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Phytoconstituents and biological activities of *Melaleuca cajuputi* Powell: A scoping review

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ABSTRACT

Melaleuca cajuputi Powell is a medicinal plant of the Myrtaceae family that is widely distributed in Asia and Southern Australia. The Major bioactive compounds reported in *M. cajuputi* powell include quinones, flavonoids, phenols, alkaloids, glycosdes, 18-cineol, α-pinene, linalool, β- caryophyllene, nerolidol, and terpenoids. Reports from several studies have shown an excellent antimicrobial effect of *M. cajuputi* Powell extracts against bacteria, viruses, protozoa, and fungal species. The plant also has remarkable insecticidal and antioxidant properties. Various toxicity experiments on rats and brine shrimps, on the other hand, have revealed a mild toxicity effect. With the potent biological activities and mild toxicity reported in *M. cajuputi* Powell, the plant could be exploited to develop potential plant-based novel drugs.

INTRODUCTION

Herbal formulations are not uncommon in treating diseases as they have been utilized to treat different diseases in humans and animals for millennia. Despite screening conducted on several other plant species, research studies on plant-based bioactive compounds remain paramount as better and safer agents with a broad spectrum of bioactivity are greatly needed (Arifullah *et al*., 2014). There is a long history of the medicinal uses of the plant in Southeast Asian countries, with some being sold in different forms for health remedies (Liew *et al*., 2020). It is an appropriate time to develop novel bioactive compounds from natural sources such as higher plants (Manga *et al*., 2018). This is due to the antimicrobial, insecticidal, and antioxidant properties these plants possess; therefore, they are accepted for everyday use in both traditional and modern medicine (Arifullah *et al*, 2014). Herbs are essential in dealing with different health conditions; this could be attributed to their enormous bioactive compounds, thus attracting the interest of researchers to the field of drug discovery (Oliveira *et al*., 2020).

Melaleuca cajuputi Powell plant is a member of the Myrtaceae family, popularly called "Gelam," "kayu putih," "paperbark," "Cajuput tree," "*Melaleuca leucadendron,*" "Cajuput oil," or "tea tree" (Sharif *et al*., 2019). The leaves are greyish-green and fragrant with a relaxing aroma. Its height ranges from 4 to 9 cm (Fig. 1). The flowers are whitish with a unique stamen with 16 cm long spikes, which are said to resemble bottlebrushes, and the encircled seeds are essential in folk medicine (Sharif *et al*., 2019). *Melaleuca* essential oil has a yellow-green color with a solid herbal aroma that is similar to eucalyptus essential oil (Wińska *et al*., 2019). The tea tree can be found naturally in tropical areas including Malaysia, Indonesia, Thailand, and Australia. *Melaleuca* forests grow well in estuaries and coastal swamps in the hot and humid tropics with a temperature range

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Figure 1. *Melaleuca cajuputi* Powell in its natural habitat (source: author).

of 17°C–33°C. The *Melaleuca*-rich region receives an average of 1.3–1.7 mm of precipitation per year, with typical monsoon conditions (Lim and Midon, 2001).

Several studies on the different parts of *M. cajuputi* Powell extracts have been reported previously (Al-Abd *et al*., 2015; Noor *et al*., 2020). However, the information obtained from these studies is extremely fragmented. Due to this, an in-depth literature review on *M. cajuputi* Powell will undoubtedly provide the necessary information which is crucial in understanding the knowledge gaps of this plant and stimulating future research opportunities. This scoping review focuses on the types of *M. cajuputi* Powell extracts examined and their phytoconstituents as well as the research findings on their biological activities.

METHODOLOGY

This review followed the methodological framework established by Arksey and O'Malley (2005). In addition, this study was processed according to the procedure of systematic database search, selection, and inclusion strategy as described by (Moher *et al*., 2009). This scoping review consisted of defining objectives, searching for relevant data, proper selection, gathering relevant information based on the study objectives, and summarizing the findings.

Relevant studies on the phytoconstituents and biological activities of *M. cajuputi* Powell published in the last two decades (2001 to 2022) were retrieved from Google, Science Direct, Google Scholar, Scopus, and PubMed. However, only research papers on *M. cajuputi* Powell written in English from January 2001 to early 2022 were reviewed. Theses, dissertations, and conference proceedings were included as well. Several key search terms were included such as "*M. cajuputi* Powell," "Gelam extracts," "tea tree," "cajuput tree," "*M. leucadendron*," "antibacterial," "antifungal," "antimicrobial," "antioxidant activities," "insecticidal," "toxicity effect," "bioactive," and "phytochemical compounds" by using the Boolean operators of AND/OR (Table 1).

Figure 2 illustrates the record selection criteria. Research articles from the various databases were first harmonized and sorted based on the titles to exclude all duplicates. Titles and abstracts were reviewed to exclude all records with inaccurate subjects or outcomes related to this review. Lastly, the full-text articles were screened further to exclude other irrelevant data.

Data recording

Relevant data regarding studies of *M. cajuputi* Powell were recorded. The information obtained consisted of various parts of the plant, such as leaves, flowers, stems, and essential oils (Fig. 3). The extraction procedures, bioactive compounds, type of biological activity, methods employed/outcomes, organisms tested, and references are shown in Table 2.

Collection, reporting, and summary of the review outcomes

All findings were recorded and summarized in Table 2. The research gaps were identified to establish a roadmap for future research to provide knowledge on novel drug discoveries from *M. cajuputi* Powell.

RESULT AND DISCUSSION

Medicinal plants are essential sources of unique bioactive compounds in creating new, effective, and safe medicines (3,311) research articles on the bioactivity of different parts of *M. cajuputi* Powell were retrieved via an electronic survey in interdisciplinary databases, with 325 duplicates removed from the list. As shown in Figure 2, The remaining 2,986 articles were then checked for title and abstract eligibility. In all, 2,892 irrelevant articles were excluded, leaving 94 possible relevant articles for full-text analysis, out of which only 34 papers were selected based on the review's selection criteria and objectives.

Ethnomedicinal uses of *M. cajuputi* Powell

Medicinal plants have been reported and investigated for natural bioproducts to control diseases and lessen reliance on conventional antibiotics worldwide (Isah *et al*., 2020). According to historical records, herbal therapy and Ayurvedic medicine have been utilized in China for over 5,000 years (Idris *et al*., 2019). Moreover, humans also have been relying heavily on natural products such as plant-based food and treatment for thousands of years (Idris *et al*., 2019). Herbal decoctions can be used in oral administration, topical application, or steaming for disease treatment, depending on the formulation and plant parts. Tablespoons, cups, and bottles are used to measure the dosage of these herbal formulations (Bunalema *et al*., 2014).

The leaves of Gelam are edible and are used to treat digestive problems, cough, common cold, and stomach pain (Daud *et al*., 2015). Meanwhile, herbal preparation made from *M. cajuputi* Powell leaves and stems is used to treat joint soreness, abdominal discomfort, and muscle ache (Wolter *et al*., 2002). Furthermore, tea tree leaves exhibit antimicrobial, antioxidant, anodyne, insect repellent, and anti-inflammatory properties and are utilized in traditional medicine to treat dyspepsia, burns, pain, and influenza (Ko *et al*., 2009).

Similarly, *M. cajuputi* Powell is an excellent producer of therapeutic essential oil that contains many phytochemicals (Hai *et al*., 2019). Steam or hydrodistillation extracts the Cajuput oil from the plant's leaves or other parts. It is utilized to heal wounds, body itch, coughs, stomach pains, asthma, and rashes in folk medicine, particularly in Southeast Asia (Toan *et al*., 2020). Additionally, the oil has a synergistic effect when combined with other plants in

Table 1. Keywords and search phrases used for literature search.

Keywords	Search phrases
#1 Biological activities	"Antimicrobial activity" OR "Antibacterial activity" OR "Antifungal agents" OR "Antioxidant activity" OR "Insecticidal effect" OR "Toxicity effects" AND "Bioactive compounds" OR "Phytochemical compounds."
#2 *M. cajuputi* Powell	"*Melaleuca* cajuputi Powell" OR "Gelam extract" OR "Tea tree" OR "Cajuput tree" OR "*M. Leucadendron*" OR "Cajeput oil".
#3	"Ethnomedicinal uses"
#4	#1, #2, AND #3

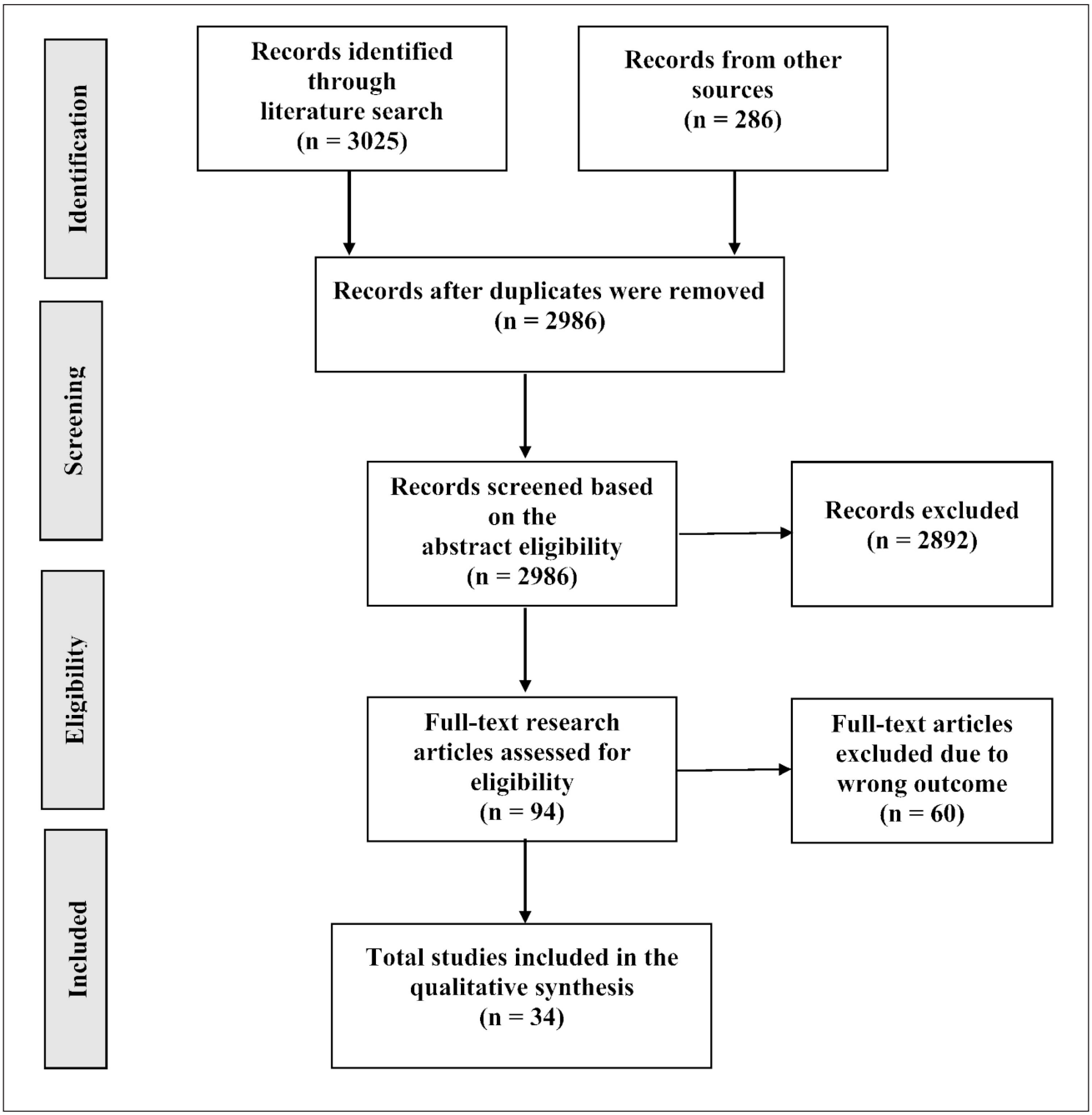

Figure 2. Record identification and selection protocol based on PRISMA guidelines (PRISMA, 2009).

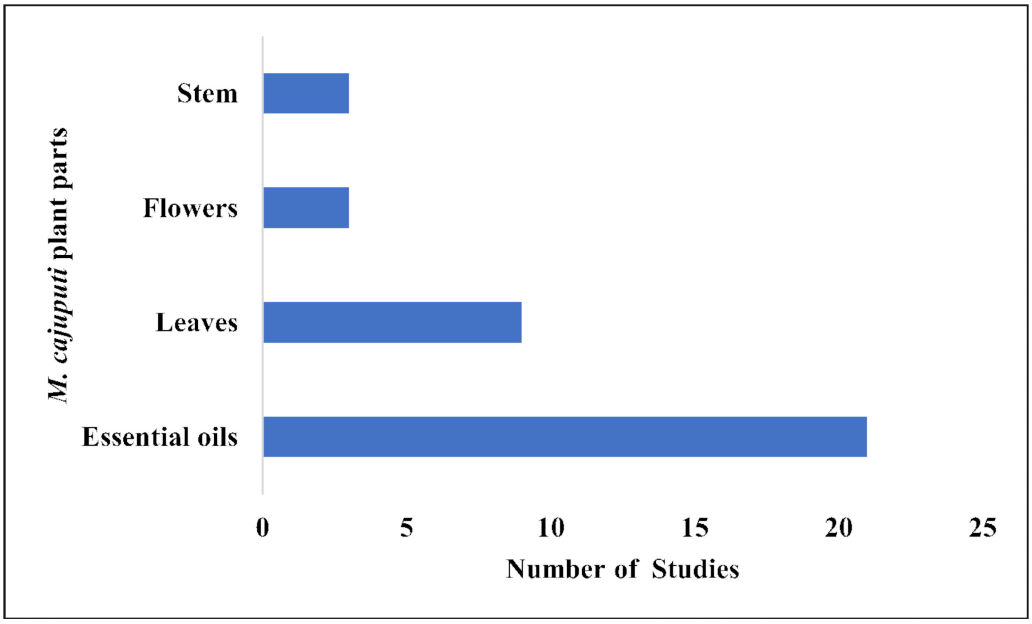

Figure 3. Bioactivity studies on the different parts of *M. cajuputi* Powell.

Table 2. Biological activities and phytochemical constituents of *M. cajuputi* Powell.

Plant part	Extraction method (solvent)	Analysis of phytoconstituents	Major phytoconstituents	Biological activities	Method/ outcomes	Organism tested (reaction)	References
Essential oil	Commercial	GC-MS/O	Active compounds reported: caryophyllene, 1,8-cineole, ylangene, α-pinene, nerolidol, and linalool	Flavoring ingredient	Nasal impact frequency	Not tested on organisms	(Septiana, Yuliana, and Wijaya *et al*., 2020)
Essential oil	Commercial	GC-MS	1,8-Cineole, β-caryophyllene, α-terpineol, α-pinene, and γ-terpinene	Flavoring agent	Metabolomics approach	Not tested on organisms	(Septiana, Yuliana, and Bachtiar *et al*., 2020)
Essential oil	Commercial	NR	NR	Antimicrobial	Broth microdilutions MIC 800–3200 µg/mL and 3,200–6,400 µg/ml against *S. aureus* and *E. coli,* respectively	*Staphylococcus aureus* DSM 1104 (S) and *E. coli* DSM 1103 (S)	(Thielmann *et al*., 2019)
Essential oil	Commercial	According to Pranarôm	Cineole, a monoterpene ether	Antibacterial	Disc diffusion (10.0 mm) at conc. of 6 µl/ paper disc	*Streptococcus pyogenes* CIP 104226 (S)	(Sfeir *et al*., 2013)
Essential oil	Commercial	NR	NR	Antifungal	Agar diffusion optimum growth inhibition at 1.5625% (*v*/*v*)	*Aspergillus flavus* IMI 242684 (S)	(Thanaboripat *et al*., 2007)

Continued

Plant part	Extraction method (solvent)	Analysis of phytoconstituents	Major phytoconstituents	Biological activities	Method/ outcomes	Organism tested (reaction)	References
Flowers	Maceration (methanol)	NR	NR	Antifilarial (targeting bacterial endosymbiont "*Wolbachia"*)	Cell culture (Aa23 cells)	Filarial worm (*B. pahangi*) and bacterial endosymbiont "*Wolbachia*" (S)	(Hnawia *et al*., 2012)
Flowers and fruit	Maceration (methanol)	Qualitative	Alkaloids, flavonoids, terpenoids, and saponins; others are quinones, steroids, tannins, and phenols	Antibacterial	MIC and MBC for flower extract were 1.67 and 2.083 mg/ml, respectively. For fruit, both MIC and MBC values were 3.334 mg/ml	*E. coli* ATCC 25922 (S)	(Isnaini *et al*., 2021)
Flowers and fruit	Maceration (methanol)	Qualitative	Alkaloids, flavonoids, terpenoids, and saponins; others are quinones, steroids, tannins, and phenols	Antifungal	Flower extract MIC and MBC were 3.125 and 25 mg/ml, respectively. Fruit extract, 3.125 and 12.5 mg/ml were the MIC and MBC, respectively	*Candida albicans* ATCC 10231 (S)	(Isnaini *et al*., 2021)
Leaves	Maceration (methanol)	NR	NR	Antimicrobial	Disc diffusion (10–20 mm) at conc. 1,000 µg/ml	*Staphylococcus aureus* (S), *Escherichia coli* (R), *C. albicans* (S), and *Aspergillus niger* (S)	(Khalaf *et al*., 2021)
Leaves	Maceration (methanol)	NR	NR	Antioxidant	IC_{50} values in the DPPH= 2,2-diphenyl-1-picrylhydrazyl assay were 34.60–60.97 µg/ml		(Khalaf *et al*., 2021)
Leaves	Maceration (methanol)	NR	NR	Antibacterial	Disc diffusion. The diameter zone of inhibition was 1.00 to 13.87 mm at 10 µl	*Shigella dysentriae* (S), *Bacillus* species (S), *Pseudomonas aeruginosa* (R), *E. coli* (R), *S. aureus* (S), *Vibrio cholerae* (S), and *Enterococcus faecalis* (S).	(Ukit *et al*., 2019)

Continued

Plant part	Extraction method (solvent)	Analysis of phytoconstituents	Major phytoconstituents	Biological activities	Method/ outcomes	Organism tested (reaction)	References
						Enterococcus faecalis ATCC 29212 (S),	
					Broth microdilutions	*P. aeruginosa* ATCC 10145 (S),	
Leaves	Maceration (ethanol)	NR	NR	Antibacterial	MIC and MBC for AgNPs were 7.81–31.25 µg/ml and 62.20–125 µg/ml, respectively	*E. coli* ATCC 25922 (S), *S. aureus* ATCC 29213 (S), *K. pneumoniae* ATCC 700603 (S), *E. coli* O157:H7 (S), *A. baumannii* ATCC 19606 (S)	(Paosen *et al*., 2017)
Leaves	Soxhlet and superficial fluid extraction (SFE) (hexane)	GC and GC/MS	Isoeugenitine, β-elemene, β-caryophyllene, α-humulene, viridiflorol, platyphyllol, β-eudesmol, bulnesol, (Z, Z)-farnesol, (E,E)-farnesal, 9-epi-β-caryophyllene, and δδ-elemene	NR	NR	Not tested on organisms	(Jajaei *et al*., 2010)
Leaves	Maceration (methanol, hexane, ethyl acetate, and dichloromethane)	NR	NR	Insecticidal	Hexane extract against *Ae. aegypti* LC_{50} 0.015 mg/cm^2 and *Aedes albopictus* 0.022 mg/cm^2 while dichloromethane extracts *Aedes aegypti* and *Ae. Albopictus,* the LC_{50} was 104.8 mg/l and 106 mg/l, respectively	*Aedes aegypti* and *Aedes albopictus*	(Bakar, 2020)
Leaves (essential oil)	Hydrodistillation	GCMS	1,8-Cineole (23.59%), (-)-α-pinene (9.12%), (-)-1S-β-pinene (5.87%), α-terpineol (4.91%), α-terpinene (4.74%), (β)-limonene (4.42%), β-caryophyllene (5.32%) and α-humulene (4.76%)	Antimycobacterial	Broth microdilution **(**resazurin microtiter assay**)** MIC values ranged between ≤0.5 and 16% (*v*/*v*)	*Mycobacterium tuberculosis* (S)	(Bua *et al*., 2020)

Continued

Plant part	Extraction method (solvent)	Analysis of phytoconstituents	Major phytoconstituents	Biological activities	Method/ outcomes	Organism tested (reaction)	References
Leaves (essential oil)	Commercial	NR	NR	Antitrichomonal	Broth microdilution MIC 0.08 ± 0.05% and 0.06 ± 0.05%	*Trichomonas vaginalis* (S)	(Thi Ha Trinh *et al*., 2021)
Leaves (essential oil)	Steam distillation (EO) organic solvent **(**methanol, aqueous, and decoction**)**	GCMS	The most dominant compounds are terpenoids (α-pinene (20.353%), β-caryophyllene (4.943%), and α-terpinene (3.556%)), α-pinene (2.026), α-phellandrene (2.974), and 4-terpineol (2.227)	Antioxidant	Folin-Ciocalteu and aluminum chloride colorimetric (4.90–19.29 mg GAE/g) TPC (0.14–13.29 mg QE/g) and TFC	Not tested on organisms	(Noor *et al*., 2020)
Leaves (essential oil)	Hydrodistillation	GCMS	Eucalyptol (27.512%), terpinolene (9.047%), γ-terpinene (8.59%), α-terpineol (4.108%), α-selinene (3.889%), α-caryophyllene (3.522%), β-eudesmene (3.359%), and 1R-α-pinene (2.158%)	Antibacterial	Disc diffusion. Activity ranged from 5 to 7 mm at 0.1 ml	*Salmonella typhimurium* NRRL-B-2354 (S), *Bacillus cereus* NRRL-B-354 (S), *S. aureus* NRRL-B-313 (S), *E. coli* NRRL-B-409 (S), and *P. aeruginosa* NRRL-B-14781 (S)	(Toan *et al*., 2020)
Leaves (essential oil)	Steam distillation	GCMS	Cineol (31.6%), terpineol (10.7%), β-selinenol (6.8%), α-eudesmol (6.7 5%), guaiol (6.5%), γ-eudesmol (4.3%), bulnesol (1.9%), β-myrcene (0.9%), terpinen-4-ol (0.9%), and linalool (0.6%)	Anticoronavirus	Docking simulation	Coronavirus (S)	(My *et al*., 2020)
Leaves (essential oil)	Steam distillation	GCMS	B-Caryophyllene (20.16%), α-terpinolene (17.0%), and α-humulene (11.91%), also β-elemene (7.62%) and γ-terpinene (5.62%)	NR	NR	Not tested on organisms	(Sharif *et al*., 2019)

Continued

Plant part	Extraction method (solvent)	Analysis of phytoconstituents	Major phytoconstituents	Biological activities	Method/ outcomes	Organism tested (reaction)	References
Leaves (essential oil)	Steam distillation	GCMS	1,8-Cineole (42–60%), α-terpineol (4–18%), caryophyllene (0.6–11%), α-selinene (6.73 %), α-pinene (3-12%), α-gurjunene (17.31%), and 2,4-pentanediol (11.44%)	NR	NR	Not tested on organisms	(Sutrisno *et al*., 2018)
Leaves (essential oil)	Steam distillation	Qualitative analysis (using wet reactions)	Saponins, reducing sugar, cardiac glycoside, coumarins and lactones, and steroids	Antimicrobial	Agar well diffusion at conc. Oil: methanol *v/v* 50 µl. The zone of inhibition ranged between 5 ± 0.085–27 ± 0.05 mm and 2 ± 0.12–19.5 ± 0.12 for bacteria and fungi, respectively	*Staphylococcus aureus* (S), *P. aeruginosa* (S), *E. coli* (S), *Klebsiella* species (S), *Acinetobacter* species (S), *Salmonella typhi* (R), *Salmonella paratyphi* (R), *Rhizopus nigricans* (R), *Candida albicans* (R), and *A. niger* (S)	(Dahiya *et al*., 2016)
Leaves (essential oil)	Hydrodistillation	GC and GCMS	Major component; 1,8-cineole (43.7 ± 0.5%)	NR	NR	Not tested on organisms	(Silva *et al*., 2007)
Leaves (essential oil)	Steam hydrodistillation	GCMS	Major chemical compounds, 2-propenoic acid (29.55%) and caryophyllene (20.04%)	Insecticidal	LC_{50} 120.99 mg/l and 222.58 mg/l for *A. aegypti* and *A. albopictus,* respectively	*Aedes aegypti* and *Aedes albopictus*	(Bakar *et al*., 2019)
Leaves (essential oil)	Steam distillation	GCMS	1,8-Cineole (53.90%), α-terpineol (9.53%), D-(+)-limonene (6.52%), and β- caryophyllene (4.11%)	Antifungal	Agar well diffusion. IC_{50} ranged from 0.44 to 7.71 mg/ml	*Fusarium oxysporum* (NBRC 31213) (S), *Thanatephorus cucumeris* (NBRC 30937) (S), and *Rhizopus oryzae* (NBRC 31005) (S)	(Pujiarti *et al*., 2011)
Leaves (essential oil)	Steam distillation	GCMS	1,8-Cineole (53.90%), α-terpineol (9.53%), D-(+)-limonene (6.52%), and β-caryophyllene (4.11%)	Antioxidant	1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay (IC_{50} 4.24 mg/ml)		(Pujiarti *et al*., 2011)

Continued

Plant part	Extraction method (solvent)	Analysis of phytoconstituents	Major phytoconstituents	Biological activities	Method/ outcomes	Organism tested (reaction)	References
Leaves (essential oil)	Commercial	NR	NR	Antifungal	Vapor-phase-mediated susceptibility assay (using 96-well microtiter plate) at 20 µl of essential oil	*Candida albicans* SC5314 (S) and *Candida glabrata* ATCC 2001 (S)	(Feyaerts *et al*., 2018)
Leaves (essential oil)	Hydrodistillation	NR	NR	Antimicrobial	Broth microdilutions at conc. of 60 µl EO sample	*Streptococcus mutans* Xc (S) and *C. albicans* (S)	(Septiana *et al*., 2019)
Leaves (essential oil)	Hydrodistillation	GCMS	Alpha-pinene (4.15%)	Enzyme inhibition (acetylcholinesterase)	Ellman's method (21.18 ± 0.54%) inhibitory activity. IC_{50} not evaluated		(Sareedenchai *et al*., 2019)
Leaves and flowers	Maceration (methanol)	LCMS and GCMS	The major compounds include Terpenoids Aromatics Phenolics Fatty acids Flavonoids	Antimicrobial	Disc diffusion (100 mg/ml) and broth dilution. The MIC was 12.5 mg/ml and MBC 25.0 mg/ml for leaves extract. For flower 12.5–25 mg/ml MIC and 25–50 mg/ml MBC	*Staphylococcus epidermidis* MTCC 3615 (S), *S. aureus* RF 122 (S), *B. cereus* ATCC 11778 (S), *Streptococcus pneumoniae* ATCC 10015 (R), *E. coli* UT181 (R), *S. typhimurium* ATCC 14028 (R), *Klebsiella pneumonia* ATCC 13883 (R), and *Pasteurella multocida* (R)	(Al-Abd *et al*., 2015)
Leaves and flowers	Maceration (methanol)	LCMS and GCMS	The major compounds include Terpenoids Aromatics Phenolics Fatty acids Flavonoids	Antioxidant	DPPH radical scavenging activity. IC_{50} value 25 µg/ml for flower extract and IC_{50} value 10 µg/ml for leaves extract		(Al-Abd *et al*., 2015)
Leaves and twigs	Reflux (ethanol)	Preparative HPLC	β-Triketone flavanone hybrid (cajuputones A, B, and C)	NR	NR	Not tested on organisms	(Xu *et al*., 2020)
Leaves and twigs (essential oil)	Hydrodistillation	GCMS	β-Elemene (5.09%). α-pyrone (10.11%), γ-terpinene (8.00%), terpinolene (9.26%), β-caryophyllene (6.36%), and 1,8-naphthyridine derivatives (10.46%)	Antifungal	Broth microdilution. 0.31–1.25 µl/ml and 0.63–1.25 µl/ml were the MICs and MFCs, respectively	*Candida albicans* ATCC 90028 (S)	(Keereedach *et al*., 2020)

Continued

Plant part	Extraction method (solvent)	Analysis of phytoconstituents	Major phytoconstituents	Biological activities	Method/ outcomes	Organism tested (reaction)	References
Stem	Maceration(methanol and ethanol)	NR	NR	Antibacterial	Broth microdilution (MIC and MBC. No activity	*Propionibacterium acnes* ATCC 6919 (R)	(Batubara *et al*., 2009)
Stem	Maceration (methanol and ethanol)	NR	NR	Lipase inhibition	Using 2,3-dimercapto-1-propanol tributyrate. No inhibition	Lipase enzyme	(Batubara *et al*., 2009)
Stem	Maceration (methanol and ethanol)	NR	NR	Antioxidant	Using DPPH assay at IC_{50} 58.41 ± 1.32 and 5.79 ± 1.13 µg/ml % inhibition		(Batubara *et al*., 2009)

NR = not reported, (R) = resistant, and (S) = susceptible.

decoction to treat rheumatoid arthritis (Toan *et al*., 2020). Externally, the utilization of *M. cajuputi* oil includes relieving neuralgia and rheumatism (typically in the form of ointments and salves), as well as toothache, cancer, worms (particularly roundworms), and infections of the genitourinary system (Silva *et al*., 2007).

Solvent selection and methods for extracting phytochemicals from *M. cajuputi* Powell extracts

Plant extraction can be performed with different solvent systems ranging from nonpolar, intermediate, and highly polar to separate and purify bioactive compounds (Ukit *et al*., 2019). The resulting filtrate is tested for bioactivity screening at different concentrations. The most common solvent systems used to extract the bioactive compounds from *M. cajuputi* Powell were methanol, ethanol, hexane, ethyl acetate, dichloromethane, and water (Table 3). Methanol, in particular, was highlighted several times in previous studies due to its excellent properties in dissolving polar and nonpolar bioactive compounds from plant material (Ukit *et al*., 2019). Bioactive compounds can be separated and isolated by using different chromatographic techniques. Subsequently, various spectrometric approaches can be employed to identify the plant's chemical structure and functional groups of extracted bioactive components (Xu *et al*., 2020).

Table 3. Solvent's system used in *M. cajuputi* Powell extraction process from 2001 to 2021.

Extraction solvent	Number of studies
Methanol	10
Ethanol	3
Hexane	2
Ethyl acetate	1
Dichloromethane	1
Aqueous	1

Phytochemical composition of *M. cajuputi* Powell

The bioactive compounds reported in *M. cajuputi* Powell extracts include monoterpenes, sesquiterpenes, flavonoids, and phenolic compounds (Table 2). Figure 4 depicts the chemical structures of the main bioactive molecules. Monoterpenes are the most common chemical compounds, with structures comprised two isoprene units and organic functional groups involving hydrocarbons (pinene, terpinene, p-cimene, and terpinene), alcohols (linalool, cineol, and 4-terpineol), and ethers like 1,8-cineol (Jajaei *et al*., 2010). Sesquiterpenes are unsaturated chemicals that are comprised of hydrocarbons (caryophyllene), oxygenated sesquiterpenes (nerolidol), and alcohols (bisabolol and nerolidol). Other organic compounds such as steroids, quinones, saponins, tannins, and alkaloids were also reported in *M. cajuputi* Powell extracts (Dahiya *et al*., 2016; Isnaini *et al*., 2021).

Plants usually produce primary metabolites such as simple sugars, amino acids, polypeptides, and lactic acid, which are found virtually in all plants as part of their regular metabolic activity. They also produce secondary metabolites such as antibiotics, poisons, organic acids, and pigments for defense purposes (Angelo, 2015). As most of the products are used for self-defense, these metabolites and pigments could contain bioactive molecules, including inulin, quinine, morphine, and codeine (Angelo, 2015). Some of these bioactive compounds reported in *M. cajuputi* Powell extracts could interfere with the cell membrane integrity and distort cell wall structure, leading to cell death. For example, terpenoids could divide lipid membranes and cause irreversible leakage of cellular components, leading to cell destruction (Sharif *et al*., 2019). Another bioactive compound is 4-terpineol, an isomer of terpineol that blocks respiration and interferes with cellular metabolism (Sharif *et al*., 2019).

Antimicrobial activity of *M. cajuputi* Powell

The antimicrobial efficacy of *M. cajuputi* Powell extracts from leaves, flowers, stem bark, and essential oil against bacteria, fungi, protozoa, and viruses was evaluated *in vitro* using agar well diffusion, disc diffusion, and broth microdilution. *Melaleuca cajuputi* Powell crude extracts showed antimicrobial activity at

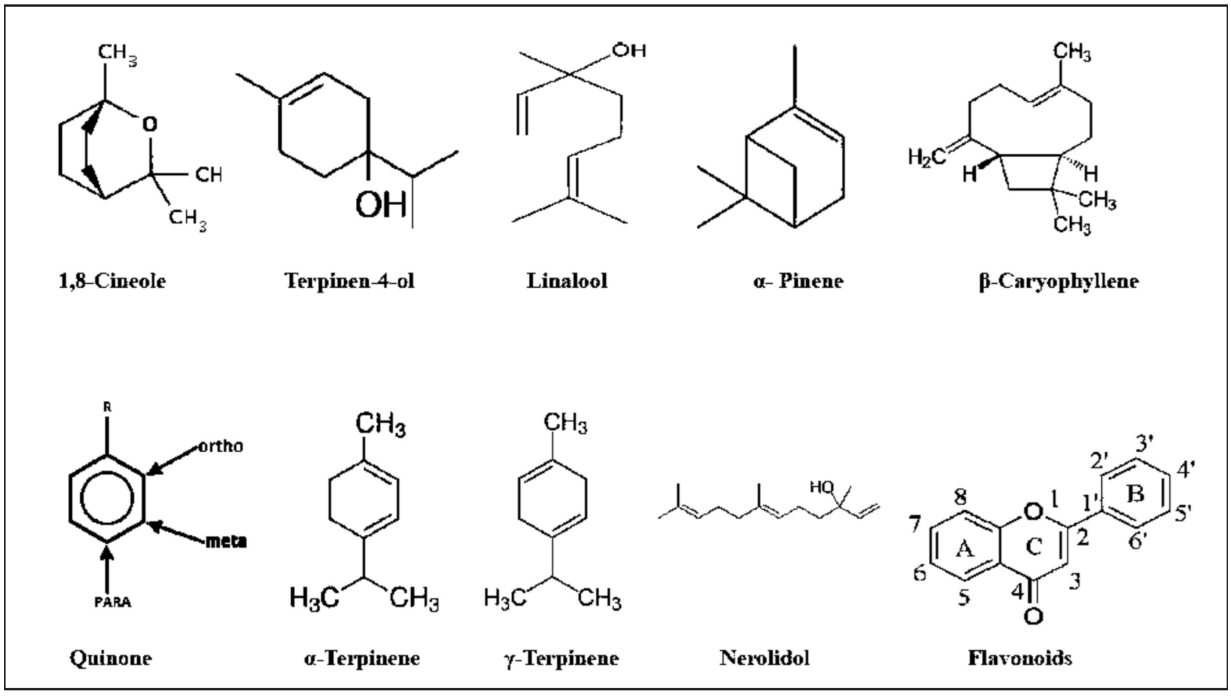

Figure 4. Major bioactive compounds reported in *M. cajuputi* Powell extracts and their chemical structures.

0.007–25.00 mg/ml and 0.062–50.0 mg/ml as minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC)values, respectively. The diameter zone of inhibition ranged from 1.00 to 27.00 mm (Table 2).

The report on the antimicrobial properties showed that *M. cajuputi* Powell extracts were effective against fungal species, bacteria, viruses, and protozoa at varying concentrations (Bua *et al*., 2020; Shivappa *et al*., 2015; Thanaboripat *et al*., 2007; Trinh *et al*., 2021).

The essential oil at a concentration of 0.714% (w/w) was reported to show antibacterial activity against pathogenic bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) (Wahab *et al*., 2022). As determined *in silico* and verified by flow cytometry and transmission electronic microscopy, *M. leucadendra* essential oil enhances cell membrane permeability and disruption as well as cell wall lysis of bacteria by inhibiting enzymes (peptidoglycan glycosyltransferase) (Bautista-Silva *et al*., 2020). According to Chaudhari *et al*. (2022), *M. cajuputi* essential oil interferes with the integrity of the plasma membrane of *Aspergillus flavus* cells by interfering with the biosynthesis of ergosterol.

When compared to other parts of the plant, Cajuput oil was far more effective against all the microorganisms tested, including the virulent coronavirus (My *et al*., 2020). Furthermore, the plant was reported to have an antifilarial effect against *Brugia pahangi* by inhibiting the bacterial endosymbiont "*Wolbachia*" (Al-Abd *et al*., 2016). Figure 5 depicts the number of microorganisms used in the previous studies.

Antioxidant properties of *M. cajuputi* Powell

Melaleuca cajuputi Powell possesses significant antioxidant activity. Different parts of the plant have several antioxidant compounds, such as α-terpineol, D-(+)-limonene, and β-caryophyllene, which possess excellent antioxidant activities (Table 2).

Several physiological processes in the human and animal body produce free radicals, and they are involved in cellular biochemical functions such as gene regulation, transcription, translation, and signaling (Pérez-Rosés *et al*., 2016). However, it is important to highlight that there must be a balance between free radicals and antioxidants for normal physiological functioning. Oxidative stress can arise when free radicals outstrip the body's ability to manage them, leading to diabetes, inflammation, cancer, and cardiovascular disease (Abubakar and Loh, 2016). Therefore, natural antioxidant compounds from a natural source, such as high plants, are essential for the body's normal physiological function (Dandashire *et al*., 2019).

Toxicological studies

There are ongoing debates on the safety of herbal medicine in modern medicine and disease treatment, but scientists have continued to be fascinated with herbal medicine. Therefore, it is essential to provide knowledge of previous reports regarding the toxicity profile of *M. cajuputi* Powell to support its usage in disease treatment.

*Melaleuca cajuput*i Powell essential oil causes termite mortality at LC_{50} = 4.60% (Roszaini *et al*., 2013). Furthermore, *M. cajuputi* Powell essential oil caused contact toxicity on *Sitophilus*

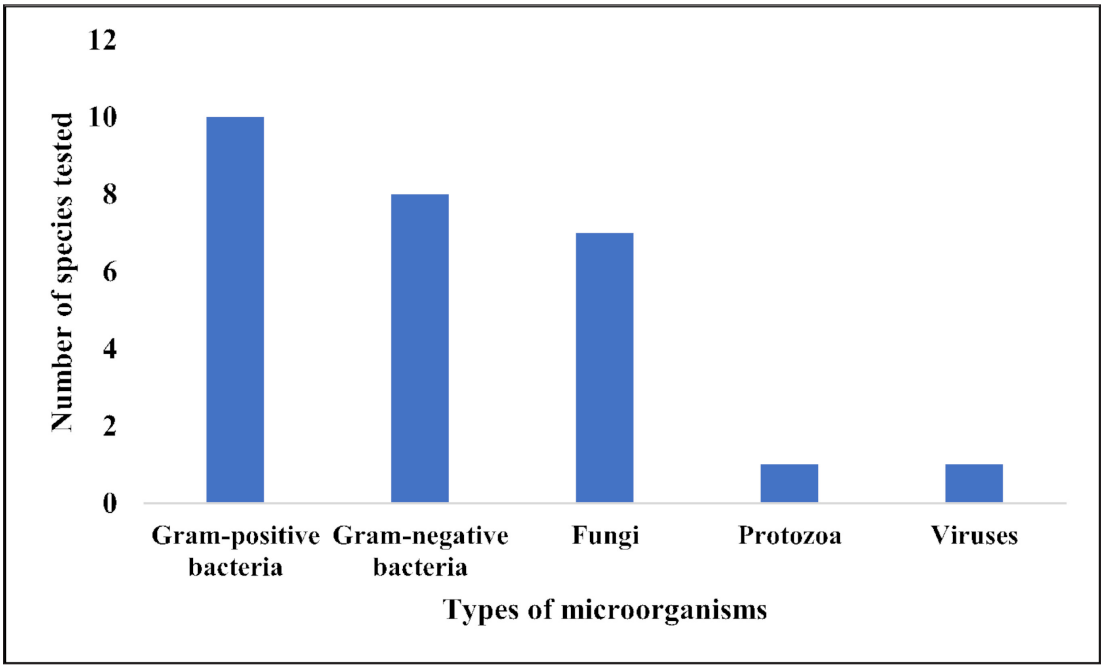

Figure 5. Types of microorganisms susceptible to *M. cajuputi* Powell extracts as reported in the various literatures (n = 27).

zeamais and *Tribolium castaneum* at LC_{50} values of 178.23 and 213.17 µl L^{-1}, respectively (Ko *et al*., 2009). Similarly, the methanolic extract of *M. cajuputi* Powell stems induced a toxicity effect on *Camponotus* sp. at LT_{50} = 84.3% (Visheentha *et al*., 2018). On the other hand, the methanolic leaves extract at doses between 50 and 200 mg/kg showed no toxic effect on Sprague-Dawley rats (Daud *et al*., 2018). However, in a brine shrimp lethality test, the extract induced a mild toxicity effect at LC_{50} 427 µg/ml (Noor *et al*., 2020). The aqueous and decoction extracts of *M. cajuputi* Powell had no toxicity effect at LC_{50} 1062 and 2477 µg/ml, respectively (Noor *et al*., 2020). According to the Meyer toxicity index, the plant extract is considered toxic when the LC_{50} is less than 1,000 µg/ml, and it is nontoxic when the LC_{50} is greater than 1,000 µg/ml (Noor *et al*., 2020). Clarkson on the other hand defined the toxicity as nontoxic if the LC_{50} is greater than 1,000 µg/ml, lowly toxic if the LC_{50} is between 500 and 1,000 µg/ml, highly toxic if the LC_{50} is between 100 and 500 µg/ml, and extremely toxic if the LC_{50} is between 0 and 100 µg/ml (Hamidi *et al*., 2014).

CONCLUSION

The extracts from *M. cajuputi* Powell showed a wide range of *in vitro* and *in vivo* biological effects. The reported phytoconstituents such as phenolic, aromatic, flavonoid, and alcohol groups could be responsible for the biological activities in the plant. The antimicrobial, antioxidant, and toxicity profiles of *M. cajuputi* Powell signified that the plant could be an excellent source of particular pharmacological active compounds. Further studies on bioassay-guided fractionation to obtain the pure compounds of *M. cajuputi* Powell extracts and the investigation of their antimicrobial mechanisms are necessary to unveil the plant's full potential as a good source of novel pharmaceutical compounds for disease remedy.

AUTHOR'S CONTRIBUTIONS

Assoc. Prof. Dr. Mohd Dasuki Sul'ain, Dr. Wan-Nor-Amilah Wan Abdul Wahab, and Isah Musa contributed to the concept and design. Dr. Wan-Nor-Amilah Wan Abdul Wahab and Isah Musa contributed to data acquisition and interpretation. Isah Musa drafted the manuscript. Prof. Dr. Wan Rosli Wan Ishak, Assoc. Prof. Dr. Hasmah Abdullahi, Dr. Wan-Nor-Amilah Wan Abdul Wahab, and Rasmaizatul Akma Rosdi critically reviewed the manuscript.

CONFLICT OF INTEREST

The authors have no known conflicts of interest.

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ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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