecanoic acid inhibits phospholipase A2, demonstrating anti-inflammatory potential.	(Zhang et al., 2023)
Squalene		Skin protection and antioxidant	Squalene resists peroxidation and quenches singlet oxygen, protecting skin from UV-induced lipid peroxidation and oxidative damage.	(Huang et al., 2009)
α-tocopherol		Antioxidant	α-Tocopherol reacts with lipid-peroxyl radicals to form α-tocopherylquinone, and in low oxygen, traps carbon-centered radicals, producing lipid-alkyl-α-tocopherols.	(Yamauchi, 2007)

Moreover, several endophytic fungi isolated from *S. sumatranus*, including *Trichoderma* sp., *Phyllosticta* sp., and *Neopestalotiopsis* sp., have demonstrated additional pharmacological activities, such as antioxidant effects, antimicrobial activity, and α-glucosidase inhibition, which may indirectly enhance the health-promoting value of the plant's derived products (Pedro et al., 2022). However, when individual compounds such as cinnamic acid and ethyl cinnamate were tested separately, their antioxidant activity was generally weak (IC₅₀ > 1000 mg/L), with the exception of gallic acid (IC₅₀ = 5.23 mg/L). This suggests that the therapeutic efficacy of the resin may rely heavily on compound synergy within the whole extract, rather than the potency of isolated constituents.

Despite these findings, considerable research gaps remain. The current evidence is primarily based on *in vitro* and *in silico* studies, with little to no *in vivo* validation. Moreover, variations in extraction protocols and a lack of standardized resin characterization hin-

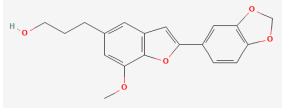
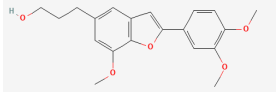
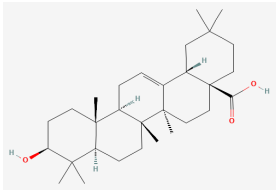
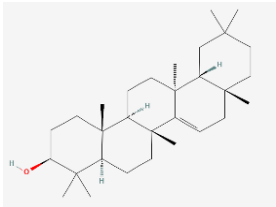
der reproducibility. Future studies should prioritize bioactivity-guided fractionation, controlled animal experiments, and toxicity assessments to validate traditional claims and explore clinical translation potential.

A pharmacological overview of *S. sumatranus* is illustrated in Fig. 9, and detailed information on its active compounds is presented in Table 9.

***Saurauia vulcani* Korth. (Actinidiaceae)**

Saurauia vulcani, locally known as *Pirdot*, is indigenous to the Lake Toba highlands in North Sumatra and holds significant ethnomedicinal value, particularly for its antidiabetic and immunomodulatory applications (Grass et al., 2020; Lubis et al., 2022). The plant is commonly prepared as an herbal decoction and is used extensively across local communities for managing metabolic disorders.

Table 9. Identified chemical compounds in *Styrax sumatranus* and associated pharmacological activities.

Compound	Chemical structure	Pharmacological benefit	Molecular activity	Reference
Egonol		Antifungal activity	Neither VP-16 nor H ₂ O ₂ alone showed genotoxic effects, but SCHE extract reduced micronuclei frequency induced by both.	(Acésio et al., 2016)
Homoegonol		Anti-inflammation	BALF, AHR, and serum Th2 cytokines were lower, with histology showing reduced iNOS and MMP-9 expression, easing airway inflammation and mucus overproduction in OVA-induced lesions.	(Shin et al., 2014)
Oleanolic acid		Anti-inflammation	The amino acid sequences of CXCR4 suggest its high potential as an anti-inflammatory drug.	(Shim et al., 2009)
Taraxerol		Antioxidant activity	Inhibition of COX-2, iNOS, and IL-1 β production occurs by blocking NF- κ B and MAPK activity in Cr (VI)-induced BNL CL.2 cells.	(Xiao et al., 2020)

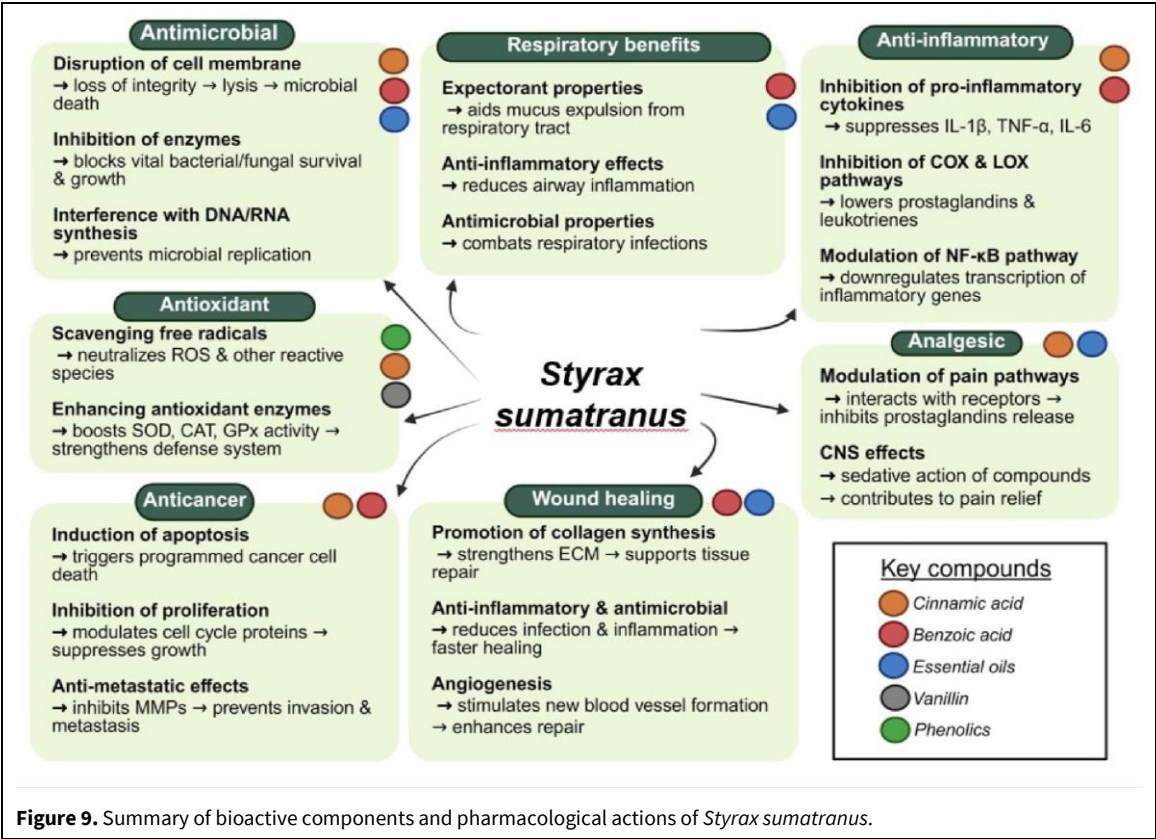


Figure 9. Summary of bioactive components and pharmacological actions of *Styrax sumatranus*.

Phytochemical analyses have revealed the presence of a broad spectrum of secondary metabolites, including alkaloids, flavonoids, saponins, triterpenoids, and tannins, which likely contribute to its di-

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verse pharmacological effects (Sitorus, 2015). Two major triterpenoid compounds, 3-hydroxy-olean-12-en-28-oic acid and 3,19-dihydroxyurs-12-en-28-oic acid, have been isolated from the leaves, both of which exhibit anti-inflammatory and antioxidant activities, as well as hepatoprotective potential (Masyita et al., 2022; Rosidah et al., 2021).

Toxicological assessments have supported the plant’s relative safety, with subchronic toxicity studies reporting LD₅₀ values ranging from 225.77 mg/L to 715.28 mg/L, depending on the extract type. No significant adverse effects on blood parameters or organ histology were reported in rodent models, supporting its traditional usage within recommended dosages.

The antidiabetic effects of *S. vulcani* have been substantiated in streptozotocin (STZ)-induced diabetic rat models. Reported outcomes include significant reductions in blood glucose levels, improvement in antioxidant enzyme profiles (e.g., SOD and CAT), and accelerated wound healing, indicating a systemic effect on both glycemic control and tissue regeneration (Spampinato et al., 2020). These findings align with the plant’s traditional use in managing metabolic syndromes.

Despite encouraging preclinical results, notable research gaps remain. No clinical trials or human ob-

servational studies have been conducted to confirm efficacy or determine optimal dosage regimens. Moreover, pharmacokinetic profiles, compound bioavailability, and formulation stability have not been evaluated. Standardization of extraction methods and compound quantification remains a crucial prerequisite for translational research.

Given its abundant availability and strong traditional support, *S. vulcani* represents a promising candidate for further development as a natural therapeutic agent, particularly in the fields of diabetes management and liver protection. A concise visual representation of its pharmacological activities is provided in Fig. 10, while a comprehensive summary of its bioactive constituents and mechanisms is presented in Table 10.

Vitis gracilis Wall. (Vitaceae)

Vitis gracilis, synonym of *Ampelocissus gracilis* (Wall.) Planch., locally known as *gagatan harimau*, is a lesser-known medicinal plant from North Sumatra traditionally utilized to improve male reproductive health and physical stamina. This ethnobotanical application is reflected in its usage among indigenous communities as a tonic to enhance fertility and sexual vitality (Ilyas et al., 2023).

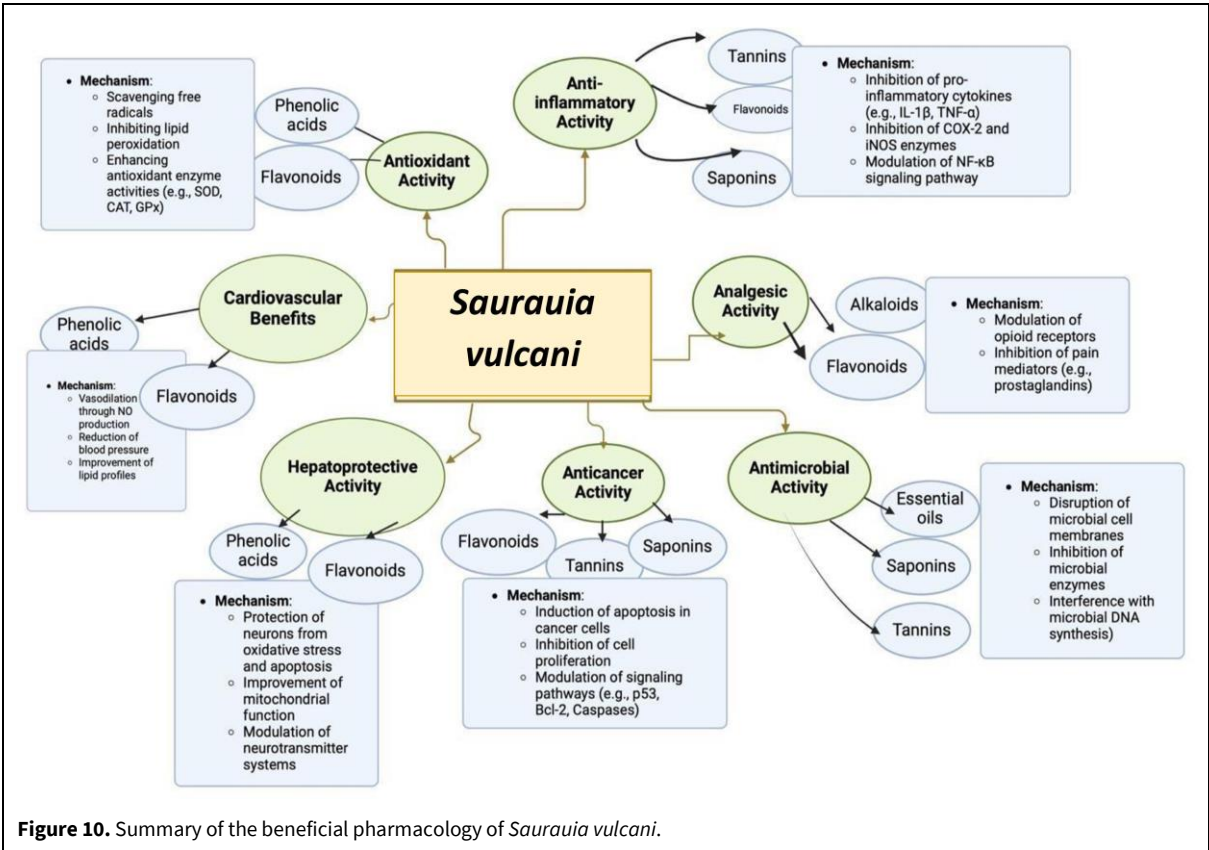
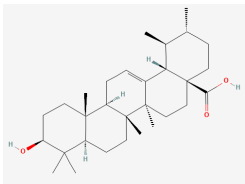
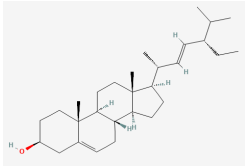
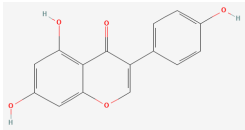
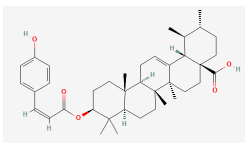
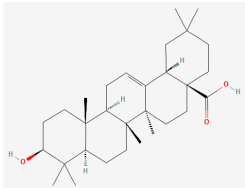
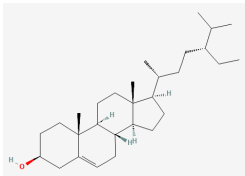
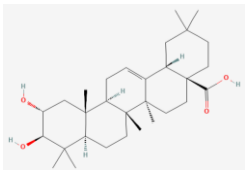
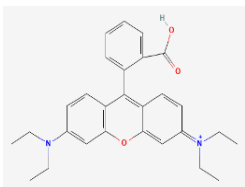
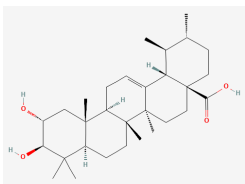


Table 10. The compounds and pharmacological molecular activity of *Saurauia vulcani*.

Compound	Chemical structure	Pharmacological benefit	Molecular activity	Reference
Ursolic acid		Immunotherapeutic agents	Genes like TNF- α , IL-6, COX-2, IL-1 β , and iNOS influence macrophage function and inflammation.	(Parisi et al., 2018)
Stigmasterol		Immunostimulant	Antigen lymphocyte extract enhances erythrocyte count and blood cell levels, and results in a histologically healthy spleen.	(Li et al., 2021)
Genistein		Immunostimulant	The extract boosts lymphocyte count, reduces IL-2 production, and protects liver tissue.	(Medoro et al., 2023)
cis-3-O-p-hydroxycinnamoyl		Anti-diabetic	The analysis showed a significant decrease in blood glucose and HbA1c levels, alongside increased SOD levels and insulin secretion ($p<0.05$).	(Pérez Gutiérrez et al., 2021)
Oleanolic acid		Hepatoprotective	The therapy group showed a significant reduction in SGOT and SGPT values.	(Giannini et al., 2005)
β -sitosterol		Anticancer	The ethyl acetate-based prickly leaf extract showed significant cytotoxic effects on WiDr cancer cells.	(Abdul Wahab et al., 2018)
maslinic acid		Anticancer	Bioactive compounds from <i>S. vulcani</i> have higher binding affinity to AKT1, GLUT1, and HIF-1 γ than doxorubicin.	(Ghosh et al., 2022)
Rhodamine B		Anticancer activity	Rhodamine B from this plant identified fifteen essential genes, including TP53, AKT1, UBC, VEGFA, BCL2, PTGS2, HIF1A, CYP3A4, NOS3, CYP7A1, ALB, SRC, MTOR, CTNNB1, and EGFR.	(Heck-Swain et al., 2022)
Corosolic acid		Antibacterial activity	Corosolic acid enhanced cefotaxime's antibacterial activity, creating a synergistic effect and increasing its drug-resistance index (DRI) against all <i>S. aureus</i> strains tested.	(Sineliuss et al., 2023)

Phytochemical analyses have identified over 30 bioactive constituents, including triterpenoids (e.g., isomasticadienonic acid, disolentin B), fatty acids (e.g., linolenic acid, quinoprene), xanthones (e.g., scor-techinone B), glycerolipids, and monoterpenoids such as terpinyl isobutyrate. These compounds are implicated in multiple biological pathways relevant to antioxidant, anti-inflammatory, and hormonal regulation.

Experimental studies support the antioxidant and anti-inflammatory potential of *V. gracilis*, with evidence indicating downregulation of pro-inflammatory cytokines such as TNF- α and upregulation of anti-inflammatory markers including IL-10 (Wasnis et al., 2022). The plant has also demonstrated beneficial effects on reproductive hormone regulation, with increased testosterone levels, improved histological architecture of testicular tissue, and modulation of caspase-3 and IL-6 expression, indicating a role in counteracting inflammation-induced infertility.

In addition to reproductive health benefits, neuro-protective activity has also been reported. Extracts of *V. gracilis* inhibited cytochrome c expression, reduced oxidative stress, and improved cognitive markers in relevant models (Balea et al., 2020). These findings suggest potential therapeutic applications in preventing neurodegenerative damage and enhancing memory function.

Despite these promising biological effects, the current body of pharmacological evidence for *V. gracilis* remains preliminary. Most studies have been limited to animal models and *in vitro* systems, with no clinical data or long-term toxicity assessments available. Moreover, detailed mechanistic investigations, dose-response evaluations, and standardization of extract composition are still lacking. Further research should focus on bioactivity-guided fractionation, formulation development, and *in vivo* validation in reproductive and neurological models. A visual summary of the pharmacological mechanisms associated with *Vitis gracilis* is provided in Fig. 11, and compound-specific pharmacological data are detailed in Table 11.

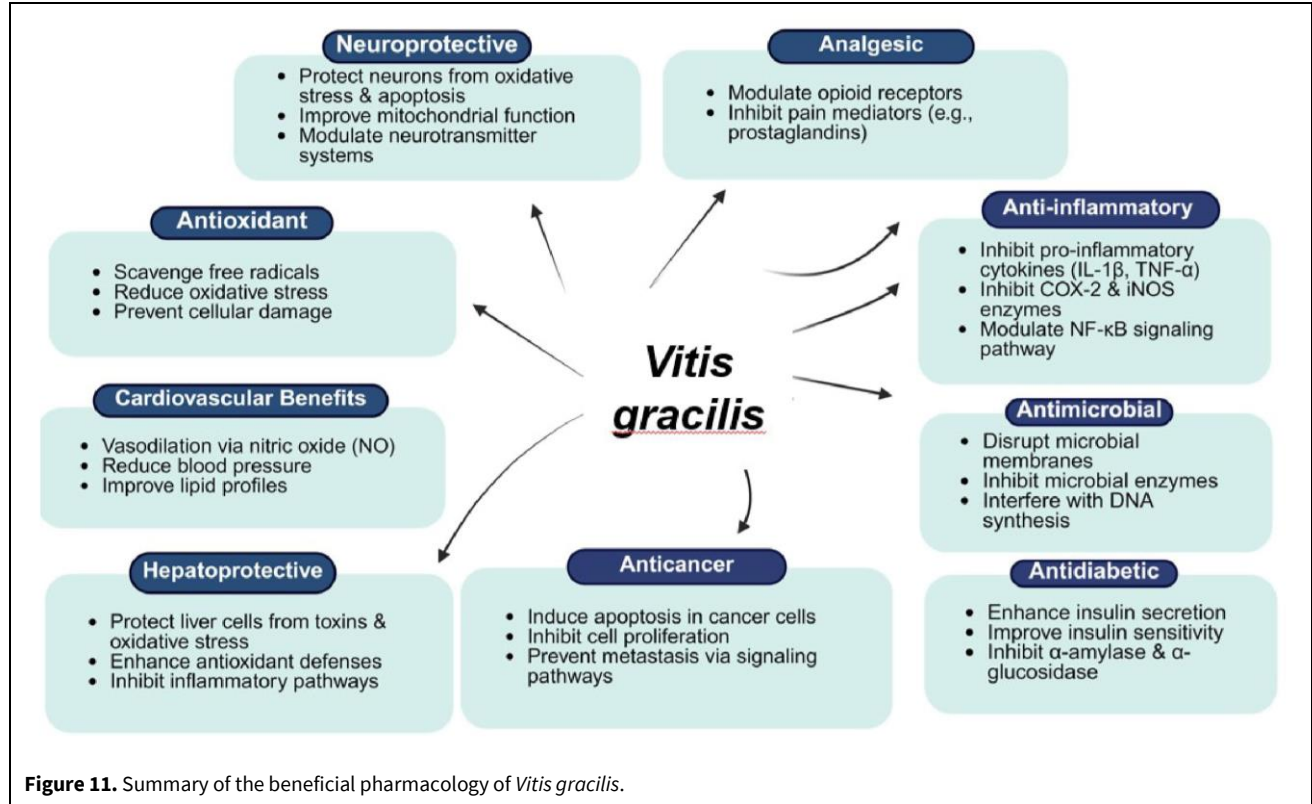


Figure 11. Summary of the beneficial pharmacology of *Vitis gracilis*.

Table 11. The compounds and pharmacological molecular activity of *Vitis gracilis*.

Compound	Chemical structure	Pharmacological benefit	Molecular activity	Reference
Arbutin		Anti-inflammation	<i>V. gracilis</i> decoction may protect the testis and reduce sexual behavior in diabetic rats.	(Ding et al., 2016)
3',4'-dimethoxy-alpha-naphthoflavone		Anti-apoptosis	Excessive swimming increases TNF- α levels and lowers IL-10, but <i>V. gracilis</i> can prevent apoptosis by affecting the intrinsic pathway and the histological expression of cytochrome c.	(Santoso et al., 2023)
Phenyl 2-hydroxybenzoate, phenyl salicylate		Anti-inflammation	<i>V. gracilis</i> at 125 mg/kg BW improves sperm concentration by lowering caspase-3 and IL-6 levels and reducing inflammation.	(Abdel- Latif et al., 2022)
Lauric acid		Anti-apoptosis	<i>V. gracilis</i> reduces cell death via cytochrome c and enhances brain and hippocampal histology through exercise.	(Karelina et al., 2021)
Norethindrone acetate		Antioxidant	The medicine works by inhibiting endometrial proliferation and modulating hormonal fluctuations to restore regular menstrual cycles.	(Hu et al., 2023)

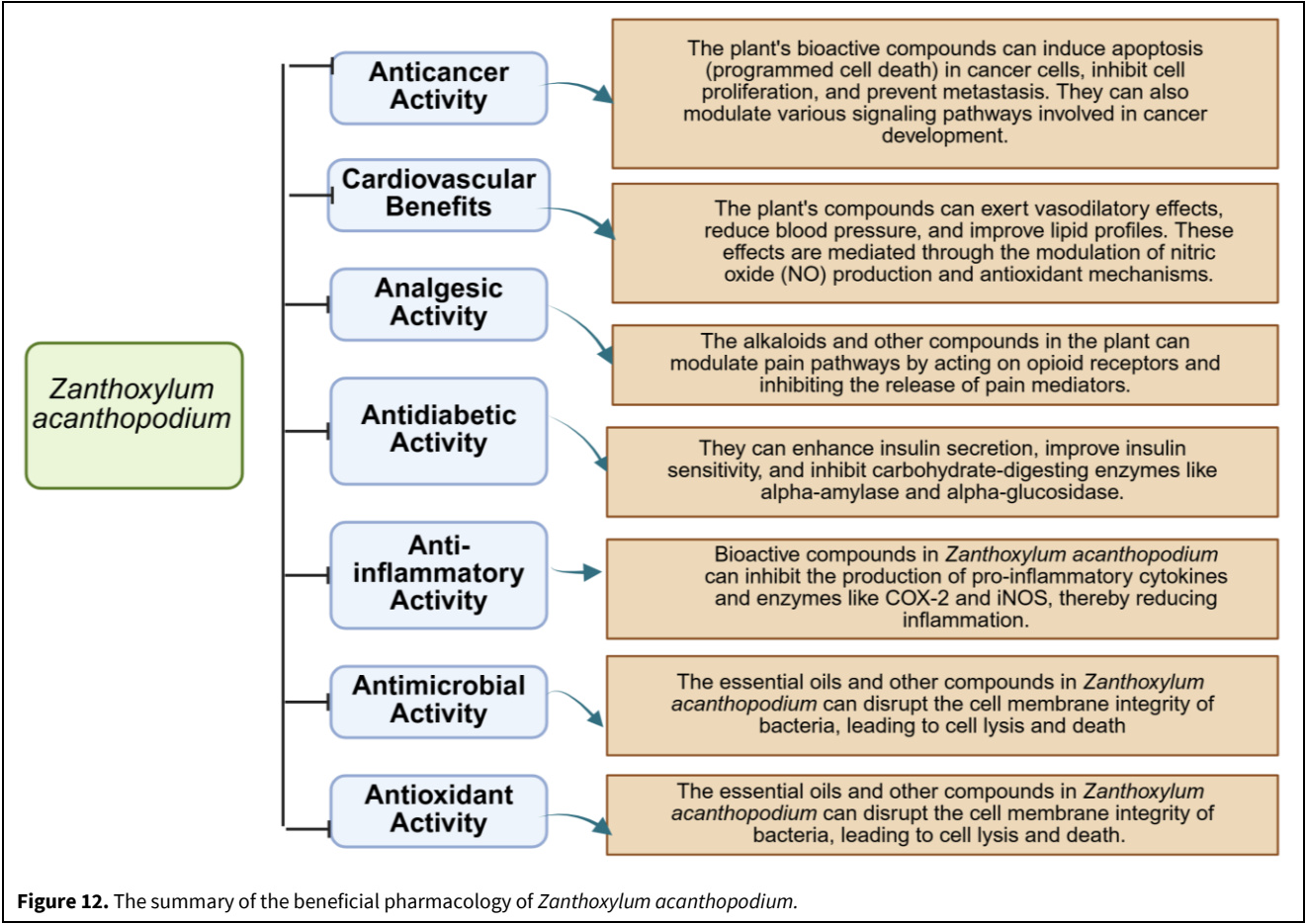
***Zanthoxylum acanthopodium* DC. (Rutaceae)**

Zanthoxylum acanthopodium, locally referred to as *andaliman*, is a culturally significant culinary and medicinal plant, particularly among the Batak communities in North Sumatra. Beyond its distinctive use as a spice, *Z. acanthopodium* has garnered attention for its broad-spectrum pharmacological properties, supported by a diverse array of bioactive compounds, including essential oils (e.g., citronellal, geraniol, linalool), flavonoids, saponins, and terpenoids (Kintamani et al., 2023).

Antibacterial activity has been confirmed through *in vitro* assays, with inhibition zones exceeding 20 mm against *Staphylococcus aureus* and *Salmonella typhimurium*, demonstrating comparable or superior efficacy to standard antimicrobial agents. These effects are attributed to the presence of synergistic secondary metabolites that disrupt microbial cell membranes and suppress pathogen viability.

The plant also exhibits anti-inflammatory activity, primarily through downregulation of pro-inflammatory mediators. In lipopolysaccharide (LPS)-stimulated macrophage models, *Z. acanthopodium* extract significantly reduced the expression of TNF- α , IL-6, and COX-2, both at the protein and gene expression levels, suggesting involvement in NF- κ B signaling inhibition and modulation of the innate immune response.

Anticancer properties have been explored in benzo[a]pyrene-induced carcinogenesis models. *Z. acanthopodium* extract reduced the expression of vascular endothelial growth factor (VEGF) and TGF- β 1, along with matrix metalloproteinase-9 (MMP-9) suppression, contributing to anti-angiogenic and anti-metastatic effects (Setiadi et al., 2022). In addition, significant hepatoprotective outcomes were observed, indicating its protective role against chemical-induced oxidative damage and inflammation in liver tissues.



Notably, nano-herbal formulations combining *Z. acanthopodium* with *R. tomentosa* have shown enhanced efficacy in preclinical models. These combinations improved wound healing, potentiated antioxidant enzyme activity, and modulated apoptosis-related pathways, including cytochrome c and FasL regulation, highlighting potential for synergistic therapeutic application (Ilyas et al., 2021; Vitale et al., 2022).

Despite compelling preclinical evidence, the absence of clinical validation, limited pharmacokinetic data, and lack of standardized extract formulations remain major limitations. Further investigations should focus on dose-response relationships, bioavailability, and long-term toxicity assessments, particularly in human trials. Future development of *Z. acanthopodium*-derived products should also address scalability and sustainability in harvesting, considering its increasing use in both culinary and medicinal contexts. An integrated overview of the pharmacological mechanisms of *Z. acanthopodium* is presented in Fig. 12, and a comprehensive summary of its bioactive

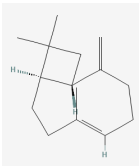
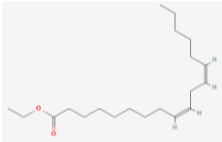
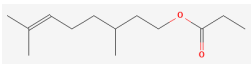
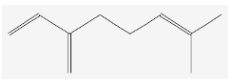
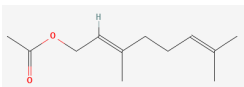
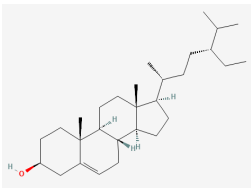
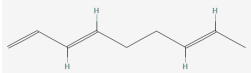
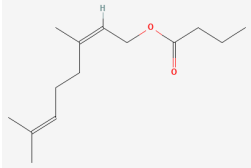
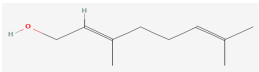
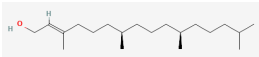
compounds and molecular activities is provided in Table 12.

Cross-species insights and limitations

The reviewed medicinal plants from North Sumatra demonstrate a broad spectrum of pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, anticancer, hepatoprotective, antidiabetic, and immunomodulatory effects. Despite their botanical diversity, several shared bioactivities and molecular mechanisms were consistently observed across species.

ROS modulation emerged as a common therapeutic pathway, primarily driven by flavonoids, phenolic acids, and triterpenoids found in species such as *P. emblica*, *G. procumbens*, and *R. tomentosa*. These antioxidants contributed to reduced oxidative stress, lipid peroxidation, and cellular damage in various experimental models. Furthermore, anti-inflammatory pathways, particularly COX-2 inhibition, NF-κB suppression, and cytokine downregulation (e.g., TNF-α, IL-6), were prominent in extracts from *P. serratifolia*, *S. sumatranus*, and *Z. acanthopodium*.

Table 12. The compounds and pharmacological molecular activity of *Zanthoxylum acanthopodium*.

Compound	Chemical structure	Pharmacological benefit	Molecular activity	Reference
E-β-caryophyllene		Anti-cancer	<i>Z. acanthopodium</i> fruit ethanolic extract reduces TNF-α, COX-2, and MMP-9 in LPS-treated macrophages and downregulates TNF-α, IL-6, iNOS, COX-2, and MMP-9 expression.	(Adrian et al., 2023)
Ethyl linoleate		Anti-cancer	Serum and cervical cancer histology showed significant reductions in IL-1β, TGF-β1, and VEGFR1 expression.	(Li et al., 2018)
Citronellyl propionate		Anti-cancer	<i>Z. acanthopodium</i> supports IL-10 in reducing aberrant cell growth, inhibiting inflammation, and suppressing tumor growth.	(Iyer and Cheng, 2012)
Myrcene		Anti-inflammation	Nanoherbal <i>Z. acanthopodium</i> reduces NOTCH1 expression in human placental trophoblasts within 30 minutes and Hes1 within 16 hours.	(Iyer and Cheng, 2012)
Geranyl acetate		Anti-cancer	In cervical cancer rats, the methanolic extract increased PI3K, induced cytochrome c, and suppressed Wnt to trigger apoptosis.	(Ilyas et al., 2022)
β-sitosterol		Antipreeclampsia	Hypertensive pregnancy in rats increased cytochrome c and FasL levels in the labyrinth, basal, and yolk sac zones.	(Situmorang et al., 2021)
5- (propenyl 2)-1,3,7-nonatriene		Anti-cancer	The IC50 was determined for T47D, 4T1, MCF-7, HeLa, and Raji cell lines.	(Solárová et al., 2020)
Neryl butanoate		Anti-inflammation	The compound inhibits proliferation, induces cell cycle arrest, and reduces COX-2 and VEGFR expression.	(Rauf et al., 2024)
Geraniol		Anti-cancer	Reduces tumor size, packed cell volume, and cell viability while improving hematological parameters.	(Aynalem et al., 2022)
Phytol		Cardioprotective activity	Reduces CtnT and CK-MB levels, indicating lower cardiotoxicity and histopathological changes.	(Yang et al., 2018)

Antimicrobial effects were widely reported, often involving essential oil constituents such as linalool, citronellal, and β-caryophyllene. These compounds acted through mechanisms such as membrane disruption, biofilm inhibition, and virulence factor suppression,

although most evidence remains confined to *in vitro* studies.

Anticancer activity was linked to apoptosis induction, cell cycle arrest, and inhibition of angiogenesis, with plants like *C. odorata*, *R. tomentosa*, and *Z. acanthopodium* demonstrating notable cytotoxicity against

multiple cancer cell lines. However, across all species, anticancer findings were derived exclusively from preclinical models, limiting clinical translatability.

In terms of cross-species limitations, several challenges were consistently observed: Heterogeneity in experimental designs, including variable extraction solvents, inconsistent dosing regimens, and diverse outcome measures, hampered direct comparison and meta-analysis; lack of standardized extract formulations made reproducibility across studies difficult, while only a minority employed bioactivity-guided fractionation or compound isolation; safety profiles, toxicological evaluations, and pharmacokinetic parameters were underreported or absent in most studies; only a few addressed subchronic toxicity or provided LD₅₀ estimates; and geographical and publication biases may have influenced the literature landscape, as most studies focused on ethnomedicinal plants already popular in local markets, potentially excluding other less-documented but therapeutically valuable species.

While the evidence supports traditional claims for many of these plants, translational gaps remain substantial. No clinical trials were identified for any of the ten species reviewed, and few studies employed validated human-relevant models. Additionally, bioavailability, herb-drug interaction, and long-term

safety data are urgently needed to bridge the gap between ethnopharmacology and evidence-based medicine.

To advance the field, future research should prioritize. For example: Standardization of extraction and testing protocols to improve inter-study comparability; bioactivity-guided isolation to identify and validate key therapeutic compounds; *in vivo* and clinical validation, especially for plants with strong preclinical profiles such as *G. procumbens*, *P. emblica*, and *R. tomentosa*; and development of a regional ethnopharmacological database to document local knowledge, guide research prioritization, and support conservation of medicinal plant biodiversity.

Furthermore, several molecular pharmacology studies have investigated the bioactive pathways through which these species exert their effects. Across different plant species, converging mechanisms were observed, including mitochondrial-mediated apoptosis, inflammatory cytokine suppression, and modulation of oxidative stress signaling.

A synthesis of these mechanisms at the protein and gene expression levels is presented in Table 13. These insights not only support traditional usage but also provide a mechanistic rationale for future drug development.

Table 13. Molecular targets and pharmacological mechanisms identified in recent studies on ten medicinal plants from North Sumatra.

No	Plant name	Molecular activities	References
1	<i>Arenga pinnata</i>	↑ Sirt1, ↓ p53; activates p38 & JNK1 MAPK; ↓ IL-1β, TNF-α, PGE ₂ , IL-6; anti-tumor via diterpenes	(Liu et al., 2017; Wu et al., 2019; Yi and Luo, 2010)
2	<i>Rhodomyrtus tomentosa</i>	Inhibits STAT3, ATM-Chk2-p53-p21 pathway; ↓ HIF-1α, IL-1β, TNF-α, MMP-9; ↑ HSP27/70/90; anticancer	(Situmorang et al., 2022; Zhang et al., 2020)
3	<i>Cananga odorata</i>	Inhibits α-amylase; active compounds (e.g., linalool) show antibacterial, insecticidal effects	Juliastuti et al., 2017; Rybak and Wojdyło, 2023)
4	<i>Phyllanthus emblica</i>	Induces G2/M arrest; ↑ Bax, caspase, Fas; ↓ Bcl-2, TNF-α, IL-6; modulates GSK-3β/Akt & lipase	Gul et al., 2022; Rizvi et al., 2017)
5	<i>Gynura procumbens</i>	↓ CYP3A4/1A2/1A1; activates SREBP-1c; ↑ glucose uptake; modulates MAPK and Ca ²⁺ influx	Fang et al., 2000; Li et al., 2015; Tan et al., 2016)
6	<i>Premna serratifolia</i>	Inhibits COX-I; strong cytotoxicity on HepG2/MCF7; antioxidant via radical scavenging; tumor-suppressive	Ahmad et al., 2023; Singh et al., 2021)
7	<i>Styrax sumatranus</i>	Inhibits COX-2, iNOS, IL-1β via NF-κB/MAPK; cinnamyl cinnamate binds CXCR4	Ju et al., 2022; Park et al., 2023)
8	<i>Saurauia vulcani</i>	Inhibits TNF-α, IL-6, COX-2, iNOS; triterpenoids bind COX-2 and TNF-α with high affinity	Lubis et al., 2022; Sinaga et al., 2021)
9	<i>Vitis gracilis</i>	↓ Caspase-3, IL-6; ↑ IL-10; modulates cytochrome c; protects reproductive & neural tissue	Chao et al., 2022; Midoen et al., 2023)
10	<i>Zanthoxylum acanthopodium</i>	↓ TNF-α, IL-6, COX-2, MMP-9; modulates VEGF, TGF-β1, PI3K, NOTCH1, and Wnt signaling	Lelyana et al., 2021; Simanullang et al., 2022)

CONCLUSION

The medicinal plants reviewed herein exhibit diverse pharmacological activities, antioxidant, anti-inflammatory, antimicrobial, anticancer, and immunomodulatory, that support their ethnomedicinal use in North Sumatra. These findings highlight the relevance of traditional knowledge as a valuable foundation for modern drug discovery.

Despite promising preclinical results, translational progress remains limited. Many studies lack standardization in extraction methods, dosage, and safety profiling. Moreover, the absence of clinical trials and pharmacokinetic data limits the applicability of current evidence in therapeutic settings. Future research should focus on bioactivity-guided fractionation, formulation development, and human trials to validate efficacy and safety. The integration of these medicinal plants into evidence-based complementary medicine frameworks may contribute to more accessible, culturally congruent, and sustainable healthcare solutions in Indonesia and beyond.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

- Abd Hamid HAZR, Mutazah SSZR, Yusoff MM (2017) *Rhodomyrtus tomentosa*: A phytochemical and pharmacological review. Asian J Pharm Clin Res 10(1): 10–16. <http://dx.doi.org/10.22159/ajpcr.2017.v10i1.12773>
- Abdel-Latif R, Fathy M, Anwar HA, Naseem M, Dandekar T., Othman EM (2022) Cisplatin-induced reproductive toxicity and oxidative stress: Ameliorative effect of kinetin. Antioxidants 11(5): 863. <https://doi.org/10.3390/antiox11050863>
- Abdul Wahab SM, Jantan I, Haque MA, Arshad L (2018) Exploring the leaves of *Annona muricata* L. as a source of potential anti-inflammatory and anticancer agents. Front Pharmacol 9: 661. <https://doi.org/10.3389/fphar.2018.00661>
- Acésio NO, de Oliveira PF, Mastrocola DFP, Lima IM de S, Munari CC, Sato VLFL, Souza AAS, Flauzino LGB, Cunha WR, Tavares DC (2016) Modulatory effect of betulinic acid on the genotoxicity induced by different mutagens in V79 cells. Evid Based Complement Alternat Med 2016: 8942730. <https://doi.org/10.1155/2016/8942730>
- Adrian, Syahputra RA, Juwita NA, Astyka R, Lubis MF (2023) Andaliman (*Zanthoxylum acanthopodium* DC.) a herbal medicine from North Sumatera, Indonesia: Phytochemical and pharmacological review. Heliyon 9(5): e16159. <https://doi.org/10.1016/j.heliyon.2023.e16159>
- Ahmad K, Asif HM, Afzal T, Khan MA, Younus M, Khurshid U, Safdar M, Saifulah S, Ahmad B, Sufyan A, Ansari SA,

Alkahtani HM, Ansari IA (2023) Green synthesis and characterization of silver nanoparticles through the *Piper cubeba* ethanolic extract and their enzyme inhibitory activities. Front Chem 11: 1065986. <https://doi.org/10.3389/fchem.2023.1065986>

- Ahmad Nazri KA, Fauzi NM, Buang F, Mohd Saad QH, Husain K, Jantan I, Jubri Z (2019) *Gynura procumbens* standardised extract reduces cholesterol levels and modulates oxidative status in postmenopausal rats fed with cholesterol diet enriched with repeatedly heated palm oil. Evid Based Complement Alternat Med 2019: 7246756. <https://doi.org/10.1155/2019/7246756>
- Akhtar MA (2022) Anti-inflammatory medicinal plants of Bangladesh – A pharmacological evaluation. Front Pharmacol 13: 809324. <https://doi.org/10.3389/fphar.2022.809324>
- Alfheaid HA, Alhowail AA, Ahmed F, Zaki AKA, Alkhalidy A (2023) Effect of various intermittent fasting protocols on hyperglycemia-induced cognitive dysfunction in rats. Brain Sci 13(2): 165. <https://doi.org/10.3390/brainsci13020165>
- Andadari L, Yuniati D, Supriyanto B, Murniati, Suharti S, Widarti A, Steven E, Sadapotto A, Winarno B, Minarningsih, Agustarini R, Muin N, Isnain W, Heryati Y, Adalina Y, Yeny I, Dewi R, Nurlia A, Riendriasari SD, Maharani KE, Nugraha LM, Narendra BH (2022) Lens on tropical sericulture development in Indonesia: Recent status and future directions for industry and social forestry. Insects 13(10): 913. <https://doi.org/10.3390/insects13100913>
- Aparna V, Dileep KV, Mandal PK, Karthe P, Sadasivan C, Haridas M (2012) Anti-inflammatory property of n-hexadecanoic acid: structural evidence and kinetic assessment. Chem Biol Drug Des 80(3): 434–439. <https://doi.org/10.1111/j.1747-0285.2012.01418.x>
- Arega M, Nardos A, Debella A, Dereje B, Terefe L, Abebe A (2023) Evaluation of anti-Inflammatory activity of the methanol extracts of *Premna schimperi* Engl (Lamiaceae) leaves in rats. J Exp Pharmacol 15: 437–447. <https://doi.org/10.2147/JEP.S432615>
- Asazawa K, Kato Y, Yamaguchi A, Inoue A (2017) The effect of aromatherapy treatment on fatigue and relaxation for mothers during the early puerperal period in Japan: A pilot study. Int J Community Based Nurs Midwifery 5(4): 365–375. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5635556/>
- Asmilia N, Fahrimal Y, Abrar M, Rinidar R (2020) Chemical compounds of malacca leaf (*Phyllanthus emblica*) after triple extraction with n-hexane, ethyl acetate, and ethanol. Sci World J 2020: 2739056. <https://doi.org/10.1155/2020/2739056>
- Aynalem M, Adem N, Wendesson F, Misganaw B, Mintesnot S, Godo N, Getawa S, Adane T, Woldu B, Shiferaw E (2022) Hematological abnormalities before and after initiation of cancer treatment among breast cancer patients attending at the University of Gondar comprehensive specialized hospital cancer treatment center. PloS One 17(8): e0271895. <https://doi.org/10.1371/journal.pone.0271895>
- Bahtiar A, Vichitphan K, Han J (2017) Leguminous plants in the Indonesian archipelago: Traditional uses and secondary metabolites. Nat Prod Commun 12(3): 461–472. <https://doi.org/10.1177/1934578X1701200338>
- Balea SS, Părvu AE, Părvu M, Vlase L, Dehelean CA, Pop TI (2020) Antioxidant, anti-inflammatory and antiproliferative effects of the *Vitis vinifera* L. var. Fetească Neagră and Pinot Noir pomace extracts. Front Pharmacol 11: 990. <https://doi.org/10.3389/fphar.2020.00990>
- Barbosa M de O, Wilairatana P, Leite GM de L, Delmondes G de A, Silva LYS da, Júnior SCA, Dantas LBR, Bezerra DS, Beltrão ICSL de, Dias D de Q, Ribeiro-Filho J, Felipe CFB, Coutinho HDM, Menezes IRA, de Kerntopf Mendonça MR (2023) *Plectranthus* species with anti-inflammatory and analgesic

- potential: A systematic review on ethnobotanical and pharmacological findings. *Molecules* 28(15): 5653. <https://doi.org/10.3390/molecules28155653>
- Benassi A, Doria F, Pirota V (2020) Groundbreaking anticancer activity of highly diversified oxadiazol scaffolds. *Int J Mol Sci* 21(22): 8692. <https://doi.org/10.3390/ijms21228692>
- Caloprisco E, Fourneron JD, Faure R, Demarne FE (2002) Unusual lactones from *Cananga odorata* (Annonaceae). *J Agric Food Chem* 50(1): 78–80. <https://doi.org/10.1021/jf0105079>
- Calvaruso M, Pucci G, Musso R, Bravatà V, Cammarata FP, Russo G, Forte GI, Minafra L (2019) Nutraceutical compounds as sensitizers for cancer treatment in radiation therapy. *Int J Mol Sci* 20(21): 5267. <https://doi.org/10.3390/ijms20215267>
- Cecerska-Heryć E, Krauze K, Szczęśniak A, Goryniak-Mikołajczyk A, Serwin N, Śleboda-Taront D, Jacek R, Heryć R, Michalczyk A, Dołęgowska B (2022) Activity of erythrocyte antioxidant enzymes in healthy women depends on age, BMI, physical activity, and diet. *J Health Popul Nutr* 41(1): 35. <https://doi.org/10.1186/s41043-022-00311-z>
- Chaikul P, Kanlayavattanukul M, Somkumnerd J, Lourith N (2021) *Phyllanthus emblica* L. (amla) branch: A safe and effective ingredient against skin aging. *J Tradit Complement Med* 11(5): 390–399. <https://doi.org/10.1016/j.jtcme.2021.02.004>
- Chang TS, Chao SY, Ding HY (2012) Melanogenesis inhibition by homoisoflavavone sappanone A from *Caesalpinia sappan*. *Int J Mol Sci* 13(8): 10359–10367. <https://doi.org/10.3390/ijms130810359>
- Chao HH, Zhang Y, Dong PY, Gurunathan S, Zhang XF (2022) Comprehensive review on the positive and negative effects of various important regulators on male spermatogenesis and fertility. *Front Nutr* 9: 1063510. <https://doi.org/10.3389/fnut.2022.1063510>
- Chen Q, Zhao X, Lu T, Yang Y, Hong Y, Tian M, Zhou Y (2021) Chemical composition, antibacterial, and anti-inflammatory activities of essential oils from flower, leaf, and stem of *Rhynchanthus beesianus*. *BioMed Res Int* 2021: 5562461. <https://doi.org/10.1155/2021/5562461>
- da Silva MG, Barbosa SLF, Silva DS, Bezerra IBM, Alves Bezerra É, Coelho AG, Pinheiro da Silva Moraes IC, Rezende-Júnior LM, do Carmo IS, Lima-Neto J de S, Comerma-Steffensen SG, Citó AM das GL, Arcanjo DDR (2022) Bioactive natural products against systemic arterial hypertension: A past 20-year systematic and prospective review. *Evid Based Complement Alternat Med* 2022: 8499625. <https://doi.org/10.1155/2022/8499625>
- de Freitas Junior RA, Lossavaro PKMB, Kassuya CAL, Paredes-Gamero EJ, Farias Júnior NC, Souza MIL, Silva-Comar FMS, Cuman RKN, Silva DB, Toffoli-Kadri MC, Silva-Filho SE (2022) Effect of ylang-ylang (*Cananga odorata* Hook. f. & Thomson) essential oil on acute inflammatory response *in vitro* and *in vivo*. *Molecules* 27(12): 3666. <https://doi.org/10.3390/molecules27123666>
- Díaz-Herrera TH, Caldas Martínez ML, Coy-Barrera E (2024) *Phyllanthus*-derived naturally-occurring products: An overview of their effects against viruses in cell models. *Curr Bioact Compd* 20(9): e260124226282. <https://doi.org/10.2174/0115734072275982231230073813>
- Dianita R, Jantan I (2017) Ethnomedicinal uses, phytochemistry and pharmacological aspects of the genus *Premna*: A review. *Pharm Biol* 55(1): 1715–1739. <https://doi.org/10.1080/13880209.2017.1323225>
- Ding C, Wang Q, Hao Y, Ma X, Wu L, Du M, Li W, Wu Y, Guo F, Ma S, Huang F, Qin G (2016) Vitamin D supplement improved testicular function in diabetic rats. *Biochem Biophys Res Commun* 473(1): 161–167. <https://doi.org/10.1016/j.bbrc.2016.03.072>
- Djeni TN, Kouame KH, Ake FD, Amoikon LS, Dje MK, Jeyaram K (2020) Microbial diversity and metabolite profiles of palm wine produced from three different palm tree species in Côte d'Ivoire. *Sci Rep* 10(1): 1715. <https://doi.org/10.1038/s41598-020-58587-2>
- El Amir D, AbouZid SF, Hetta MH, Shahat AA, El-Shanawany MA (2014) Composition of the essential oil of the fruits of *Phyllanthus emblica* cultivated in Egypt. *J Pharm Chem Biol Sci* 2(3): 202–207.
- Elfati D, Faulina SA, Rahayu LM, Aryanto A, Dewi RT, Rachmat HH, Turjaman M, Royyani MF, Susilowati A, Hidayat A (2022) Culturable endophytic fungal assemblages from *Styrax sumatrana* and *Stryax benzoin* and their potential as antifungal, antioxidant, and alpha-glucosidase inhibitory resources. *Front Microbiol* 13: 974526. <https://doi.org/10.3389/fmicb.2022.974526>
- Fang X, Yu SX, Lu Y, Bast RCJ, Woodgett JR, Mills GB (2000) Phosphorylation and inactivation of glycogen synthase kinase 3 by protein kinase A. *Proc Natl Acad Sci USA* 97(22): 11960–11965. <https://doi.org/10.1073/pnas.220413597>
- Fantini M, Benvenuto M, Masuelli L, Frajese G V, Tresoldi I, Modesti A, Bei R (2015) *In vitro* and *in vivo* antitumoral effects of combinations of polyphenols, or polyphenols and anticancer drugs: Perspectives on cancer treatment. *Int J Mol Sci* 16(5): 9236–9282. <https://doi.org/10.3390/ijms16059236>
- Fatmah F, Lestari F, El-Matury HJ (2022) Social, economic, cultural resilience, and discipline role of the North Sumatera Province Government in the COVID-19 management. *J Pengelolaan Sumberdaya Alam Lingkung* 12(2): 330–334. <https://doi.org/10.29244/jpsl.12.2.330-334>
- Fattaheian-Dehkordi S, Hojjatifard R, Saeedi M, Khanavi M (2021) A review on antidiabetic activity of *Centaurea* spp.: A new approach for developing herbal remedies. *Evid Based Complement Alternat Med* 2021: 5587938. <https://doi.org/10.1155/2021/5587938>
- Fazil M, Nikhat S (2022) Why the “sugars” in traditional Unani formulations are a pivotal component: A viewpoint perspective. *J Integr Med* 20(2): 91–95. <https://doi.org/10.1016/j.joim.2022.01.002>
- Ghosh R, Samanta P, Sarkar R, Biswas S, Saha P, Hajra S, Bhowmik A (2022) Targeting HIF-1α by natural and synthetic compounds: A promising approach for anti-cancer therapeutics development. *Molecules* 27(16): 5192. <https://doi.org/10.3390/molecules27165192>
- Giannini EG, Testa R, Savarino V (2005) Liver enzyme alteration: a guide for clinicians. *Can Med Assoc J* 172(3): 367–379. <https://doi.org/10.1503/cmaj.1040752>
- Gonelimali FD, Lin J, Miao W, Xuan J, Charles F, Chen M, Hatab SR (2018) Antimicrobial properties and mechanism of action of some plant extracts against food pathogens and spoilage microorganisms. *Front Microbiol* 9: 1639. <https://doi.org/10.3389/fmicb.2018.01639>
- Grass I, Kubitz C, Krishna VV, Corre MD, Mußhoff O, Pütz P, Drescher J, Rembold K, Ariyanti ES, Barnes AD, Brinkmann N, Brose U, Brümmer B, Buchori D, Daniel R, Darras KFA, Faust H, Fehrmann L, Hein J, Wollni M (2020) Trade-offs between multifunctionality and profit in tropical smallholder landscapes. *Nature Commun* 11(1): 1186. <https://doi.org/10.1038/s41467-020-15013-5>
- Greenwell M, Rahman PKSM (2015) Medicinal plants: Their use in anticancer treatment. *Int J Pharm Sci Res* 6(10): 4103–4112. [https://doi.org/10.13040/ijpsr.0975-8232.6\(10\).4103-12](https://doi.org/10.13040/ijpsr.0975-8232.6(10).4103-12)
- Grogan SP, D'Lima DD (2010) Joint aging and chondrocyte cell death. *Int J Clin Rheumatol* 5(2): 199–214. <https://pmc.ncbi.nlm.nih.gov/articles/PMC2909784/>

- Gul M, Liu ZW, Iahtisham-UI-Haq, Rabail R, Faheem F, Walayat N, Nawaz A, Shabbir MA, Munekata PES, Lorenzo JM, Aadil RM (2022) Functional and nutraceutical significance of amla (*Phyllanthus emblica* L.): A review. *Antioxidants* 11(5): 816. <https://doi.org/10.3390/antiox11050816>
- Han Z, Meng L, Huang X, Tan J, Liu W, Chen W, Zou Y, Cai Y, Huang S, Chen A, Zhan T, Huang M, Chen X, Tian X, Zhu Q (2022) Inhibition of p38 MAPK increases the sensitivity of 5-fluorouracil-resistant SW480 human colon cancer cells to noscapine. *Oncol Lett* 23(2): 52. <https://doi.org/10.3892/ol.2021.13170>
- Heck-Swain KL, Li J, Ruan W, Yuan X, Wang Y, Koeppen M, Eltzschig HK (2022) Myeloid hypoxia-inducible factor HIF1A provides cardio-protection during ischemia and reperfusion via induction of netrin-1. *Front Cardiovasc Med* 9: 970415. <https://doi.org/10.3389/fcvm.2022.970415>
- Hiranrat A, Mahabusarakam W, Carroll AR, Duffy S, Avery VM (2012) Tomentosones A and B, hexacyclic phloroglucinol derivatives from the Thai shrub *Rhodomyrtus tomentosa*. *J Org Chem* 77(1): 680–683. <https://doi.org/10.1021/jo201602y>
- Hong S, Cai W, Huang Z, Wang Y, Mi X, Huang Y, Lin Z, Chen X (2020) Ginsenoside Rg3 enhances the anticancer effect of 5-FU in colon cancer cells via the PI3K/AKT pathway. *Oncol Rep* 44(4): 1333–1342. <https://doi.org/10.3892/or.2020.7728>
- Hu N, Zhang Q, Wang H, Yang X, Jiang Y, Chen R, Wang L (2021) Comparative evaluation of the effect of metformin and insulin on gut microbiota and metabolome profiles of type 2 diabetic rats induced by the combination of streptozotocin and high-fat diet. *Front Pharmacol* 12: 794103. <https://doi.org/10.3389/fphar.2021.794103>
- Hu X, Shao P, Liu X, Han L, Gui L, Cai Z, Qi M, Dai C (2022) Study on the anti-inflammatory effect and mechanism of yuxuebi tablet based on network pharmacology. *ACS Omega* 7(36): 32784–32794. <https://doi.org/10.1021/acsomega.2c04641>
- Hu X, Wu H, Yong X, Wang Y, Yang S, Fan D, Xiao Y, Che L, Shi K, Li K, Xiong C, Zhu H, Qian Z (2023) Cyclical endometrial repair and regeneration: Molecular mechanisms, diseases, and therapeutic interventions. *MedComm* 4(6): e425. <https://doi.org/10.1002/mco2.425>
- Huang ZR, Lin YK, Fang JY (2009) Biological and pharmacological activities of squalene and related compounds: Potential uses in cosmetic dermatology. *Molecules* 14(1): 540–554. <https://doi.org/10.3390/molecules14010540>
- Idris M, Sukandar ER, Purnomo AS, Martak F, Fatmawati S (2022) Antidiabetic, cytotoxic and antioxidant activities of *Rhodomyrtus tomentosa* leaf extracts. *RSC Adv* 12(39): 25697–25710. <https://doi.org/10.1039/d2ra03944c>
- Ilyas S, Hutahaean S, Rosidah R, Situmorang PC (2021) Diabetic wound healing in FGF expression by nano herbal of *Rhodomyrtus tomentosa* L. and *Zanthoxylum acanthopodium* fruits. *Pak J Biol Sci* 24(3): 401–408
- Ilyas S, Santoso P, Midoen Y, Situmorang P (2023) Improvement of spermatozoa concentration due to maximal exercise with *Vitis gracilis* Wall. *J Pharm Pharmacogn Res* 11(5): 874–886. https://doi.org/10.56499/jppres23.1685_11.5.874
- Ilyas S, Simanullang RH, Hutahaean S, Rosidah R, Situmorang PC (2022) Suppression of Wnt expression by increasing PI3K in rats cervical carcinoma by andaliman (*Zanthoxylum acanthopodium*). *Pak J Biol Sci* 25(1): 29–36. <https://doi.org/10.3923/pjbs.2022.29.36>
- Ilyas S, Situmorang PC (2021) Role of heat shock protein 70 (HSP-70) after giving nanoherbal haramonting (*Rhodomyrtus tomentosa*) in preeclamptic rats. *Pak J Biol Sci* 24(1): 139–145. <https://doi.org/10.3923/pjbs.2021.139.145>
- Iskander A, Yan LJ (2022) Cisplatin-induced kidney toxicity: Potential roles of major NAD(+)-dependent enzymes and plant-derived natural products. *Biomolecules* 12(8): 1078. <https://doi.org/10.3390/biom12081078>
- Iyer SS, Cheng G (2012) Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. *Crit Rev Immunol* 32(1): 23–63. <https://doi.org/10.1615/critrevimmunol.v32.i1.30>
- Jabbar AAJ, Alamri ZZ, Abdulla MA, Salehen NA, Salim Amur Al Sinawi Z, Alfaifi SM (2023) Hepatoprotective effects of *Gynura procumbens* against thioacetamide-induced cirrhosis in rats: Targeting inflammatory and oxidative stress signalling pathways. *Heliyon* 9(9): e19418. <https://doi.org/10.1016/j.heliyon.2023.e19418>
- Jadid N, Kurniawan E, Himayani CES, Andriyani, Prasetyowati I, Purwani KI, Tjahjaningrum ITD (2020) An ethnobotanical study of medicinal plants used by the Tengger tribe in Ngadisari village, Indonesia. *PLoS One* 15(7): e0235886. <https://doi.org/10.1371/journal.pone.0235886>
- Jang HY, Kim GB, Kim JM, Kang SY, Youn HJ, Park J, Ro SY, Chung EY, Park KH, Kim JS (2023) Fisetin inhibits UVA-induced expression of MMP-1 and MMP-3 through the NOX/ROS/MAPK pathway in human dermal fibroblasts and human epidermal keratinocytes. *Int J Mol Sci* 24(24): 17358. <https://doi.org/10.3390/ijms242417358>
- Jdaini K, Alla F, Mansouri F, Parmar A, Elhoumaizi MA (2023) Optimizing the extraction of phenolic antioxidants from date palm fruit by simplex-centroid solvent mixture design. *Heliyon* 9(1): e12738. <https://doi.org/10.1016/j.heliyon.2022.e12738>
- Jermnak U, Supsavhad W, Kunakornsawat S, Jaroensong T, Watcharasi P, Visitnonthachai D, Pairor S, Phaochoosak N (2022) Anti-cancer potentials of *Gynura procumbens* leaves extract against two canine mammary cancer cell lines. *Vet Med Sci* 8(1): 69–84. <https://doi.org/10.1002/vms3.684>
- Jin J, Kim MJ, Dhandapani S, Tjhang JG, Yin JL, Wong L, Sarojam R, Chua NH, Jang IC (2015) The floral transcriptome of ylang ylang (*Cananga odorata* var. *fruticosa*) uncovers biosynthetic pathways for volatile organic compounds and a multifunctional and novel sesquiterpene synthase. *J Exp Bot* 66(13): 3959–3975. <https://doi.org/10.1093/jxb/erv196>
- Jo M, Lee J, Kim HG, Kim JK, Kim H, Shin KK, Bach TT, Eum SM, Lee JS, Choung ES, Yang Y, Kim KH, Sung GH, Yoo BC, Cho JY (2021) Anti-inflammatory effect of *Barringtonia angusta* methanol extract is mediated by targeting of Src in the NF-κB signalling pathway. *Pharm Biol* 59(1): 797–808. <https://doi.org/10.1080/13880209.2021.1938613>
- Jobaer MA, Ashrafi S, Ahsan M, Hasan CM, Rashid MA, Islam SN, Masud MM (2023) Phytochemical and biological investigation of an indigenous plant of Bangladesh, *Gynura procumbens* (Lour.) Merr.: Drug discovery from nature. *Molecules* 28(10): 4186. <https://doi.org/10.3390/molecules28104186>
- Ju Z, Li M, Xu J, Howell DC, Li Z, Chen FE (2022) Recent development on COX-2 inhibitors as promising anti-inflammatory agents: The past 10 years. *Acta Pharm Sin B* 12(6): 2790–2807. <https://doi.org/10.1016/j.apsb.2022.01.002>
- Juliausti J, Miko A, Ramli N, Emilda E, Lajuna L, Yuniwati C, Fithriany F, Anita A, Sari Y, Veri N (2017) The effect of ethanol extract of ylang-ylang flower (*Cananga odorata*) on vascular and kidney histology in menopausal mice. *Clin Nutr Exp* 15: 1–8. <https://doi.org/10.1016/j.yclnex.2017.08.001>
- Kalam SN, Dowland S, Lindsay L, Murphy CR (2022) Porosomes in uterine epithelial cells: Ultrastructural identification and characterization during early pregnancy. *J Morphol* 283(11): 1381–1389. <https://doi.org/10.1002/jmor.21504>
- Karelina K, Schneiderman K, Shah S, Fitzgerald J, Cruz RV, Oliverio R, Whitehead B, Yang J, Weil ZM (2021) Moderate intensity treadmill exercise increases survival of newborn hippocampal neurons and improves neurobehavioral

- outcomes after traumatic brain injury. *J Neurotrauma* 38(13): 1858–1869. <https://doi.org/10.1089/neu.2020.7389>
- Khairunnisa A, Angio MH (2023) Inventory of local fruit plants, *Phyllanthus emblica* of Purwodadi Botanical Garden collection, potential antimicrobial and antiviral compounds, and distribution in Indonesia Pros Sem Nas Masy Biodiv Indon 9: 22–28. <https://doi.org/10.13057/psnmbi/m090104>
- Kintamani E, Batubara I, Kusmana C, Tiryana T, Mirmanto E, Asoka SF (2023) Essential oil compounds of andaliman (*Zanthoxylum acanthopodium* DC.) Fruit varieties and their utilization as skin anti-aging using molecular docking. *Life* 13(3): 754. <https://doi.org/10.3390/life13030754>
- Kitwetcharoen H, Phannarangsee Y, Klanrit P, Thanonkeo S, Tippayawat P, Klanrit P, Klanrit P, Yamada M, Thanonkeo P (2024) Functional kombucha production from fusions of black tea and Indian gooseberry (*Phyllanthus emblica* L.). *Heliyon* 10(24): e40939. <https://doi.org/10.1016/j.heliyon.2024.e40939>
- Labbozzetta M, Poma P, Tutone M, McCubrey JA, Sajeva M, Notarbartolo M (2022) Phytol and heptacosane are possible tools to overcome multidrug resistance in an *in vitro* model of acute myeloid leukemia. *Pharmaceuticals* 15(3): 356. <https://doi.org/10.3390/ph15030356>
- Lalrinzuali K, Vabeiryureilai M, Jagetia GC (2016) Investigation of the anti-inflammatory and analgesic activities of ethanol extract of stem bark of sonapatha *Oroxylum indicum* *in vivo*. *Int J Inflamm* 2016: 8247014. <https://doi.org/10.1155/2016/8247014>
- Laomethakorn P, Tayeh M, Samosorn S, Tananyuthawongse C, Watanapokasin R (2023) 13-Butoxyberberine bromide inhibits migration and invasion in skin cancer A431 cells. *Molecules* 28(3): 991. <https://doi.org/10.3390/molecules28030991>
- Lavanya G, Voravuthikunchai SP, Towatana NH (2012) Acetone extract from *Rhodomyrtus tomentosa*: A potent natural antioxidant. *Evid Based Complement Alternat Med* 2012: 535479. <https://doi.org/10.1155/2012/535479>
- Lee D, Lee WY, Jung K, Kwon YS, Kim D, Hwang GS, Kim CE, Lee S, Kang KS (2019) The inhibitory effect of cordycepin on the proliferation of MCF-7 breast cancer cells, and its mechanism: An investigation using network pharmacology-based analysis. *Biomolecules* 9(9): 414. <https://doi.org/10.3390/biom9090414>
- Lelyana S, Widyarman A, Amtha R (2021) Indonesian andaliman fruit (*Zanthoxylum acanthopodium* DC.) extract suppresses the expression of inflammatory mediators on fibroblasts cells *in vitro*. *Pharm Sci Asia* 48(5): 491–497. <https://doi.org/10.29090/psa.2021.05.20.064>
- Li H, Liu ZL, Lu L, Buffet P, Karniadakis GE (2021) How the spleen reshapes and retains young and old red blood cells: A computational investigation. *PLoS Comput Biol* 17(11): e1009516. <https://doi.org/10.1371/journal.pcbi.1009516>
- Li K, Yao F, Xue Q, Fan H, Yang L, Li X, Sun L, Liu Y (2018) Inhibitory effects against α -glucosidase and α -amylase of the flavonoids-rich extract from *Scutellaria baicalensis* shoots and interpretation of structure-activity relationship of its eight flavonoids by a refined assign-score method. *Chem Centr J* 12(1): 82. <https://doi.org/10.1186/s13065-018-0445-y>
- Li XJ, Mu YM, Li TT, Yang YL, Zhang MT, Li YS, Zhang WK, Tang HB, Shang HC (2015) *Gynura procumbens* reverses acute and chronic ethanol-induced liver steatosis through MAPK/SREBP-1c-dependent and -independent pathways. *J Agric Food Chem* 63(38): 8460–8471. <https://doi.org/10.1021/acs.jafc.5b03504>
- Limsuwan S, Trip EN, Kouwen TR, Piersma S, Hiranrat A, Mahabusarakam W, Voravuthikunchai SP, van Dijk JM, Kayser O (2009) Rhodomyrtone: A new candidate as natural antibacterial drug from *Rhodomyrtus tomentosa*. *Phytomedicine* 16(6–7): 645–651. <https://doi.org/10.1016/j.phymed.2009.01.010>
- Liu Q, Xiao XH, Hu LB, Jie HY, Wang Y, Ye WC, Li MM, Liu Z (2017) Anhuinoside C ameliorates collagen-induced arthritis through inhibition of MAPK and NF- κ B signaling pathways. *Front Pharmacol* 8: 299. <https://doi.org/10.3389/fphar.2017.00299>
- Lubis MF, Zaitun Hasibuan PA, Syahputra H, Surbakti C, Astyka R (2022) *Saurauia vulcani* (Korth.) as herbal medicine potential from North Sumatera, Indonesia: A literature review. *Heliyon* 8(4): e09249. <https://doi.org/10.1016/j.heliyon.2022.e09249>
- Mali PY (2016) Pharmacological potentials of *Premna integrifolia* L. *Anc Sci Life* 35(3): 132–142. <https://doi.org/10.4103/0257-7941.179864>
- Mansouri MT, Hemmati AA, Naghizadeh B, Mard SA, Rezaie A, Ghorbanzadeh B (2015) A study of the mechanisms underlying the anti-inflammatory effect of ellagic acid in carrageenan-induced paw edema in rats. *Indian J Pharmacol* 47(3): 292–298. <https://doi.org/10.4103/0253-7613.157127>
- Masyita A, Mustika Sari R, Dwi Astuti A, Yasir B, Rahma Rumata N, Emran T Bin, Nainu F, Simal-Gandara J (2022) Terpenes and terpenoids as main bioactive compounds of essential oils, their roles in human health and potential application as natural food preservatives. *Food Chem X* 13: 100217. <https://doi.org/10.1016/j.fochx.2022.100217>
- Medoro A, Davinelli S, Colletti A, Di Micoli V, Grandi E, Fogacci F, Scapagnini G, Cicero AFG (2023) Nutraceuticals as modulators of immune function: A review of potential therapeutic effects. *Prevent Nutr Food Sci* 28(2): 89–107. <https://doi.org/10.3746/pnf.2023.28.2.89>
- Mehdi SF, Pusapati S, Anwar MS, Lohana D, Kumar P, Nandula SA, Nawaz FK, Tracey K, Yang H, LeRoith D, Brownstein MJ, Roth J (2023) Glucagon-like peptide-1: A multi-faceted anti-inflammatory agent. *Front Immunol* 14: 1148209. <https://doi.org/10.3389/fimmu.2023.1148209>
- Mehmood MH, Siddiqi HS, Gilani AH (2011) The antidiarrheal and spasmolytic activities of *Phyllanthus emblica* are mediated through dual blockade of muscarinic receptors and Ca^{2+} channels. *J Ethnopharmacol* 133(2): 856–865. <https://doi.org/10.1016/j.jep.2010.11.023>
- Midoen YH, Ilyas S, Santoso P, Situmorang PC (2023) Effect of maximal physical exercise on apoptosis via cytochrome c in hippocampus cells after administration of *Vitis gracilis* Wall. *J Pharm Pharmacogn Res* 11(2): 297–307. https://doi.org/10.56499/JPPRES22.1563_11.2.297
- Moon GH, Lee Y, Kim EK, Chung KH, Lee KJ, An JH (2021) Immunomodulatory and anti-inflammatory effects of asiatic acid in a DNCB-induced atopic dermatitis animal model. *Nutrients* 13(7): 2448. <https://doi.org/10.3390/nu13072448>
- Mou K, Dash P (2016) A comprehensive review on *Gynura procumbens* leaves. *Int J Pharmacogn* 3: 167–174. [https://doi.org/10.13040/IJPSR.0975-8232.IJP.3\(4\).167-174](https://doi.org/10.13040/IJPSR.0975-8232.IJP.3(4).167-174)
- Mukherjee A, Das B (2024) The role of inflammatory mediators and matrix metalloproteinases (MMPs) in the progression of osteoarthritis. *Biomater Biosyst* 13: 100090. <https://doi.org/10.1016/j.bbiosy.2024.100090>
- Mustaqim WA, Hartiningtias D (2021) *Cananga odorata* (Lam.) Hook. f. & Thomson Annonaceae. In: *Ethnobotany of the Mountain Regions of Southeast Asia*. Springer International Publishing, Cham, pp 225–238. https://doi.org/10.1007/978-3-030-14116-5_164-1
- Nagoor Meeran MF, Javed H, Al Taei H, Azimullah S, Ojha SK (2017) Pharmacological properties and molecular mechanisms of thymol: Prospects for its therapeutic potential and pharmaceutical development. *Front Pharmacol* 8: 380. <https://doi.org/10.3389/fphar.2017.00380>
- Nguyen PY, Astell-Burt T, Rahimi-Ardabili H, Feng X (2021) Green space quality and health: A systematic review. *Int J Environ*

- Res Public Health 18(21): 11028. <https://doi.org/10.3390/ijerph182111028>
- Nwabor OF, Leejae S, Voravuthikunchai SP (2021) Rhodomymrtone accumulates in bacterial cell wall and cell membrane and inhibits the synthesis of multiple cellular macromolecules in epidemic methicillin-resistant *Staphylococcus aureus*. Antibiotics 10(5): 543. <https://doi.org/10.3390/antibiotics10050543>
- Oliveira Amorim AP, Campos de Oliveira MC, de Azevedo Amorim T, Echevarria A (2013) Antioxidant, iron chelating, and tyrosinase inhibitory activities of extracts from *Talinum triangulare* leach stem. Antioxidants 2(3): 90–99. <https://doi.org/10.3390/antiox2030090>
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372: n71. <https://doi.org/10.1136/bmj.n71>
- Pan Z, Zhang X, Yu P, Chen X, Lu P, Li M, Liu X, Li Z, Wei F, Wang K, Zheng Q, Li D (2019) Cinobufagin induces cell cycle arrest at the G2/M phase and promotes apoptosis in malignant melanoma cells. Front Oncol 9: 853. <https://doi.org/10.3389/fonc.2019.00853>
- Parisi L, Gini E, Baci D, Tremolati M, Fanuli M, Bassani B, Farronato G, Bruno A, Mortara L (2018) Macrophage polarization in chronic inflammatory diseases: killers or builders? J Immunol Res 2018: 8917804. <https://doi.org/10.1155/2018/8917804>
- Park HK, Nguyen LP, Nguyen TU, Cho M, Nguyen HT, Hurh S, Kim HR, Seong JY, Lee CS, Ham BJ, Hwang JI (2023) The N-terminus of CXCR4 splice variants determines expression and functional properties. PloS One 18(5): e0283015. <https://doi.org/10.1371/journal.pone.0283015>
- Patil SA, Patil VS, Malgi AP, Hupparage VB, Mallapur SP, Naik RR (2023) *Cananga odorata* (Ylang-Ylang) modulate pathways involved in cancer: Gene set enrichment and network pharmacology approach. Int J Ayurvedic Med 14(2): 453–463. <https://doi.org/10.47552/ijam.v14i2.3434>
- Pedro AC, Paniz OG, Fernandes I de AA, Bortolini DG, Rubio FTV, Haminiuk CWI, Maciel GM, Magalhães WLE (2022) The importance of antioxidant biomaterials in human health and technological innovation: A review. Antioxidants 11(9): 1644. <https://doi.org/10.3390/antiox11091644>
- Pérez Gutiérrez RM, Muñiz-Ramírez A, García-Campoy AH, Mota Flores JM (2021) Evaluation of the antidiabetic potential of extracts of *Urtica dioica*, *Apium graveolens*, and *Zingiber officinale* in mice, zebrafish, and pancreatic β -cell. Plants 10(7): 1438. <https://doi.org/10.3390/plants10071438>
- Phuong DTL, Van Phuong N, Le Tuan N, Cong NT, Hang NT, Thanh LN, Hue VT, Vuong NQ, Ha NTT, Popova M, Trusheva B, Bankova V (2023) Antimicrobial, cytotoxic, and α -glucosidase inhibitory activities of ethanol extract and chemical constituents isolated from *Homotrigona apicalis* propolis—*In vitro* and molecular docking studies. Life 13(8): 1682. <https://doi.org/10.3390/life13081682>
- Prananda AT, Dalimunthe A, Harahap U, Simanjuntak Y, Peronika E, Karosekali NE, Hasibuan PAZ, Syahputra RA, Situmorang PC, Nurkolis F (2023) *Phyllanthus emblica*: A comprehensive review of its phytochemical composition and pharmacological properties. Front Pharmacol 14: 1288618. <https://doi.org/10.3389/fphar.2023.1288618>
- Qi S, Calvi BR (2016) Different cell cycle modifications repress apoptosis at different steps independent of developmental signaling in *Drosophila*. Mol Biol Cell 27(12): 1885–1897. <https://doi.org/10.1091/mbc.E16-03-0139>
- Quranayati Q, Iqhrammullah M, Saidi N, Nurliana N, Idroes R, Nasution R (2022) Cytotoxicity and phytochemical profiles of *Phyllanthus emblica* stem barks with *in silico* drug-likeness: Focusing on antidiabetic potentials. J Adv Pharm Technol Res 13(4): 281–285. <https://doi.org/10.4103/japtr.japtr.319.22>
- Rahmawaty, Ismail MH, Rauf A, Batubara R, Elena Sitorus EW, Simamora Z, Ginting EF (2023) Land characteristics and land suitability assessment for *Styrax* sp. in Humbang Hasundutan Regency, North Sumatra, Indonesia. Heliyon 9(7): e16936. <https://doi.org/10.1016/j.heliyon.2023.e16936>
- Rajendran R, Krishnakumar E (2010) Anti-arthritic activity of *Premna serratifolia* Linn., wood against adjuvant induced arthritis. Avicenna J Med Biotechnol 2(2): 101–106. <https://pubmed.ncbi.nlm.nih.gov/23407688/>
- Rauf A, Wilairatana P, Joshi PB, Ahmad Z, Olatunde A, Hafeez N, Hemeg HA, Mubarak MS (2024) Revisiting luteolin: An updated review on its anticancer potential. Heliyon 10(5): e26701. <https://doi.org/10.1016/j.heliyon.2024.e26701>
- Reule S, Drawz PE (2012) Heart rate and blood pressure: Any possible implications for management of hypertension? Curr Hypertens Rep 14(6): 478–484. <https://doi.org/10.1007/s11906-012-0306-3>
- Richter G, Hazzah T, Hartsel JA, Eades J, Hickory B, Makriyannis A (2021) Chapter 38 - *Cannabis sativa*: An overview. In Gupta RC, Lall R, Srivastava A (eds.), Nutraceuticals (Second Edition). Academic Press, pp. 603–624. <https://doi.org/10.1016/B978-0-12-821038-3.00038-0>
- Rizvi W, Fayazuddin M, Singh O, Syed SN, Moin S, Akhtar K, Kumar A (2017) Anti-inflammatory effect of *Fumaria parviflora* leaves based on TNF- α , IL-1, IL-6 and antioxidant potential. Avicenna J Phytomed 7(1): 37–45. <https://pubmed.ncbi.nlm.nih.gov/28265545/>
- Rosidah R, Widjaja SS, Pertiwi D, Yuandani Y, Simanjuntak NJP, Satria D (2021) Phytochemical constituent and subchronic toxicity evaluation of ethanol extract of *Saurauia vulcani*. RASAYAN J Chem 14(3): 1441–1446. <https://dx.doi.org/10.31788/RJC.2021.1436135>
- Rui L (2014) Energy metabolism in the liver. Compr Physiol 4(1): 177–197. <https://doi.org/10.1002/cphy.c130024>
- Rumahorbo CGP, Situmorang PC, Zagoto ERMP, Nisfa L, Hasanah U (2023) Effects of micro-colloidal *Rhodomymrtus tomentosa* on MMP9, GLUT-1, and IL-1 β expression in *Rattus norvegicus* cervical cancer. J Pharm Pharmacogn Res 11(3): 537–546. <https://doi.org/10.56499/jppres23.1618.11.3.537>
- Rybak M, Wojdyło A (2023) Inhibition of α -amylase, α -glucosidase, pancreatic lipase, 15-lipoxygenase and acetylcholinesterase modulated by polyphenolic compounds, organic acids, and carbohydrates of *Prunus domestica* fruit. Antioxidants 12(7): 1380. <https://doi.org/10.3390/antiox12071380>
- Saha S, Al Amin GM, Khan MS, Goswami B, Afroz F, Habib MA, Akter S, Banu TA (2023) Assessment of antibacterial activity and cytotoxic effects of *in vitro* and *in vivo* plant parts of a medicinal plant *Gynura procumbens* (Lour.) Merr. Heliyon 9(12): e22954. <https://doi.org/10.1016/j.heliyon.2023.e22954>
- Saha S, Rebouh NY (2023) Anti-osteoarthritis mechanism of the Nrf2 signaling pathway. Biomedicines 11(12): 3176. <https://doi.org/10.3390/biomedicines11123176>
- Sampath C, Srinivasan S, Freeman ML, Gangula PR (2020) Inhibition of GSK-3 β restores delayed gastric emptying in obesity-induced diabetic female mice. Am J Physiol Gastrointest Liver Physiol 319(4): G481–G493. <https://doi.org/10.1152/ajpgi.00227.2020>
- Santoso P, Ilyas S, Midoen Y, Situmorang P (2023) Effect of *Vitis gracilis* Wall. administration on maximal swimming exercise

- apoptosis via cytochrome c in rat lung cells. *J Pharm Pharmacogn Res* 11(3): 381–390. https://doi.org/10.56499/jppres23.1603_11.3.381
- Saqban LH, Abdul Alamir Mezher Z, Hussain Ali I (2022) Cytotoxic effect of the crude alcoholic extract of the fruits of *Citrullus colocynthis* on human hepatocyte carcinoma (Hep-G2). *Arch Razi Instit* 77(4): 1389–1395. <https://doi.org/10.22092/ARI.2022.357807.2104>
- Sartinah A, Nugrahani I, Ibrahim S, Anggadiredja K (2022) Potential metabolites of Arecaceae family for the natural anti-osteoarthritis medicine: A review. *Heliyon* 8(12): e12039. <https://doi.org/10.1016/j.heliyon.2022.e12039>
- Sedky NK, Abdel-Kader NM, Issa MY, Abdelhady MMM, Shamma SN, Bakowsky U, Fahmy SA (2023) Co-delivery of ylang ylang oil of *Cananga odorata* and oxaliplatin using intelligent pH-sensitive lipid-based nanovesicles for the effective treatment of triple-negative breast cancer. *Int J Mol Sci* 24(9): 8392. <https://doi.org/10.3390/ijms24098392>
- Selvam TN, Venkatakrishnan V, Damodar KS, Elumalai P (2012) Antioxidant and tumor cell suppression potential of *Premna serratifolia* Linn leaf. *Toxicol Int* 19(1): 31–34. <https://pmc.ncbi.nlm.nih.gov/articles/PMC3339242/>
- Setiadi AYL, Karmawan LU, Yanti (2022) Anti-arthritis and anti-inflammatory effects of andaliman extract and nanoandaliman in inflammatory arthritic mice. *Foods* 11(22): 3576. <https://doi.org/10.3390/foods11223576>
- Shim H, Oishi S, Fujii N (2009) Chemokine receptor CXCR4 as a therapeutic target for neuroectodermal tumors. *Semin Cancer Biol* 19(2): 123–134. <https://doi.org/10.1016/j.semcancer.2008.11.004>
- Shin IS, Ahn KS, Shin NR, Jeon CM, Kwon OK, Chin YW, Lee K, Oh SR (2014) Homoeogonol attenuates the asthmatic responses induced by ovalbumin challenge. *Arch Pharm Res* 37: 1201–1210. <https://doi.org/10.1007/s12272-013-0327-8>
- Silvério MRS, Espindola LS, Lopes NP, Vieira PC (2020) Plant natural products for the control of *Aedes aegypti*: The main vector of important arboviruses. *Molecules* 25(15): 3484. <https://doi.org/10.3390/molecules25153484>
- Simanullang RH, Situmorang PC, Ginting L, Tarigan ER, Syahputra RA, Chairunisa C, Maliki MF (2022) PDGF- β and IL-18 expressions on carcinoma cervical by *Rhodomyrtus tomentosa*. *Pak J Biol Sci* 25(11): 986–992. <https://doi.org/10.3923/pjbs.2022.986.992>
- Sinaga E, Ilyas S, Hutahaean S, Sitorus P (2021) Hepatoprotective activity of pirdot leaves (*Saurauia vulcani* Korth) ethanol extract in laboratory rats (*Rattus norvegicus*) and characterization of bioactive compounds using a molecular docking approach. *Open Access Maced J Med Sci* 9(A): 1265–1270. <https://doi.org/10.3889/oamjms.2021.7624>
- Sinelius S, Lady J, Yunardy M, Tjoa E, Nurcahyanti AD (2023) Antibacterial activity of *Lagerstroemia speciosa* and its active compound, corosolic acid, enhances cefotaxime inhibitory activity against *Staphylococcus aureus*. *J Appl Microbiol* 134(8): lxad171. <https://doi.org/10.1093/jambio/lxad171>
- Singh C, Anand SK, Tiwari KN, Mishra SK, Kakkar P (2021) Phytochemical profiling and cytotoxic evaluation of *Premna serratifolia* L. against human liver cancer cell line. *3 Biotech* 11(3): 115. <https://doi.org/10.1007/s13205-021-02654-6>
- Sitorus P (2015) Characterization simplisia and ethanolic extract of pirdot (*Saurauia vulcani* Korth) leaves and study of antidiabetic effect in alloxan-induced diabetic mice. *Int J Chemtech Res* 8: 789–794.
- Situmorang PC, Ilyas S, Hutahaean S, Rosidah (2021) Effect of nano herbal andaliman (*Zanthoxylum acanthopodium*) fruits in NOTCH1 and Hes1 expressions to human placental trophoblasts. *Pak J Biol Sci* 24(1): 165–171. <https://doi.org/10.3923/pjbs.2021.165.171>
- Situmorang PC, Ilyas S, Syahputra RA, Sari RM, Nugraha AP, Ibrahim A (2024) *Rhodomyrtus tomentosa* as a new anticancer molecular strategy in breast histology via Her2, IL33, EGFR, and MUC1. *Front Pharmacol* 15: 1345645. <https://doi.org/10.3389/fphar.2024.1345645>
- Situmorang PC, Ilyas S, Siahaan DAS, Restuati M, Sari ER, Chairunisa C, Maliki MF (2022) Effect of *Rhodomyrtus tomentosa* Hassk. on HIF1 α and VEGF expressions on hypertension placental. *J Pharm Pharmacogn Res* 10(6): 1076–1086. https://doi.org/10.56499/jppres22.1517_10.6.1076
- Soares GABE, Bhattacharya T, Chakrabarti T, Tagde P, Cavalu S (2021) Exploring pharmacological mechanisms of essential oils on the central nervous system. *Plants* 11(1): 21. <https://doi.org/10.3390/plants11010021>
- Solárová Z, Lisková A, Samec M, Kubatka P, Büsselberg D, Solár P (2020) Anticancer potential of lichens' secondary metabolites. *Biomolecules* 10(1): 87. <https://doi.org/10.3390/biom10010087>
- Spampinato SF, Caruso GI, De Pasquale R, Sortino MA, Merlo S (2020) The treatment of impaired wound healing in diabetes: looking among old drugs. *Pharmaceuticals* 13(4): 60. <https://doi.org/10.3390/ph13040060>
- Tan HL, Chan KG, Pusparajah P, Lee LH, Goh BH (2016) *Gynura procumbens*: An overview of the biological activities. *Front Pharmacol* 7: 52. <https://doi.org/10.3389/fphar.2016.00052>
- Tan JN, Mohd Saffian S, Buang F, Jubri Z, Jantan I, Husain K, Mohd Fauzi N (2020) Antioxidant and anti-inflammatory effects of genus *Gynura*: A systematic review. *Front Pharmacol* 11: 504624. <https://doi.org/10.3389/fphar.2020.504624>
- Tan LTH, Lee LH, Yin WF, Chan CK, Abdul Kadir H, Chan KG, Goh BH (2015) Traditional uses, phytochemistry, and bioactivities of *Cananga odorata* (Ylang-Ylang). *Evid Based Complement Alternat Med* 2015: 896314. <https://doi.org/10.1155/2015/896314>
- Vitale S, Colanero S, Placidi M, Di Emidio G, Tatone C, Amicarelli F, D'Alessandro AM (2022) Phytochemistry and biological activity of medicinal plants in wound healing: An overview of current research. *Molecules* 27(11): 3566. <https://doi.org/10.3390/molecules27113566>
- Vo TS, Ngo DH (2019) The health beneficial properties of *Rhodomyrtus tomentosa* as potential functional food. *Biomolecules* 9(2): 76. <https://doi.org/10.3390/biom9020076>
- Wasnis NZ, Ilyas S, Hutahaean S, Silaban R, Situmorang PC (2022) Effect of *Vitis gracilis* Wall (gagatan harimau) in the recovery of gastrocnemius muscle cells and cytochrome c expression of *Mus musculus*. *J Pharm Pharmacogn Res* 10(2): 303–309. https://doi.org/10.56499/jppres21.1208_10.2.303
- Wu H, Lei Y, Lu J, Zhu R, Xiao D, Jiao C, Xia R, Zhang Z, Shen G, Liu Y, Li S, Li M (2019) Effect of citric acid induced crosslinking on the structure and properties of potato starch/chitosan composite films. *Food Hydrocoll* 97: 105208. <https://doi.org/10.1016/j.foodhyd.2019.105208>
- Wu Q, Wang X, Cui T, Zhang Z, Wang F, Ma G (2021) Study on the effects of *Phyllanthus emblica* extract on anti-aging and hair growth promotion. *China Surfact Detergent Cosmetics* 51(12): 1208–1214. <https://doi.org/10.3969/j.issn.1001-1803.2021.12.007>
- Xia DD, Han XY, Zhang Y, Zhang N (2023) Chemical constituents and their biological activities from genus *Styrax*. *Pharmaceuticals* 16(7): 1043. <https://doi.org/10.3390/ph16071043>
- Xiao Z, Liu W, Mu YP, Zhang H, Wang XN, Zhao CQ, Chen JM, Liu P (2020) Pharmacological effects of salvianolic acid B

- against oxidative damage. *Front Pharmacol* 11: 572373. <https://doi.org/10.3389/fphar.2020.572373>
- Xu Y, Tang G, Zhang C, Wang N, Feng Y (2021) Gallic acid and diabetes mellitus: Its association with oxidative stress. *Molecules* 26(23): 7115. <https://doi.org/10.3390/molecules26237115>
- Yamauchi R (2007) Addition products of alpha-tocopherol with lipid-derived free radicals. *Vitam Horm* 76: 309–327. [https://doi.org/10.1016/S0083-6729\(07\)76011-9](https://doi.org/10.1016/S0083-6729(07)76011-9)
- Yang X, Liu N, Li X, Yang Y, Wang X, Li L, Jiang L, Gao Y, Tang H, Tang Y, Xing Y, Shang H (2018) A review on the effect of traditional Chinese medicine against anthracycline-induced cardiac toxicity. *Front Pharmacol* 9: 444. <https://doi.org/10.3389/fphar.2018.00444>
- Yi J, Luo J (2010) SIRT1 and p53, effect on cancer, senescence and beyond. *Biochim Biophys Acta* 1804(8): 1684–1689. <https://doi.org/10.1016/j.bbapap.2010.05.002>
- Yoo HC, Yu YC, Sung Y, Han JM (2020) Glutamine reliance in cell metabolism. *Exp Mol Med* 52(9): 1496–1516. <https://doi.org/10.1038/s12276-020-00504-8>
- Yousefbeyk F, Vatandoost H, Golfakhrabadi F, Mirzaee Z, Abai MR, Amin G, Khanavi M (2018) Antioxidant and larvicidal activity of areal parts of *Scrophularia striata* against malaria vector *Anopheles stephensi*. *J Arthropod Borne Dis* 12(2): 119–126. <https://pmc.ncbi.nlm.nih.gov/articles/PMC6091803/>
- Zhang JX, Yuan WC, Li CG, Zhang HY, Han SY, Li XH (2023) A review on the mechanisms underlying the antitumor effects of natural products by targeting the endoplasmic reticulum stress apoptosis pathway. *Front Pharmacol* 14: 1293130. <https://doi.org/10.3389/fphar.2023.1293130>
- Zhang N, Zhang L, Feng L, Yao L (2018) *Cananga odorata* essential oil reverses the anxiety induced by 1-(3-chlorophenyl) piperazine through regulating the MAPK pathway and serotonin system in mice. *J Ethnopharmacol* 219: 23–30. <https://doi.org/10.1016/j.jep.2018.03.013>
- Zhang X, Cheng J, He P, Zhu J, Chen Z, Miao S, Wang G, Jiang J, Wang Y (2020) Active monomer RTR-1 derived from the root of *Rhodomyrtus tomentosa* induces apoptosis in gastric carcinoma cells by inducing ER stress and inhibiting the STAT3 signaling pathway. *Cancer Manag Res* 12: 3117–3129. <https://doi.org/10.2147/CMAR.S237201>
- Zhao S, Lin G, Duan W, Zhang Q, Huang Y, Lei F (2021) Design, synthesis, and antifungal activity of novel longifolene-derived diacylhydrazine compounds. *ACS Omega* 6(13): 9104–9111. <https://doi.org/10.1021/acsomega.1c00217>

AUTHOR CONTRIBUTION:

Contribution	Rumahorbo CGP	Situmorang PC
Concepts or ideas		x
Design		x
Definition of intellectual content		x
Literature search	x	x
Experimental studies		
Data acquisition	x	x
Data analysis	x	x
Statistical analysis		
Manuscript preparation	x	x
Manuscript editing	x	x
Manuscript review	x	x

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Supplementary Data

Table S1. Results of article quality analysis using the AXIS tool.

Authors	Study	AXIS tool questions																				Score	Quality	Positive responses (%)
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20			
Situmorang et al. (2021)	Cohort	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	16	High	80
Ahmad Nazri et al. (2019)		Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	16	High	80
Dianita & Jantan (2017)		Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	15	High	75
Chao et al. (2022)	Case-control	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	15	High	75
Asmilia et al. (2020)	Observational	Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	N/A	Yes	Yes	Yes	Yes	No	Yes	13	Medium	65
Ahmad K et al. (2023)		Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	N/A	Yes	Yes	Yes	No	No	Yes	13	Medium	65
Elfiati et al. (2022)		Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	N/A	Yes	Yes	Yes	Yes	No	Yes	13	Medium	65
Dianita & Jantan (2017)		Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	N/A	Yes	Yes	Yes	Yes	No	Yes	14	Medium	70

Response criteria: Yes: complies; No: does not comply; N/A: not applicable.