REVIEW ARTICLE
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Antibacterial alternatives using the potential of the ant nest plant (*Myrmecodia* spp.)

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Abstract

New antimicrobial materials have drawn research and development attention due to antimicrobial resistance. Antimicrobial resistance is expected to pose a significant challenge to life in the future. This review comprehensively elucidates the potential of *Myrmecodia* spp. as an antibacterial agent by systematically selecting and reviewing the majority of relevant studies published in the past 10 years and retrieved from Scopus, PubMed, Web of Science, and related books. *Myrmecodia* spp. is a non-parasitic plant that grows as an epiphyte. These essential nutrients for the body, including flavonoids, alkaloids, polyphenols, tannins, and saponins, are found within plants. *Myrmecodia* spp.'s compound functions as an antibacterial agent. This review synthesizes information from multiple sources detailing *Myrmecodia* spp.'s antibacterial capacity through various testing methods.

Keywords: active compound, antibacterial, feed additive, health, *Myrmecodia* spp.

Introduction

Plants with health-promoting and food-secure bioactive compounds are naturally endowed by nature [1]. Indonesia, with its abundant tropical diversity, is unique. Native Indonesian plants with emerging active compounds are emerging as alternatives for enhancing the livestock sector [2–6]. Lisnanti *et al.* [7] further highlight *Pluchea indica* L.'s role in maintaining livestock health and boosting production through its bioactive compounds. According to Suwignyo *et al.* [8], implementing restriction and refeeding practices can boost livestock production. *Myrmecodia* spp., a plant that often grows on big trees in South-east Asia to New Zealand [9], holds intriguing antibacterial properties.

In rural Papua, swollen parts of *Myrmecodia* spp. are used as a substitute for medical treatment. Conditions including stomach ulcers, hemorrhoids, nosebleeds, back pain, skin rashes, allergies, gout disorders, stroke, coronary heart disease, tuberculosis, tumors, cancer, hepatitis, rheumatism, and diarrhea can be treated with water boiled with *Myrmecodia* spp. [9, 10]. Environmental pollution in developing countries poses a significant threat to public health, according to Baihaqi *et al.* [5].

Myrmecodia spp. is an epiphytic plant with ant-nest shaped spaces or holes. It derives support from other plants. While not harmful to their hosts, this plant varies from parasitic ones as it does not cause harm [11]. This plant's active components enhance chicken egg fertility [12], regulate broiler chicken's fat and liver proportions [13], and shield them from H5N1 virus attacks [14]. According to Atanasov *et al.* [15], the future use of natural ingredients in traditional Indonesian medicine will be cost-effective and have minimal side effects.

This review aimed to explore the potential of active compounds from *Myrmecodia* spp. as an alternative antibacterial agent, as well as to prevent cases of antimicrobial resistance.

Content/Compound/Substance of *Myrmecodia* spp.

Myrmecodia spp. contains antibacterial flavonoids, alkaloids, saponins, polyphenols, tannins, and essential nutrients. The ant nest plant's primary bioactive compound is flavonoid. Research on anti-cancer effects of bioactive terpenoids isolated from

ant nest plants in Papua against ovarian cell lines remains unexplored [9]. Bhat *et al.* [16] reported their antimicrobial mechanism as membrane damaging. According to Tao *et al.* [17], flavonoids exhibit antioxidant properties, safeguarding cells from damage inflicted by free radicals. Flavonoids can bind to and disrupt both extracellular and integral proteins, resulting in cell wall rupture due to intolerable cytoplasmic pressure. Tannins were reported to inhibit bacterial proteases by binding to bacterial cell walls [18]. Flavonoids, as phenolic compounds, bind to proteins and obstruct microbial enzyme functions, disrupting metabolic pathways.

Saponins can cause cell lysis by increasing membrane permeability. Saponins induce microbial cell lysis or rupture on interaction. Alkaloids interfere with the peptidoglycan component of bacterial cells, thereby inhibiting their growth. Polyphenols denature cell proteins and damage cell membranes, thus demonstrating antibacterial activity. The efficacy of phenol as an antibacterial agent varies with its concentration. The thin phospholipid layer during bacterial division makes the cell more susceptible to phenol damage [19].

Tannins inhibit bacteria by damaging their cell membranes. Tannins contribute to enzyme binding through their astringent properties [20]. Tannins inhibit the function of antimicrobial enzymes such as cellulose pectinase and xylanase, contributing to their antimicrobial effect. Tannins can poison cell membranes, inactivate enzymes, and disrupt cellular functions and genetic material, ultimately poisoning and killing bacteria. Tannins function as antibacterial agents by forming protein complexes and participating in hydrophobic interactions. Formation of hydrogen bonds between tannins and bacterial protein enzymes can lead to denaturation and disruption of metabolism. Tannins, including tannic acid, can impair metabolism, cell wall and protein synthesis, and enzyme function [21].

Potential of *Myrmecodia* spp. as an Antibacterial Agent

According to Achmad *et al.* [22], the *Myrmecodia* spp. flavonoid extract suppresses the growth of *Streptococcus mutans*, with the degree of suppression increasing as concentration rises. The ethanol extracts at concentrations of 25% and 50%, as well as *Myrmecodia* spp. decoction, were found to be effective against *Escherichia coli* [23]. The ethanol extracts showed greater inhibition than *Myrmecodia* spp. decoctions. The width of the inhibition zone was directly related to the concentration of ethanol extract of *Myrmecodia* spp. The antibacterial activity of these alternative agents, when tested using active plant compounds, falls into the same categories reported by Ernilasari *et al.* [24]: Weak (<10–20 mm) and strong (more than 20–30 mm). *Myrmecodia* spp. tubers can be administered for an extended time, according to Attamimi *et al.* [25]. *Myrmecodia* spp. tubers contain antibacterial properties and their crude extract enhances these capabilities. The antibacterial properties of *Myrmecodia* spp. tubers are more potent than those of other natural plants. Soviati *et al.* [26] discovered that *Myrmecodia* spp. inhibits the formation of biofilms by *Streptococcus sanguinis* and *Treponema denticola*. The *Myrmecodia* spp. extract can replace antibiotics to prevent bacterial proliferation in the oral cavity. *Myrmecodia pendans* methanol extract has a minimum biofilm eradication concentration (MBEC) and may serve as an alternative endodontic irrigation solution, according to Kuswandani *et al.* [27]. The inhibition zone diameters for *E. coli*, as measured by Retnaningsih and Dayanti [28], were 10.95 mm, 12.24 mm, 13.89 mm, 15.02 mm, and 18.22 mm at concentrations of 20%, 40%, 60%, 80%, and 100%, respectively. Chloramphenicol caused an inhibition zone of 33.50 mm. The extract from *Myrmecodia* spp. suppresses *E. coli* growth due to its antibacterial properties.

The study by Astuti *et al.* [29] found that *Myrmecodia* spp. extract at a concentration of 25% prevented the growth of *Porphyromonas gingivalis*, with an average inhibition zone measuring 17.03 ± 0.832 mm. *Myrmecodia* spp. extract inhibited *P. gingivalis* growth with an average zone of 18.75 ± 1.10 mm at a 50% concentration. Efendi and Hertiani [30] examined *Myrmecodia* spp. extract's antimicrobial activity against *E. coli*, *Staphylococcus aureu*s, and *Candida albicans* utilizing the maceration technique with 70% ethanol and 5% dimethyl sulfoxide as solvents. The ethanol extract of *Myrmecodia* spp. showed antimicrobial activity against all tested microorganisms, as determined by its concentration-dependent inhibitory potential and alternative antibacterial agents.

Myrmecodia spp. extract is effective against a range of bacterial strains, including *S. aureus*, *Klebsiella pneumoniae*, and *Streptococcus dysenteriae*, both Gram-negative and Gram-positive [25]. *Myrmecodia* spp.'s flavonoid extract hinders *S. mutans* growth, amplifying inhibition as concentration increases [22]. Antibacterial mechanisms of *Myrmecodia* spp. were investigated through molecular docking by Satari *et al.* [31]. Bioflavonoids show the strongest binding affinity towards most proteins. Biflavonoids form noncompetitive inhibitions by binding to three distinct residues. These compounds can function as leads for creating antibacterial agents in diverse pathways.

Myrmecodia spp. extracts hindered the growth of both *Enterococcus faecalis* and *S. mutans*. The polarity of the solvent affected the inhibitory potentials against *E. faecalis* and *S. sanguinis*. An inhibition zone of 28.5 mm was reported for *S. mutans* [32], yielding the strongest results. The inhibition zone diameter of ethyl acetate extracted from *Myrmecodia* spp., which reportedly showed maximum bacterial growth inhibition by Binartha *et al.* [33], was 21 mm, and its alternative antibacterial power directly corresponded to

the concentration. The ant nest saffron lozenges (*M. pendans*) were 7.5% more effective than chewed nest lozenges [34]. Kurnia *et al.* [35] reported that extracts from *Myrmecodia* spp. contained phenolic compounds, such as steroids, steroid glycosides, triterpenoids, and phloroglucinol, which inhibited bacterial growth. Two new flavonoid derivatives were identified through the Kirby–Bauer method using active plant compounds as inhibitors. *Myrmecodia* spp. contains flavonoids that exhibit the potential to suppress the growth of *E. faecalis*, indicating potential alternative treatments using herbal remedies and the discovery of antibacterial agents for combating pathogenic dental caries [36]. The minimum biofilm inhibition concentration for terpenoid active compounds against *S. mutans* is 50 parts per million (ppm), while the MBEC is reached within 1 min at 40%. Compounds from *M. pendans* with terpenoid structure demonstrate potential for alternative antibacterial uses, particularly in biofilm inhibition [37]. The secondary metabolites from *M. pendans* are effective as therapeutic anti-QS agents [38].

Astuti *et al.* [39] identified flavonoids and tannins as bioactive compounds in *M. pendans*, ant nest plants. Ant nest plants display antibacterial properties. Alibasyah *et al.* [40] found that compounds derived from *M. pendans* ethyl acetate extract, specifically diterpenoids and biflavonoids, exhibit antibacterial properties against *P. gingivalis*, as determined by the Kirby–Bauer method. In the study, six iridoids showed antibacterial activity against *S. aureus*, each with a minimum inhibitory concentration (MIC) above 100 μg/mL, while the MICs for the other two were 19.57 and 39.06 μg/mL. Nurdin *et al.* [41] found that *M. pendans* Merr (Rubiaceae) microparticles from Papua Island, Indonesia, encapsulated in polylactic-co-glycolic acid and containing terpenoids, inhibited the growth of *E. faecalis*. Scanning electron microscope, Fourier-transform infrared spectroscopy, and ultraviolet–visible spectrometry results on *M. pendans* Merr were consistent with those using the encapsulation method. In the terpenoid bacteria test, encapsulated *E. faecalis* colonies exhibited greater activity than nonencapsulated ones.

The ethyl acetate extract of the ant nest plant was identified as containing phenolics, tannins, flavonoids, and terpenoids through phytochemical analyses. The antibacterial activity of the ethyl acetate fraction against *S. sanguinis* was stronger than chlorhexidine gluconate, with MIC values of 31.25 ppm and 0.49 ppm, respectively [42]. The aqueous extract of *Myrmecodia* spp. outperforms other extracts in anticancer activity, according to Soeksmanto *et al.* [43]. The IC_{50} values were different for water extract A (the inhibition of cancer cells growth: HeLa and MCM-B2), with HeLa having a lower value (27.61 ppm) compared to MCM-B2 (54.76 ppm), and for water extract B, where HeLa had a slightly higher value (29.36 ppm) but MCM-B2 had a notably higher value (74.20 ppm). The water extract showed greater anticancer potential than the ethyl acetate and n-butanol extracts.

The ant nest plant's active terpenoid compound matches chlorhexidine's effect on *S. mutans* biofilms for a minute, but the disparity emerges at 30 min. The expression of *S. mutans* ATCC 25175 biofilm's mRNA is associated with terpenoids from ant nest plant isolates [44]. Ant nest plants may yield new antibacterial compounds. The crude extract of ant nest plants, tested by Crisnaningtyas and Rachmadi [45], restrained the growth of *Salmonella* spp., *E. coli*, and *Bacillus* spp. Astuti *et al.* [46] found that an ethanol extract from *M. pendans* hindered *Fusobacterium nucleatum* growth.

The non-polar solvent n-hexane from the ant nest plant was effective against *E. faecalis* cps2 at a concentration of 80%. About 20% ethyl acetate solvent of the ant nest plant fraction inhibited growth of *E. faecalis* cps2, while 60% water solvent was needed. The ethyl acetate extract from ant nest plants yields superior results compared to those obtained using n-hexane or water solvents according to Binartha *et al.* [33]. Rabil *et al.* [44] found that treating *S. mutans* ATCC 25175 biofilms with *M. pendans* terpenoid and chlorhexidine for 30 min caused distinct damage to the cell membranes of the *S. mutans* ATCC 25175. Terpenoid compounds extracted from *Myrmecodia* spp. at a concentration of 78.13 ppm suppress *S. sanguinis* growth, according to Attamimi *et al.* [25]. According to Apriyanti *et al.* [28], the ant nest plant extract suppresses *S. mutans*.

M. pendans' ethyl acetate fraction (50 μg/mL) led the lymphocyte proliferation assay with the most activity, whereas *M. tuberosa*'s ethanol extract (50 μg/mL) produced the highest macrophage phagocytic index. *M. pendans* tubers have potential as immunomodulatory agents [47]. Sudiono *et al.* [48] reported that although there was no difference in the contents of phytochemical compounds of both 70% ethanol and boiling water extracts of the ant nest plant, these compounds serve as antibacterial, anticancer, and antioxidant agents. As a significant source, this plant yields various flavonoids and phenolic compounds. About 70% ethanol extract of *M. pendans* did not harm fibroblasts in the 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide assay. Greater extract concentrations led to more viable cells and lower inhibition rates of cell growth. The new research increases our comprehension of the ant nest plant's herbal benefits, particularly its antibacterial and anticancer properties, without causing harm to normal cells. Yusni *et al.* [49] prepared gMPAE through spray-drying, yielding irregularly-shaped microparticles characteristic of spray-dried formulations. In the subacute toxicity study, no significant differences were observed in the physical or behavioral characteristics of either the placebo-treated or gMPAE-treated mice compared to controls. Twenty-eight and 14 days of treatment showed no mortality or toxic effects.

Conclusion

Myrmecodia spp. is employed in traditional medicine. Bacteria, including *S. mutans*, *E. coli*, *S.*

sanguinis, *T. denticola*, *S. aureus*, *K. pneumoniae*, *S. dysenteriae*, *P. gingivalis*, *C. albicans*, *E. faecalis*, *Salmonella* spp., *Bacillus* spp., and *F. nucleatum*, can be inhibited and suppressed using its extract as an alternative antibacterial agent. The medicinal value of this plant lies in the individual compounds, the mechanisms of which are known or yet to be discovered. This potential exceeds that of traditional ethnomedicine used by native communities. More evidence is required to confirm the ability of *Myrmecodia* spp. to combat pathogenic bacteria.

Author's Contributions

EFL and WPL: Developed the idea of this review. EFL and ZAB: Drafted the manuscript. WPL and EPH: Revised and edited the manuscript. MAA: Participated in preparing and critical checking of this manuscript. ABY: Edited the references. All authors have read, reviewed, and approved the final manuscript.

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Competing Interests

The authors declare that they have no competing interests.

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