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A Review on Medicinal Properties of Myrmecodia pendans: Active Constituents, Pharmacological Insight and Mechanisms of Action Update

Faisal Kuswandani[1]*, Felisha Febriane Balafif[2], Nuroh Najmi[3], Anggun Rafisa[4]
[1]Pharmacy, Department of Oral Biology, Faculty of Dentistry, Universitas Padjadjaran, Indonesia.
[2]Microbiology, Department of Oral Biology, Faculty of Dentistry, Universitas Padjadjaran, Indonesia
[3]Anatomy Pathology, Department of Oral Biology, Faculty of Dentistry, Universitas Padjadjaran, Indonesia
[4]Physiology, Department of Oral Biology, Faculty of Dentistry, Universitas Padjadjaran, Indonesia

Abstract— *Plants have long served as a rich source of bioactive compounds and therapeutic agents used in the treatment of various disea ses throughout human history. For centuries, people in Southeast Asia have used Myrmecodia pendans, a member of the Rubiaceae family, to treat a variety of ailments, including nausea, infections, diarrhea, inflammation, ulcers, gout, muscle pain, metabolic disorders, and even breast cancer, in addition to its immunomodulatory effects. Phytochemical investigations have identified a diverse array of secondary metabolites in this plant, including flavonoids, phenolic acids, tannins, and polysaccharides, which are believed to contribute to its pharmacological potential. This review aims to comprehensively summarize the pharmacological activities of M. pendans, with a specific focus on its bioa ctive constituents and the underlying mechanisms of action.*

Keywords— *Myrmecodia pendans, pharmacology, phytotherapy*

I. Introduction

Medicinal plants play a crucial role in drug discovery, especially in biodiversity-rich regions with a strong ethnobotanical tradition like Indonesia. These plants are recognized sources of bioactive compounds that possess a wide range of pharmacological properties.[1,2] Some of these plants are *Myrmecodia pendans* (Rubiaceae), commonly known as sarang semut in the local vernacular. This species has been traditionally used in Papua, Indonesia, to treat various ailments, including nausea, infections, diarrhea, inflammation, gastric ulcers, gout, muscle pain, metabolic disorders, and breast cancer. It is also recognized for its immunomodulatory effects. The plant's unique bulbous forms, which are packed with tunnels, show its symbiotic connection to ant colonies, and these forms are collected for therapeutic applications.[1]

Phytochemical studies have revealed that *M. pendans* contains a wide range of secondary metabolites, notably flavonoids, phenolic acids, tannins, and polysaccharides, which are associated with its pharmacological activities. Recent research has highlighted the plant's promising anti-cancer, anti-inflammatory, and antimicrobial properties, suggesting its potential as an alternative or complementary therapeutic agent.[3–8]

Despite increasing scientific interest no comprehensive review exists that integrates active constituent, pharmacological activities and the underlying mechanisms of action on *M. pendans*. This article aims to bridge that gap by exploring the bioactive constituents of M. pendans, their associated pharmacological activities, and the molecular mechanisms involved in mediating its therapeutic effects.

II. Literature Sources and Search strategy

An extensive literature search was conducted using search terms such as "*Myrmecodia pendans*" or "*Myrmecodia pendens"* combined with "pharmacological activity" across multiple electronic databases, including Google Scholar, ScienceDirect, and PubMed. No restrictions were applied regarding the year of publication. Retrieved articles were critically assessed for relevance based on their descriptions of the pharmacological effects of *M. pendans* pharmacological activities. Additionally, the references cited within these articles were examined to extract further relevant data. This review synthesizes both historical and recent findings, focusing on the plant's active compounds, pharmacological activities and their mechanisms of action.

III. Review

Botanical and Anatomical Description of Myrmecodia pendans

Myrmecodia pendans belongs to the Rubiaceae family, which also includes genera such as Myrmecodia, Hypnophytum, Anthorriza, Myrmephytum, and Squamellaria. Hydnophytum formicarum and Myrmecodia tuberosa are included, *Myrmecodia pendans* is known for its pharmacological activity.[9] The Myrmecodia genus comprises approximately 26 species, primarily found in Indonesia, Malaysia, the Philippines, and the Solomon Islands. This plant is endemic to Papua, Indonesia, where it exhibits great diversity.[2] *Myrmecodia pendans* is an epiphytic plant that grows on the trunks of large trees, such as *Melaleuca leucadendra* and *Casuarina junghuhniana*. Approximately 80% of these plants can be found in wilderness areas of tropical rainforests.[10] The plant is characterized by its swollen, bulb-like hypocotyl, which forms a symbiotic relationship

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with ant colonies. These structures contain intricate tunnels and chambers, providing shelter for ants while benefiting from the organic debris and protection they provide (Figure1).[11]

Figure 1. *Myrmecodia pendans*

Phytochemical Constituents

The proximate composition analysis of *M. pendans* has shown the following values: moisture content at 4.36%, crude protein at 2.75%, crude fat at 2.68%, crude fiber at 4.84%, ash at 3.22%, and total carbohydrates at 82.15%.[12] In addition to its nutritional profile, phytochemical screening has identified a wide range of bioactive constituents that responsible to its pharmacological activities. This includes flavonoids, phenolic compounds, alkaloids, tannins, saponins, glycosides, terpenoids, and triterpenoids.[1,13]

Among these, flavonoids—considered the most prominent class of phenolic compounds—have been recognized as major constituents in the Myrmecodia genus. Specific flavonoids identified include kaempferol, luteolin, rutin, quercetin, apigenin, rosmarinic acid, procyanidin B1 and its polymer, gallic acid, (+)-catechin, caffeic acid, p-coumaric acid, and ferulic acid.[2] Further studies have isolated and characterized various other bioactive constituents in *M. pendans*, including butein, biflavonoids, 3"-methoxy-epicatechin-3-O-epicatechin, benzoic acid, pomolic acid, betulin, β-sitosterol tridecanoil glucopyranose, guaiacol, 4-methylcatechol, 2,6-dimethoxyphenol, and anthocyanins (Table 1).[2,13–16]

The bioactive compounds of Myrmecodia pendans are primarily extracted from its tuber using polar solvents such as ethanol and methanol. Among the isolated constituents, flavonoids and phenolic compounds have garnered considerable attention due to their wide range of pharmacological activities. Flavonoids, a class of polyphenolic compounds derived from the 2-phenylchromane backbone, are commonly found in various fruits, vegetables, and medicinal plants. These compounds are recognized for their diverse biological effects, which include antioxidant, anticarcinogenic, antibacterial, anti-inflammatory, antiviral, antiproliferative, and antiallergic activities.[16]

Recent studies have shown that the concentrations of these phytochemicals in *M. pendans* can vary based on factors such as geographic origin, extraction method, and the maturity of the plant at harvest.[12,16] For instance, ethanol extracts of *M. pendans* have been reported to contain high levels of total phenolic content (TPC), measured at 330.61 ± 2.13 mg GAE/g, and total flavonoid content (TFC), ranging from 48.5 to 63.28 ± 1.75 mg QE/g.[16,17] Notably, the ethyl acetate fraction contained an even higher TFC, reaching 91.5 mg QE/g.[17] In contrast, extracts obtained using the Supercritical Carbon Dioxide (SC-CO_2) method yielded significantly lower TPC and TFC values— 16.41±1.08 mg GAE/g and 2.96 ± 0.15 mg QE/g respectivly. This is likely due to the lipophilic nature of SC-CO_2, which may limit the solubility of polar compounds such as flavonoids.[12] Further chemical profiling using High-Performance Liquid Chromatography (HPLC) enabled the identification and quantification of specific flavonoid constituents in the ethanol extract. The identified flavonoids include kaempferol (13.767 mg/g), apigenin (4.700 mg/g), quercetin (0.030 mg/g), luteolin (0.005 mg/g), and rutin (0.003 mg/g).[16]

TABLE 1. *M. pendens* active compound [2,13–16]

Compound	Class	Subclass/Group
Kaempferol	Flavonoid	Flavonol
Luteolin	Flavonoid	Flavone
Rutin	Flavonoid	Flavonol glycoside (quercetin)
Quercetin	Flavonoid	Flavonol
Apigenin	Flavonoid	Flavone
Procyanidin B1	Flavonoid	Proanthocyanidin (dimer)
Procyanidin polymer	Flavonoid	Condensed tannin
(+)-Catechin	Flavonoid	Flavan-3-ol
Butein	Flavonoid	Chalcone
Biflavonoid	Flavonoid	Flavonoid dimer
3″-Methoxy-epicatechin dimer	Flavonoid	Proanthocyanidin (condensed tannin)
Anthocyanin	Flavonoid	Glycosylated anthocyanidins (plant pigments)
Pomolic acid	Triterpenoid	Pentacyclic triterpenoid (ursane)
Betulin	Triterpenoid	Pentacyclic triterpenoid (lupane)
β-Sitosterol tridecanoil glycoside	Phytosterol	Sterol glycoside with fatty acid
Guaiacol	Phenol	Methoxyphenol (o-methoxyphenol)
4-Methylcatechol	Phenol	Methylated catechol derivative
2,6-Dimethoxyphenol (Syringol)	Phenol	Dimethoxyphenol
Gallic acid	Phenolic acid	Hydroxybenzoic acid
Caffeic acid	Phenolic acid	Hydroxycinnamic acid
p-Coumaric acid	Phenolic acid	Hydroxycinnamic acid
Ferulic acid	Phenolic acid	Hydroxycinnamic acid
Benzoic acid	Phenolic acid	Simple aromatic acid (C6-C1)
Rosmarinic acid	Polyphenol	Caffeic acid ester

Pharmacological Activities and Mechanism of action
Anti-inflammatory and wound healing Effects

Inflammation is a crucial physiological response that protects tissues from physical, chemical, or microbial injury. When triggered, immune cells release important pro-inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and

nuclear factor-kappa B (NF-κB). These mediators play vital roles in initiating and regulating the body's defense mechanisms against pathogenic threats. However, prolonged or excessive inflammation can lead to tissue damage and contribute to the development of chronic diseases.[18,19]

M. pendans has demonstrated notable in vivo anti-inflammatory activity. In animal study, administration of its ethanol extract significantly reduced systemic TNF-α levels and facilitated the healing of *Porphyromonas gingivalis*-induced pulp inflammation in Sprague-Dawley rats. The therapeutic effects observed were comparable to those of calcium hydroxide ($Ca(OH)_2$).[20,21] Histopathological evaluations of the inflamed pulp tissue indicated a reduction in inflammatory cell infiltration and improved vascularization following treatment. Notably, administering the extract for four consecutive days resulted in a marked improvement in tissue healing.[20] s. Supporting these findings, an in vivo and in silico study by Falya et al. identified several key bioactive constituents of *M. pendans*, including quercetin, cholesta-22,24-dien-5-ol, and procyanidin B1. These compounds demonstrated strong binding affinities (−8.4 to −10.2 kcal/mol) with critical molecular targets involved in inflammation and tissue regeneration, such as matrix metalloproteinases (MMPs), epidermal growth factor receptor (EGFR), and fibroblast growth factor receptor (FGFR). These interactions suggest that *M. pendans* may exert its anti-inflammatory and regenerative effects by modulating MMP activity and activating receptor-mediated signaling pathways related to tissue repair as shown in table 2.[20]

TABLE 2. *M. pendans* anti-inflammatory and regenerative effects by modulating MMP activity and activating receptor-mediated signaling pathways related to tissue repair

No	Compound	Binding affinity (kcal/mol)		
		MMP	EGFR	FGFR
1	Quercetin	-9.6		
2	Cholesta-22,24-dien-5-ol, 4,4-dimethyl-(22E)-4,4-dimethylcholesta-22,24-dien-6-ol		-9.1	
3	Procyanidin B1			-9.3

Inhibiting MMPs may enhance the stability of the extracellular matrix (ECM), which, in turn, facilitates tissue regeneration and wound healing. At the same time, activating EGFR stimulates downstream signaling pathways like MAPK and PI3K/Akt, which are crucial for promoting keratinocyte proliferation and migration—both essential processes for effective wound closure. Similarly, activating FGFR has been linked to the initiation of angiogenic pathways, contributing to vascular remodeling and tissue repair. These mechanism insights are further supported by an in vivo study that highlights the wound healing potential of *M. pendans*. The topical application of a 0.1% ethyl acetate hydrogel formulation derived from *M. pendans* significantly improved the healing process in a diabetic animal model.[17]

Antimicrobial Effects

The rapid emergence of antimicrobial resistance has significantly complicated the treatment of infectious diseases, underscoring the urgent need for novel antimicrobial agents. Myrmecodia pendans has shown broad-spectrum antimicrobial activity against various Gram-positive and Gram-negative bacterial species, including *Staphylococcus aureus*[22], *Porphyromonas gingivalis*[7,23], *Streptococcus sanguinis, Treponema denticola*[24,25], *E. faecalis*[13], *Streptococcus mutans*[26], *Klebsiella pneumoniae, Streptococcus dysenteriae*[25], *Escherichia coli, Salmonella spp, Bacillus spp., Fusobacterium nucleatum*,[3,27] *and Shigella dysenteriae*[28].

In vitro tube dilution assays conducted by Majid et al. demonstrated that *M. pendans* extract inhibited *S. aureus* with a minimum inhibitory concentration (MIC) of 125 mg/mL and a minimum bactericidal concentration (MBC) of 500 mg/mL. The same study reported activity *against methicillin-resistant Staphylococcus aureus* (MRSA), with an MIC of 500 mg/mL.[22] Other study found that *M. pendans* suseptible to *Porphyromonas gingivalis (P. gingivalis),* a key pathogen in periodontal biofilm. Its ethanol extracts produced inhibitory zones at 25% and 50% concentrations in disc diffusion assays.[23] Whereas, microdilution tests revealed an MIC of 1.95 mg/mL, comparable to *M. tuberosa*.[10] For *S. sanguinis*, another important contributor to dental plaque and periodontal disease, methanol extracts of *M. pendans* showed an MIC of 9.77 µg/mL, while terpenoid isolates exhibited higher MICs around 78.13 µg/mL.[25,29]

Antibacterial activity of *M. pendans* against *E. faecalis* was also confirmed.[30] Kuswandani and collegue reported that microdillution assay obtain MIC values ranging from 49 to 390 µg/mL, depending on the extract and fraction used. Notably, a combination of *M. pendans* hexane and ethyl acetate fractions exhibited superior activity against *E. faecalis*, likely due to the extraction of both non-polar and semipolar bioactive compounds.[1]

Biofilms contribute to microbial persistence and resistance to antimicrobials. It makes bacteria become 1000 times more resistant to antibacterial than organisms that cannot form biofilms.[8] Alibasyah and collegue found that a high concentration (75% and 100%) of methanol extract of M. pendans inhibit *P. gingivalis* biofilm formation.[7] However due to the high extract consentration, it was consider less effective as antibofilm of *P. gingivalis*. *M. pendans* ethanol extracts showed potent antibiofilm activity against *S. sanguinis* and *T. denticola* at 100% concentration, comparable to 0.2% chlorhexidine.[24] Another study using microtiter-plate assays demonstrated that *M. pendans* methanol extract could eradicate *E. faecalis* biofilms, with minimum biofilm eradication concentration (MBEC) values of 100 mg/mL (1 minute) and 25 mg/mL (30 minutes).[8] The n-hexane fraction (1%) displayed inhibitory activity against S. mutans, with a zone of inhibition measuring 10.45 mm in disk diffusion method.[30–32] A specific terpenoid compound ($C_{31}H_{50}O_3$) isolated from *M. pendans* exhibited strong antibacterial and antibiofilm activities against *S. mutans*, with an MIC of 40 µg/mL and minimum biofilm inhibitory concentration (MBIC) of 50 µg/mL, indicating greater sensitivity compared to S. sanguinis.[26] Beyond antibacterial effects, *M. pendans* also demonstrates antifungal activity. An aqueous fraction was shown to inhibit *Candida albicans*, with an MIC of 1,250

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µg/mL. The relatively high MIC may be due to the low solubility of active compounds in water.[6]

The antimicrobial efficacy of M. pendans is primarily attributed to its rich content of flavonoids, alkaloids, phenols, saponins, tannins, and terpenoids. Flavonoids exert antibacterial effects by inhibiting nucleic acid synthesis (e.g., DNA gyrase, topoisomerase), disrupting cytoplasmic membranes, impairing energy metabolism, and interfering with bacterial adhesion and biofilm formation. Structural modifications such as hydroxylation, methylation, geranylation or prenylation may influence their bioactivity. [33]

Alkaloids, particularly due to their nitrogen-containing structures, may inhibit bacterial efflux pumps and alter membrane fatty acid content, thereby increasing membrane permeability. Sanguinarine, for example, has been shown to impair biofilm formation and act synergistically with vancomycin by enhancing bacterial sensitivity. Phenolic acids like gallic and ferulic acid disrupt membrane integrity by altering charge, pore formation, and hydrophobicity, leading to intracellular leakage.[34] Saponins damage cell wall and cell membranes, impair the stability of the cytoplasmic membrane and cause cell leakage[8]. Tanin compromise cell wall and membrane stability through hydrolysis of ester bonds, resulting in increased permeability and volume reduction of the cell.[6,8]

Terpenoids exhibit broad antimicrobial properties, including inhibition of efflux pumps, interference with membrane integrity, and disruption of ergosterol biosynthesis. Ergosterol biosynthesis important for lipid biosynthesis in lipidbilayer and affecting membrane integrity. These effects may be attributed to the hydroxyl groups and hydrophobic nature of terpenoids, which facilitate enzyme inactivation and membrane penetration.[34,35] Studies using SEM, flow cytometry, and confocal microscopy have confirmed these mechanisms.[35]

Terpenoid exhibit antibacterial activity agains multi drugs resistant (MDR) pathogen by disrupting membrane lipid; the action is conditional upon the amount of lipid present in the bacterial membrane.[36] Furthermore, terpenoids show antibiofilm activity, although the precise mechanisms remain under investigation.[35]

Targeting bacterial cell wall biosynthesis, particularly peptidoglycan synthesis enzymes such as *N*-acetylglucosamine enolpyruvyl transferase (MurA) and *N*-acetylglucosamine reductase (MurB), represents a promising antimicrobial strategy. In silico studies by Gartika et al.[37] demonstrated that M. pendans bioactive compounds bind effectively to MurA and MurB (binding affinities ranging from −6.84 to −11.25 kcal/mol) as shown in table 3. Molecular docking also confirmed interactions with other essential bacterial targets, including bacterial enzymes that important in cell wall biosynthesis (penicillin-binding proteins/PBPs), virulence and biofilm formation (Sortase A/SrtA), protein synthesis (DNA gyrase, RNA polymerase, ribosomal proteins), and quorum-sensing regulators (cytolysin M (ClyM), FsrB, GBAP, and PgrX). Moreover, the synergistic potential of *M. pendans* with conventional antibiotics has been observed, suggesting its utility as an adjunct agent for combating drug-resistant infections.[13]

Table 3. Binding affinity of the compound against bacterial proteins

No	Compound	Binding affinity (kcal/mol)							
		PBP	MurB	SrtA	DNA Gyrase	ClyM	FsrB	GBAP	PgrX
Flavonoid compound									
1	butein	-6.9	-7.2	-5.6	-6.6	-8.3	-5.8	-5.5	-6.6
2	biflavonoid	-11.2	-11.5	-7.6	-8.6	-10.4	-7.7	-6.9	-8.5
3	3''-methoxyepicatechin-3-O-epicatechin	-10.5	-9.5	-7.0	-8.3	-9.4	-7.1	-6.3	-9.0
Phenolic compound									
4	2-dodecyl-4-hydroxylbenzaldehyde	-8.0	-7.9	-6.5	-7.1	-7.8	-6.0	-5.3	-6.3
5	2-dodecyl-4-hydroxylbenzaldehyde	-7.5	-8.4	-6.4	-7.2	-8.5	-5.8	-5.2	-6.7
Terpenoid compound									
6	pomolic acid	-10.1	-8.8	-7.1	-7.9	-8.9	-6.6	-6.0	-7.4
7	betulin	-7.5	-6.4	-6.7	-8.1	-7.9	-6.1	-5.3	-6.4
8	sitosterol-(6'-O-tridecanoil)-3-O-ß-D-glucopyranoside	-8.1	-6.8	-5.4	-6.0	-8.3	-6.7	-4.6	-6.4

Antioxidant activities

The antioxidant/free radical scavenging activity of *M. pendans* extracts has been primarily evaluated using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. This widely accepted method measures a compound's ability to donate hydrogen atoms or electrons, which neutralizes free radicals and forms resonance-stabilized radical intermediates.[16] Numerous studies have shown that *M. pendans* exhibits strong DPPH radical scavenging activity, which associated strongly with its high flavonoid and polyphenol content. These phytochemicals are recognized for their ability to reduce oxidative stress, a key factor contributing to inflammation, microbial resistance, and various chronic diseases.[12,16]

The antioxidant activity of *M. pendans* varies depending on the extraction method and solvent polarity. *M. pendans* ethanol extracts obtained through water bath extraction have demonstrated superior antioxidant activity, with IC_{50} values ranging from 96.09 to 96.21 µg/mL. This result comparable to ascorbic acid antioxidant activity.[16] In comparison, the aqueous and ethyl acetate fractions exhibited IC_{50} values of 224.21 ± 17.08 µg/mL and 105.98 ± 8.32 µg/mL, respectively.[15] Notably, extracts obtained via supercritical CO_2 (SC-CO_2) extraction showed significantly lower antioxidant activity, with an IC_{50} of 3620 ± 120 µg/mL, likely due to the limited solubility of polar antioxidant compounds in the non-polar SC-CO_2 solvent.[12] Overall, the results from the DPPH assay indicate that ethanol extracts of *M. pendans* possess the highest antioxidant potential, with activity levels comparable to those of ascorbic acid. Additionally, the extract's ability to scavenge free radicals grew as its concentration increased, demonstrating the dose-responsiveness of its antioxidant activity.

Antidiabetic and antihyperlipidemic activities

Diabetes Melitus is highly prevalent metabolic disorder that continues to increase in incidence rates worldwide each year.[38] Chronic hyperglycemia in diabetic patients disrupts lipid metabolism, leading to elevated cholesterol levels. This dysregulation promotes the progression of atherosclerosis,

significantly increasing the risk of coronary artery disease, heart attacks, and strokes by approximately two to three times.[39] Several preclinical studies have demonstrated the hypoglycemic effects of *M. pendans* extracts. Both water and ethanol extracts of *M. pendans* have been shown to significantly reduce blood glucose levels in diabetic rats and mice.[40–42] In one study, oral administration of the *M. pendans* water extract at a dose of 360 mg /200 gBB for 21 days lowered blood glucose levels to 134.66 ± 2.59 mg/dL, comparable to the positive control (glibenclamide), which reduced glucose levels to 122.44 ± 0.51 mg/dL.[40] In another study, the *M. pendans* ethanol extract at 400 mg/kgBB resulted in blood glucose reduction to 239 mg/dL.[41] Additionally, in mice, a dose of 100 mg/kgBB of the ethanol extract decreased blood glucose to approximately 127 mg/dL, slightly outperforming glibenclamide, which produced a glucose level of 152 mg/dL.[42] Furthermore, *M. pendans* ethanol extract has been shown to improve lipid profiles in a type 2 diabetes mellitus rat model by reducing triglyceride and low-density lipoprotein (LDL) levels, while increasing high-density lipoprotein (HDL) levels and mitigating atherosclerotic changes.[41]

The antidiabetic and antihyperlipidemic properties of *M. pendans* are largely attributed to its rich flavonoid content. Flavonoids are known to inhibit carbohydrate-hydrolyzing enzymes such as α-glucosidase, maltase, and amylase, which helps reduce postprandial blood glucose levels. Additionally, flavonoids may enhance glucose uptake by upregulating glucose transporter-4 (GLUT4) expression and inhibiting intestinal glucose absorption.[43] They also facilitate cholesterol efflux through the activation of the PPARγ–LXRα–ABCA1/ABCG1 signaling pathway, helping to prevent atherosclerosis. Moreover, flavonoids modulate the activity of cholesterol-regulating enzymes such as HMG-CoA reductase, a key enzyme in hepatic cholesterol biosynthesis.[44]

Phytochemical analysis indicates that *M. pendans* contains tannins, which may also contribute to its antidiabetic effects. Tannins can promote insulin release, lower intestinal glucose absorption, and block the activity of α-glucosidase and amylase. Additionally, they have been reported to promote the regeneration of pancreatic β-cells and lower plasma and cardiac triglyceride levels.[45,46] In summary, existing evidence supports the potential of M. pendans as a promising natural agent for the management of diabetes and dyslipidemia.

IV. Conclusion

M. pendans is a promising medicinal plant with well-documented anti-inflammatory, antimicrobial, antioxidant, antidiabetic and antihyperlipidemic activities properties. Its pharmacological potential is primarily attributed to its rich phytochemical composition, particularly the presence of flavonoids, phenolic compounds, alkaloids, tannins, saponins, glycosides, terpenoids, and triterpenoids. Althoug in silico, in vitro and in vivo studies have provided substantial evidence supporting its therapeutic efficacy, further clinical investigations and the development of standardized formulations are essential to facilitate its integration into contemporary medical practic.

Conflicts of Interest
The authors declare no conflict of interest.
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