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Melaleuca cajuputi Powell Essential Oil: A Review of Botanical, Phytochemical and Pharmacological Properties

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ABSTRACT

Melaleuca cajuputi Powell essential oil (MCEO) is widely used in Malay traditional medicine for the treatment of stomach cramps, cough, acne, insect bites, thrush problems and many more. The demand for medicinal applications of MCEO is gradually increasing among the Southeast Asian community. All information regarding MCEO was collected via internet sources such as Google Scholar, Elsevier, PubMed, Baidu Scholar, Web of Science and local books. Meta-analysis method was performed to identify all publications or relevant books regarding the MCEO range from 1998 to 2021. The main bioactive compounds of MCEO include terpenes, esters, aldehydes and alkenes. Scientific research on MCEO has revealed a wide range of pharmacological activities such as contact and fumigant toxicity, repellence, antibacterial activity and many more. The MCEO has a huge potential for pharmaceutical and nutraceutical applications, but comprehensive toxicity studies must be conducted to ensure their safety. Research on pharmacokinetics studies and potential drug interactions with standard-of-care medications is still limited, which calls for additional studies, particularly in humans. Further assessments and clinical trials should be performed before it can be integrated into medicinal practices.

Keywords: Essential oil, *Melaleuca cajuputi* Powell, nutritional, phytochemistry, traditional medicine

INTRODUCTION

Geographical Distribution of *Melaleuca cajuputi* Powell

Melaleuca cajuputi Powell (MC) (http://www.theplantlist.org), is locally known as "gelam" or "pokok kayu putih" belongs to the Myrtaceae family, which can be found in the humid and hot climate zones of the Asia continent until Australia. It grows indigenously around the riverbanks, inlands, coastal and sub-coastal regions (Daud *et al.*, 2015). This species is well adapted to seasonally infertile soils, salt-water flooding or flooded soils, but not to saline waterlogged conditions. In swamp areas, MC forms open forests, pure forests or woodlands, while in less swampy areas, it grows in an extensive range with acacias, eucalyptus and other *Melaleuca* species (Doran, 1999).

Melaleuca cajuputi Powell Characteristics

Melaleuca cajuputi has several botanical names, such as cajaput tree, paper bark tea tree and swamp tea tree (Wiliams, 2011). Besides that, it is also synonymised with *M. saligna, Myrtus saligna, M. minor, M. trinervis, M. lancifolia, M. leucadendron, M. leucadendron variety lancifolia, M. leucadendron variety cajuputi,* and *M. leucadendron variety minor* (Wiliams, 2011). Moreover, this plant is classified into three different subspecies, which are MC subspecies *cajuputi*, MC subspecies *cumingiana* and MC subspecies *platyphylla* (Wiliams, 2011). It can grow up to 25 m with a single flexible trunk and a wide-range of adventitious root systems (Doran, 1999) (Figure 1).

The leaves are silky-hairy, dark green in color and alternately arranged in a lanceolate shape (Daud *et al.*, 2015) (Figure 2). The apex is acute, finely coriaceous and plain, with oil glands and prominent veins, whereas the petiole is compressed into a concave-convex shape with a single, double or triple inflorescence (Doran, 1999). The rachis is densely pilose with an enlarged anthesis. Moreover, the bracts are striate, caduceus and villous, but the bracteoles are absent (Doran, 1999).

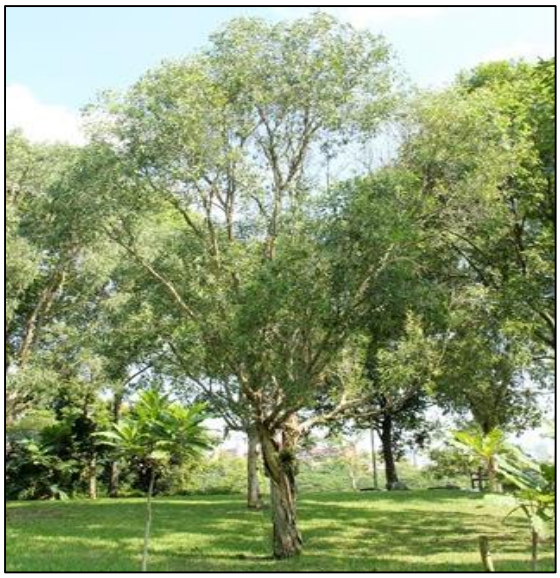

Figure 1. *Melaleuca cajuputi* Powell trees (Tan *et al.*, 2010)

Figure 2. Leaves of *Melaleuc*a *cajuputi* Powell (Tan *et al.,* 2010)

The flowers are greenish-white and grow in triads along the stems; the sepals are hairy and have sub-cylindrical tubules that adnate to the ovary, as shown in Figure 3 (Doran, 1999). Besides that, MC honey (MCH) is produced by *Apis dorsata* bees from the MC flowers (Doran, 1999). There are five petal-like spatulates with a sub-orbicular blade that is covered with branched veins and glands (Doran, 1999). The stamens are whitish and hairless, arranged in bundles with seven to ten filaments attached to the claw upper margin (Doran, 1999). The anthers, pistil and style have lengths of 0.4 – 0.55 mm, 1 mm and 6 – 9 mm, respectively (Doran, 1999). The fruits are produced in small cup-shaped capsules that consist of abundantly lined and tiny seeds (3 – 3.5 mm x 3.5 – 4 mm) (Doran, 1999). The bark is papery, coated and fibrous with a whitish or greyish colour that covers the branches and trunks (Doran, 1999).

Figure 3. Flowers of *Melaleuc*a *cajuputi* Powell (Tan *et al.,* 2010)

MATERIALS AND METHODS

Research Strategy

In this review article all of literature was searched based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses which was performed to identify publications studying the *Melaleuca cajuputi* Powell essential oil (MCEO). Seven databases which were Google Scholar, Elsevier, PubMed, Baidu Scholar, Web of Science and local books were used using keywords "*Melaleuca cajuputi* Powell essential oil". All articles or books regarding MCEO were taken from years 1998 – 2021. In this article, the botanical properties, phytochemical and pharmacological properties of MCEO were further discussed. In order to increase the sensitivity of searched data the first 100 hits of searched databases sorted by relevance were included in the analysis. Besides that, all articles or books regarding MCH, news, letters or non-English language were excluded from relevant criteria.

RESULTS

Study selection: The primary search identified 90 articles that gathered through Google Scholar, Elsevier, PubMed, Baidu Scholar, Web of Science database and local books. Among these, only 35 research articles and eight books were met with the inclusion criteria.

Phytochemical Compounds in MCEO

Terpenes

Previous research found that monoterpenes (α-pinene, β-pinene, Myrcene, γ-terpinene, terpinolene and 3,7-Dimethyl-1,3,7-octatriene) account for approximately 1.7% w/w of MCEO phytocompounds, while sesquiterpenes (16.8% w/w) contribute approximately 16.8% (β-maaliene, β-caryophyllene, eremophyllene, β-elemene, sativene, ledene, γ-cadinene, alloaromadendrene (De Colmenares *et al.,* 1998) and cyclopentene,3-isopropenyl-5,5-dimethyl (Jayakumar *et al.,* 2021) (Table 1). Moreover, in other studies, monoterpenes such as limonene and 1,8-cineole were spotted in MCEO (Orchard *et al.,* 2017). Terpenes are made up of isoprene molecules that consist of five carbon atoms accompanied by double bonds (Buckle, 2015). The monoterpenes consist of two isoprene units with 10 carbon atoms, sesquiterpenes consist of three isoprene units with 15 carbon atoms; the diterpenes consist of four isoprene units with 20 carbon atoms; the triterpenes consist of six isoprene units with 30 carbon atoms; and the tetrapenes consist of eight isoprene units with 40 carbon atoms (Aldred *et al.,* 2009; Buckle, 2015). Aside from that, MCEO contains monoterpenoid molecules, which are formed during a biochemical reaction by the addition of heteroatoms to monoterpene molecules (Kabir *et al.,* 2020). Monoterpenoid molecules include 1,8 cineole (De Colmenares *et al.,* 1998, Susanto *et al.,* 2003), α-terpineol, γ-terpineol (De Colmenares *et al.,* 1998), 2-bornanone and bicyclo[2.2.1]heptane, 2,2,3-trimethyl (Jayakumar *et al.,* 2021). Furthermore, sesquiterpenes alcohols such as nerolidol and α-bisabolol are found in MCEO (De Colmenares *et al.,* 1998).

Table 1. The phytochemical compounds that can be found in MCEO

Phytochemical compounds group	Types of phytochemical compounds	References
Monoterpene	α-pinene, β-pinene, myrcene, γ-terpinene, terpinolene and 3,7-dimethyl-1,3,7-octatriene, limonene,	De Colmenares *et al.* (1998)
	α-terpinene, α-phellandrene, 4-terpineol, p-cymene, α-pinene and α-phellandrene,	Noor *et al.* (2021)
Sesquiterpenes	β-maaliene, β-caryophyllene, eremophyllene, β-elemene, sativene, ledene, γ- cadinene, alloaromadendrene and cyclopentene,3-isopropenyl-5,5-dimethyl	De Colmenares *et al.* (1998), Jayakumar *et al.* (2021)
	humulune and β-caryophyllene,	Noor *et al.* (2021)
Sesquiterpenes alcohol	nerolidol, and α-bisabolol	De Colmenares *et al.* (1998)
Sesquiterpenoid	caryophyllene oxide, globulol, calarene	(Noor *et al.,* 2021)
Monoterpenoid	1,8 cineole	De Colmenares *et al.*, (1998), Susanto *et al.* (2003)
	α-terpineol, γ-terpineol, 2-bornanone and bicyclo[2.2.1]heptane, 2,2,3-trimethyl	De Colmenares *et al.* (1998), Jayakumar *et al.* (2021)
	β-linalool, eucalyptol	Noor *et al.* (2021)
Ester	methyl benzoate	De Colmenares *et al.* (1998)
	isobornyl acetate and benzyl benzoate	Jayakumar *et al.* (2021)
Alkane and alkene	bicyclo[2.2.1]heptane, 2,2,3-trimethyl	Jayakumar *et al.* (2021)
Aldehyde	benzaldehyde	De Colmenares *et al.* (1998)
	acetaldehyde, (3,3-dimethylcyclohexylidene)-, (e)	Jayakumar *et al.* (2021)
Phenylpropanoid	eugenol, methyleugenol	Noor *et al.* (2021)

Ester, aldehyde and alkane

Examples of esters that are found in MCEO are methyl benzoate (De Colmenares *et al.,* 1998), isobornyl acetate and benzyl benzoate (Jayakumar *et al.,* 2021). Esters are carbon atoms that have three other atoms bound to them (an oxygen to a double bond, an oxygen to a single bond, and a carbon to a single bond) (Ouellette & Rawn, 2015). Moreover, the oxygen that is singly bound is also bonded with another carbon (Ouellette & Rawn, 2015). Moreover, aldehydes that are found in MCEO are benzaldehyde (De Colmenares *et al.,* 1998) and acetaldehyde, (3,3-dimethylcyclohexylidene)-(E) (Jayakumar *et al.,* 2021). Aldehydes are compounds that contain one or more carbon-to-carbon double bonds that

are either saturated or unsaturated and are accompanied by a terminal carbonyl moiety (Conklin & Bhatnagar, 2010). Furthermore, the only alkane found in MCEO is bicycle [2.2.1] heptane, 2,2,3 -trimethyl (Jayakumar *et al.*, 2021). All alkanes are composed of a single bond between two carbons and are said to be saturated with general formula of C_nH_{2n+2} (da Rosa & Ordóñez, 2022).

Nutritional Composition of MC Leaves

Nutritional properties are defined as essential substances required for a healthy human body's development and physiological processes, such as carbohydrates, minerals, amino acids or proteins, polyphenols, enzymes and vitamins (Samuel *et al.*, 2020). The moisture content of MC leaves was reported to be adequate (2.74%), as it should not exceed 14% (Noor *et al.*, 2021). High moisture content is able to cause deterioration of formulations in drugs and herbs due to microorganism activity, enzymes, oxidation and hydrolysis processes (Noor *et al.*, 2021). Moreover, according to the European Pharmacopoeia, the ash content was within an acceptable limit, showing low mineral adulteration, contamination or substitution (Noor *et al.*, 2021). The crude fat content in MC leaves was low (4.83%), but higher compared to *Moringa oleifera* Lam (2.23%) and sweet potato (0.38% – 1.91%) leaves (Noor *et al.*, 2021). The calorie content of MC leaves can be considered high (4974 Cal/g) and can be used for the development of dietary supplements compared to other herbs such as *M. oleifera* Lam leaves (3397 Cal/g) and *Lippia javanica* (Burm.f.) Spreng (506.4 Cal/g) (Noor *et al.*, 2021). Besides that, both crude and dietary fibers were 36.3% and 9.49%, which were higher compared to water spinach (17.67%) (Noor *et al.*, 2021). High-fiber foods are able to increase serum cholesterol, bile acid excretion and the digestion process, but they also lead to intestinal irritation and decreased nutrient bioavailability (Noor *et al.*, 2021). The protein and carbohydrate contents were both 78.25% and 6.42%, respectively (Noor *et al.*, 2021).

Pharmacological Properties

Contact and fumigant toxicity

Fumigants toxicity are referred to as lethal gas permeation (aerosols, smokes or fogs) that exist at ambient pressures and temperatures and are able to cause a lethal effect on living organisms, especially pests (Davis, 2003) (Table 2). Besides that, at concentrations of 37, 56, 94, 130, 185, 296, 370, 444 and 556 μL^{-1} air, MCEO is able to cause fumigant toxicity to *Tribolium castaneum* and *Sitophilus zeamais* after 3, 6, 12 and 24 h of exposure (Ko *et al.*, 2009). The lethal concentration for 50% population (LC_{50}) and lethal concentration for 95% population (LC_{95}) values for *S. zeamais* are 178.23 μL^{-1} and 408.54 μL^{-1}, while for *T. castaneum*, they are 213.17 μL^{-1} and 376.1 μL^{-1} (Ko *et al.*, 2009). Based on these findings, the contact and fumigant toxicities might be caused by the chemical composition of MCEO (α-pinene, limonene, α-terpinene and α-terpineol) (Ko *et al.*, 2009). Moreover, the LC_{50} of MCEO is 4.60% and the feeding inhibition value is 73.33% at concentrations of 0.5%, 1%, 2% and 3% against *Coptotermes curvignathus* Holmgren termites, which might be due to the presence of chemical compositions such as quinone, flavonoids, terpenoids and fatty acids (Roszaini *et al.*, 2013). Apart from that, MCEO at a concentration of 40 µl/L exerted a fumigant toxicity effect with a 72% mortality rate of *Rhyzopertha dominica* after exposure for 24 hours (Jayakumar *et al.*, 2021). MCEO had a LC_{50} of 25.60 µl/L against *R. dominica* (Jayakumar *et al.*, 2021). The total protein content of MCEO increased by 0.5% at sub-lethal concentration for 30% population (LC_{30}), while it decreased by about 13.6% at LC_{50} (Jayakumar *et al.*, 2021). At the same time, the activity of acetylcholinesterase was increased in both LC_{30} and LC_{50} up to 9.7%, and 11.4%, respectively (Jayakumar *et al.*, 2021). Besides that, the activity of alpha carboxylesterase was increased in both LC_{30} and LC_{50} up to 7.5% and 11.4%, while the activity of beta carboxylesterase was also increased in both LC_{30} and LC_{50} up to 22.5% and 15.2% (Jayakumar *et al.*, 2021).

Moreover, the activity of glutathione-s-transferase was increased significantly ($p \leq 0.05$) in the LC_{50} concentration (Jayakumar *et al.*, 2021). The contact toxicity refers to toxic substances that cause harm to living organisms when they contact the body's surface (Ko *et al.*, 2009). MCEO at concentrations of 10%, 20%, 30% and 40% is able to cause contact toxicity towards *T. castaneum* and *S. zeamais* during 24 hour treatments (Ko *et al.*, 2009). The lethal

doses for 50% population (LD_{50}) and lethal doses for 95% population (LD_{95}) contact toxicity for *T. castaneum* are 0.143 and 0.296 µL per insect, respectively, while those for *S. zeamais* are 0.062 and 0.111 µL per insect (Ko *et al.*, 2009). Based on the result, MCEO is more effective against *S. zeamais* (Ko *et al.*, 2009).

Repellence activity

Repellence activities refer to the prevention of arthropods from flying, landing or feeding on the host by using certain repellents that act at a certain distance or locally (Szelényi *et al.*, 2020). MCEO at concentrations of 0.5, 1, 2 and 3% able to repel *Coptotermes curvignathus* Holmgren termites with a LC_{50} of 4.60, probably due to the presence of chemical compositions such as quinone, flavonoids, terpenoids and fatty acids (Roszaini *et al.*, 2013). Furthermore, due to the presence of chemical compositions such as α-pinene, limonene, α-terpinene and α-terpineol during a two hours and five hours exposure, MCEO was able to repel *T. castaneum* and *S. zeamais* at 0.5%, 1%, 1.5% and 2% (Ko *et al.*, 2009). On the other hand, studies conducted by other researchers showed that, MCEO at 10% was able to prevent *Aedes* (*Ae.*) *albopictus, Ae. aegypti, Anopheles (An.) dirus* and *Culex* (*Cx.*) *quinquefasciatus* with a mean repellent activity of 0.7 h (*Ae. aegypti*), 7.9 h (*Ae. albopictus*), 8.0 h (*An. dirus*) and 6.9 h (*Cx. quinquefasciatus*) (Tawatsin *et al.*, 2006). In the meanwhile, at 0.01%, MCEO was able to prevent the deposition of *Ae. aegypti* eggs at an 87.9% rate (Tawatsin *et al.*, 2006).

In different studies, MCEO at 1, 2, 5 and 10% was able to repel *Ae. aegypti* and *Ae. albopictus* (Bakar *et al.*, 2009). In five seconds, the total average discharge for *Ae. aegypti* and *Ae. albopictus* ranged between 11.4 – 14.7 g and 12.7 – 15.4 g, while in 10 seconds, the total average discharge for *Ae. aegypti* and *Ae. albopictus* ranged between 19.1 – 25.3 g and 22.9 – 24.6 g (Bakar *et al.*, 2009). Besides that, MCEO at concentrations of 5% and 10% produced a better repellent effect compared to 1% and 2% against time exposure (Bakar *et al.*, 2009). At a concentration of 1%, the mortality values for five seconds of exposure were 1.4% ± 1.40 and 2.0% ± 0.83 for *Ae. albopictus* and *Ae. aegypti*, while within 10 seconds of exposure, knockdown values were produced at a range of 5.8% ± 0.68 and 10.2% ± 1.83 (Bakar *et al.*, 2009). The mortality values for *Ae. albopictus* and *Ae. aegypti* for 10 seconds of exposure were 16.0% ± 1.82 and 27.6% ± 4.81 (Bakar *et al.*, 2009). At 2% concentration, the mean percentage knockdown for *Ae. aegypti* and *Ae. albopictus* was both 6.0% ± 1.16 and 14.0% ± 3.09, while the mortality value was between 23.8% ± 2.59 to 38.4% ± 4.01 (Bakar *et al.*, 2009). At 5% concentration, the knockdown values within five seconds for *Ae. aegypti* and *Ae. albopictus* were both 9.2% ± 2.56 and 20.8% ± 5.57, while within 10 seconds they were 14.0% ± 3.09 and 23.4% ± 3.42 (Bakar *et al.*, 2009). The mortality rates for *Ae. aegypti* and *Ae. albopictus* in five seconds were 32.6% ± 6.16 and 47.8% ± 3.22, while in 10 seconds they were 51.4% ± 1.74 and 56.6% ± 3.63 (Bakar *et al.*, 2009). At a concentration of 10%, the knockdown rates for *Ae. aegypti* and *Ae. albopictus* ranged from 26.0% ± 2.61 to 36.6% ± 1.61 and 28.6% ± 3.02 to 37.5% ± 1.3 (Bakar *et al.*, 2009). The mortality rates in 10% concentration for *Ae. aegypti* and *Ae. albopictus* were 60.2% ± 6.54 to 64.0% ± 5.72 and 60.8% ± 3.22 to 61.4% ± 2.22 (Bakar *et al.*, 2009). The knockdown response at concentrations of 1% and 2% was less than 5% to produce a normal distribution, so no knockdown-time (KT) values in 50% of the population (KT_{50}) or knockdown-time values in 95% of the population (KT_{95}) were obtained (Bakar *et al.*, 2009). At concentrations of 5%, the KT_{50} values for *Ae. albopictus* and *Ae. aegypti* were more than 7,000 minutes when exposed for five seconds, while for 10 seconds, the KT_{50} values for *Ae. aegypti* were higher than for *Ae. albopictus* (Bakar *et al.*, 2009). Apart from that, at a concentration of 10% exposure for 10 seconds, produced KT_{50} values of about 168.84 minutes and 123.71 minutes for *Ae. aegypti* and *Ae. albopictus* were produced (Bakar *et al.*, 2009). Long-term exposure and high doses produced better knockdown and mortality rates (Bakar *et al.*, 2009). Moreover, a previous study reported that MCEO at concentrations of 10, 50, 80, 100 and 120 mg/L was able to repel *Ae. albopictus* and *Ae. aegypti* by exerting a larvicidal effect, while at concentrations of 0.026, 0.03, 0.034 and 0.04 mg/cm^2, MCEO repels both mosquitoes via an adulticidal effect, both in a dose dependent manner (Bakar, 2020). The mortality rate of *Ae. albopictus* was lower compared to *Ae. aegypti* in both larvicidal and adulticidal effects (Bakar, 2020). The larvicidal and adulticidal effects

observed might be due to the presence of chemical compositions such as 2-propenoic acid caryophyllene (Bakar, 2020).

In other studies, topical application of MCEO at a concentration of 10% on the skin was able to produce complete protection and reduce *Ae. aegypti* within an hour of exposure (Zainon *et al.,* 2019). The percentages of protection and reduction were both 66.58±3.06 and 93.05±0.78 (Zainon *et al.,* 2019). Moreover, in the mist diffuser formed, MCEO at 5% was able to repel *Ae. aegypti* starting at 30 minutes and was able to produce complete protection during three hours of exposure (Zainon *et al.,* 2019). The repelling activity might be due to the presence of phytochemical compounds such as β-caryophyllene, caryophyllene, citral, α-pinene, linalool, terpinene-4-ol, chavicol, γ-terpinene, limonene, , α-terpineol, myrcene, p-cymene and 1,8-cineole (Zainon *et al.,* 2019). Apart from that, MCEO is able to repel *Trogoderma granarium* with a 96.7% mortality rate at 1000 ppm after six days of exposure and high larvicidal activity after seven days of exposure by exerting inhibitory action against acetylcholinesterase (AChE) activity (Kavallieratos *et al.,* 2021).

Antibacterial and antifungal activities

The antibacterial and antifungal activities refer to the chemical substance that is either derived from a biological source or synthesised by chemical synthesis and is able to inhibit or destroy bacterial and fungal growth (Hamoud *et al.,* 2012; Barzic & Ioan, 2015). The MCEO is able to inhibit bacteria and fungi such as *Staphylococcus epidermidis, S. aureus,* methicillin-resistant *S. aureus* (MRSA) clinical isolate (CI) strain, methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *enterococcus* (VRE) CI strain, vancomycin-resistant *enterococcus* (VRE), *Streptococcus pyogenes, Bacillus subtilis S. agalactiae, S. oralis, Acinetobacter baumanii, Klebsiella pneumonia, Escherichia coli, Pseudomonas aeruginosa, Candida parapsilosis, C. albicans* and *C. glabrata* with a minimum inhibitory concentration (MIC) value range of 0.3 to 40 mg/ml and a minimum microbicidal concentration (MMC) value range of 0.3 to more than 40 mg/ml during the 24 hours incubation period (Hamoud *et al.,* 2012). The antibacterial and antifungal activities observed could be attributed to the presence of monoterpenes (1,8-cineol, caryophyllene, limonene, terpineolene, α-terpineol, α-caryophyllene and linalool), which have the ability to increase cytoplasmic membrane permeability and fluidity, inhibit cell respiration, alter membrane-embedded protein conformation, and affect ion transport (Hamoud *et al.,* 2012). Moreover, MCEO also exerts an antibacterial effect against acne pathogens (*Streptococcus aureus, S. epidermidis, P. aeruginosa, Propionibacterium acnes, E. coli,* gentamicin -methicillin resistant *S. aureus* and MRSA), fungal pathogens (*C. albicans, M. canis* and *T. mentagrophytes*) and bacteria that induce body odor (*Brevibacterium agri, B. linens* and *B. epidermidis*) with MIC ranges of 0.25 to 2 mg/ml (Orchard *et al.,* 2017). The highest MIC effects were spotted against *Microsporum canis* (0.25 mg/ml) and *Trichophyton mentagrophytes* (0.38 mg/ml) (Orchard *et al.,* 2017). The antibacterial properties might have occurred due to the presence of phytocompounds such as 1,8-cineole and limonene (Orchard *et al.,* 2017). In another study, MCEO was able to inhibit *A. baumanii, C. albicans, E. coli, Enterococcus faecalis, K. pneumonia, P. aeruginosa, Salmonella typhimurium, Serratia marcescens, Aeromonas sobria* (Hammer *et al.,* 1999), *S. pyogenes* (Sfeir *et al.,* 2013) and *S. aureus* (Hammer *et al.,* 1999; Domokos *et al.,* 2019). A high MIC value was shown for *A. sobria, A. baumanii, C. albican, E. coli* and *S. aureus* (Hammer *et al.,* 1999). The antibacterial properties might be due to the presence of monoterpenes, monoterpenic alcohols, flavonoids and sesquiterpenes (Sfeir *et al.,* 2013; Domokos *et al.,* 2019).

In the meantime, MCEO was able to inhibit *E. coli, B. cereus* and *S. aureus* at concentrations of 50, 75 and 100%, as shown by reaction orders of 0.4460, 0.8235 and 0.6928, respectively (Musta *et al.,* 2022). MCEO is able to exert an antifungal effect against *C. albican* resistant strains (S7/1, U6/2, U15/1 and U8/1) by initiating fungicidal activity and lowering the expression of the multidrug resistance protein 1 (MDR1) efflux pump gene (Keereedach *et al.,* 2020). The MICs and microbial fuel cells (MFCs) ranged from 0.31 to 1.25 µl/ml and 0.63 to 1.25 µl/ml (Keereedach *et al.,* 2020).

Table 2. The pharmacological activities found in MCEO

Pharmacology	Method used	Mechanism of action	References
Contact toxicity	*Coptotermes curvignathus* Holmgren termite	The presence of chemical compositions (quinone, flavonoids, terpenoids, and fatty acids) that cause contact toxicity.	(Roszaini *et al.* (2013)
	Tribolium castaneum and *Sitophilus zeamais*	The contact and fumigant toxicities might be caused by the chemical composition of MCEO (α-pinene, limonene, α-terpinene and α-terpineol)	Ko *et al.* (2009)
	Rhyzopertha dominica	The fumigant toxicity effect was mediated by the alteration of acetylcholinesterase, carboxylesterase and glutathione-s-transferase activities	Jayakumar *et al.* (2021)
Repellence activity	*Tribolium castaneum* and *Sitophilus zeamais*	The repellent activity might be caused by the chemical composition of MCEO (α-pinene, limonene, α-terpinene and α-terpineol)	Ko *et al.* (2009)
	Coptotermes curvignathus Holmgren termites	The repellent activity occurs due to the presence of chemical compositions such as quinone, flavonoids, terpenoids and fatty acids	Roszaini *et al.* (2013)
Repellence activity	*Ae. albopictus, Ae.aegypti*, *Cx. quinquefasciatus*, *An. dirus*,	The repellent activity occurs due to the presence of chemical compositions such as flavonoids and terpenoids	Tawatsin *et al.* (2006)
	Ae. aegypti and *Ae. albopictus*		Bakar *et al.* (2009)
Repellence activity	*Ae. aegypti* and *Ae. albopictus*	Exerted larvicidal and adulticidal effects might be due to the presence of chemical compositions such as 2-propenoic acid caryophyllene	Bakar (2020)
	Ae. aegypti	Repellent activity might be due to the presence of phytochemical compounds such as β - caryophyllene, caryophyllene, citral, α-pinene, linalool, terpinene-4-ol, chavicol, γ-terpinene, limonene, , α-terpineol, myrcene, p-cymene and 1,8-cineole	Zainon *et al.* (2019)
Repellence activity	*Trogoderma granarium*	Adulticidal and larvicidal activity by exerting inhibitory action against acetylcholinesterase activity	Kavallieratos *et al.* (2021)
Antibacterial	*Streptococcus pyogenes*	Presence of monoterpenes, monoterpenic alcohols, flavonoids and sesquiterpenes	Sfeir *et al.* (2013)
	Staphylococcus aureus		Domokos *et al.* (2019)
	Escherichia coli, *Bacillus cereus* and *Staphylococcus aureus*		Musta *et al.* (2022)
	Escherichia coli and *Staphylococcus aureus*	Initiating bacteriostatic activity	Wibowo *et al.* (2021)
	Acinetobacter baumanii, *Candida albicans*, *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumonia*, *Pseudomonasaeruginosa*, *Salmonella typhimurium*, *Serratia marcescens*, *Staphylococcus aureus* and *Aeromonas sobria*		Zainon *et al.* (2019)
Antibacterial	*Acinetobacter baumanii*, *Candida albicans*, *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumonia*, *Pseudomonasaeruginosa*, *Salmonella typhimurium*, *Serratia marcescens*, *Staphylococcus aureus* and *Aeromonas sobria*		Hammer *et al.* (1999)
Antibacterial	*Staphylococcus epidermedis*, *Staphylococcus aureus*, MRSA CI strain, MRSA, VRE CI strain, VRE, *Streptococcus pyogenes*, *Bacillus subtilis* *Streptococcus agalactiae*, *Streptococcus oralis*, *Acinetobacter baumanii*, *Klebsiella pneumonia*, *Escherichia coli*, *Pseudomonas aeruginosa*,	The presence of monoterpenes (1,8-cineol, caryophyllene, limonene, terpineolene, α- terpineol, α- caryophyllene and linalool) that are able to enhance cytoplasmic membrane permeability and fluidity, inhibit cell respiration, alter membrane-embedded protein conformation and induce ion transport processes, thus leading to cell death	Hamoud *et al.* (2012)

Table 2. Continued

Pharmacology	Method used	Mechanism of action	References
Antibacterial	*Streptococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa, Propionibacterium acnes, Escherichia coli*, gentamicin -methicillin resistant *S. aureus* (MRSA), *Candida albicans, Microsporum canis, Trichophyton mentagrophytes, Brevibacterium agri, Brevibacterium linens* and *Brevibacterium epidermidis*	Presence of phytocompounds (1,8-cineole and limonene)	Orchard *et al.* (2017)
Antibacterial	*Streptococcus mutans* and *Candida albicans*	*Streptococcus mutans* is inhibited by preventing it from forming insoluble glucan, and *Candida albicans* is inhibited by preventing the yeast from forming hyphae	Septiana *et al*. (2019)
	Mycobacterium tuberculosis strains (Mtb-15, Mtb-13, Mtb-12, Mtb-11, Mtb-10, Mtb-9 and Mtb-1) and non-tuberculous mycobacteria (*Mycobacterium abscessus-1, Mycobacterium abscessus-2* and *Mycobacterium simiae*		Bua *et al.* (2020)
	Streptococcus mutans	Reduced the expression of DNA in *S. mutans* and increased pyruvate oxidase mRNA expression, which lead to an increase in hydrogen peroxide production and *S. sanguinis* colonisation	Wijaya *et al.* (2020)
Antifungal	*Candida parapsilosis, Candida albicans and Candida glabrata*	The presence of monoterpenes (1,8-cineol, caryophyllene, limonene, terpineolene, α- terpineol, α- caryophyllene and linalool) that are able to enhance cytoplasmic membrane permeability and fluidity, inhibit cell respiration, alter membrane-embedded protein conformation and ion transport processes, thus leading to cell death	Hamoud *et al.* (2012)
Antifungal	*Candida albican* resistant strains (S7/1, U6/2, U15/1, and U8/1)	Initiating fungicidal activity and lowering the expression of the MDR1 efflux-pump gene	Keereedach *et al.* (2020)
Antiparasite	*Trichomonas vaginalis*	Exercising cytotoxicity effect	Trinh *et al.* (2021)
Acetylcholinesterase inhibitor	Acetylcholinesterase inhibition assay	The presence of chemical constituents such as α-pinene	Petrachaianan *et al.* (2019)
Antivirus	SARS-CoV-2	Inhibition of angiotensin-converting enzyme 2 protein and PDB6LU7 due to the presence of phytochemical compounds	My *et al.* (2020)

MCEO at concentration of 50 µg/µl is able to inhibit *E. coli* (4.39 ± 0.48 mm) and *S. aureus* (4.62 ± 0.39 mm), while at 25 µg/µl it is able to inhibit *E. coli* (3.44 ± 0.34 mm) and *S. aureus* (3.08 ± 0.33 mm) via bacteriostatic activity (Wibowo *et al.*, 2021). MCEO is able to inhibit *Mycobacterium tuberculosis* (Mtb) strains such as Mtb-15, Mtb-13, Mtb-12, Mtb-11, Mtb-10, Mtb-9 and Mtb-1 with MIC ranges from 0.5% to 16% (v/v) and non-tuberculous mycobacteria (*M. abscessus-1, M. abscessus-2* and *M. simiae*) with MIC ranges from 0.5 to 4% (v/v) (Bua *et al.*, 2020). The MCEO that was formulated into sucrose cajaput candy and non-sucrose cajaput candy was able to prevent *Streptococcus mutans* growth that caused dental caries by reducing the expression of *S. mutans* DNA and increasing pyruvate oxidase messenger ribonucleic acid (mRNA) expression, which led to an increase in hydrogen peroxide production and *S. sanguinis* colonisation (Wijaya *et al.*, 2020). Moreover, cajuput candy was able to inhibit *S. mutans* by preventing it from forming insoluble glucan and inhibit *C. albicans* by preventing the yeast from forming hyphae (Septiana *et al.*, 2019).

Antiparasite and antivirus

MCEO was found to be cytotoxic to *Trichomonas vaginalis* after 24 hours (MIC value = 0.03 to 0.25%) and 48 hours (MIC value

= 0.02 to 0.25%) (Trinh *et al.,* 2021). Besides that, MCEO is able to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by inhibiting the angiotensin-converting enzyme 2 (ACE2) protein and main protease (PDB6LU7) (My *et al.,* 2020). The 70.9% inhibitory capability of both proteins was contributed by the presence of ten different types of phytochemical compounds in MCEO (My *et al.,* 2020). The most powerful anticorona virus activity started with terpineol, followed by guaiol, linalool, cineol, β-selinenol, α-eudesmol and γ-eudesmol (My *et al.,* 2020).

Acetylcholinesterase inhibitor

Acetylcholinesterase (AChE) functions to terminate neurotransmission by degrading acetylcholine (Richbart *et al.,* 2021). This enzyme is found near postsynaptic neuromuscular junctions, which include muscles and nerves (McHardy *et al.,* 2017). A previous study reported that MCEO at 0.1 mg/ml was able to inhibit AChE activity at a rate of 21.18 ± 0.54% (Petrachaianan *et al.,* 2019). The inhibition activity that occurred might have been due to the presence of chemical constituents such as α-pinene (Petrachaianan *et al.,* 2019).

CONCLUSION

This review article focused on botany, phytochemical content, nutritional properties and pharmacological properties. Based on currently available information, several different classes of compounds were reported in MCEO, as stated in Table 1. The most dominant compounds in MCEO belong to the terpenoids group, which makes it a good drug candidate for anti-insect, anti-microbial, anti-plasmodial, antiviral, anti-cancer, antidiabetic and antidepressant uses (Cox-Georgian *et al.,* 2019). However, all these studies are limited to the preclinical level, so it is necessary to establish a clinical model for the future development of high efficacy drugs that use traditional medicine.

Traditionally, MCEO is commonly used as a treatment for mental and physical illnesses, to improve life quality, or as a preventative (Daud *et al.,* 2015). According to a previous study, humans have already used plants as medicine for almost 60,000 years (Yuan *et al.,* 2016). So, a lot of experience and knowledge has already been accumulated regarding the identification, selection, best time to obtain and preparation method of specific plants to treat certain illnesses. However, several research gaps need to be identified for better application of MCEO. Firstly, further study regarding the phytocompounds should be conducted to discover the actual lead compounds, their pharmacokinetics, pharmacodynamics and toxicological features, as well as how to reduce the toxicity of drugs and improve drug efficacy to create a potent drug with low toxicity effects. Secondly, a suitable method to analyse the crude extract and compounds also needs to be developed and established, as it is going to provide sufficient preliminary scientific documentation and will be able to be used as a guideline for new drug quality evaluation and clinical utility. Thirdly, there is limited toxicology and drug interaction data for MCEO, so a comprehensive study is needed to demonstrate the quality, safety and efficacy of both crude extracts and isolated compounds. Last but not least, extensive research regarding all MCEO extracts in terms of metabolism, pharmacology and toxicology should be conducted. This article emphasised the potential use of different MC extracts as new therapeutic drug candidates, providing baseline data for future research as well as introducing new methods to correctly use medical plants for human health.

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