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 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 cajuput tree, paper bark tea tree and swamp tea tree (Williams, 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 (Williams, 2011). Moreover, this plant is classified into three different subspecies, which are MC subspecies cajuputi, MC subspecies cumingiana and MC subspecies platyphylla (Williams, 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).
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 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).

**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, 5,5-dimethylcyclohexylidene, 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 (Jayakumar 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 monoterpen 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

<table>
<thead>
<tr>
<th>Phytochemical compounds group</th>
<th>Types of phytochemical compounds</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoterpene</td>
<td>α-pinene, β-pinene, myrcene, γ-terpinene, terpinolene and 3,7-dimethyl-1,3,7-octatriene, limonene, α-terpinene, α-phellandrene, 4-terpineol, p-cymene, α-pinene and α-phellandrene.</td>
<td>De Colmenares et al. (1998) Noor et al. (2021)</td>
</tr>
<tr>
<td>Sesquiterpenes</td>
<td>β-maaliene, β-caryophyllene, 5,5-dimethylcyclohexylidene, sativene, ledene, γ-cadinene, alloaromadendrene and cyclopentene,3-isopropenyl-5,5-dimethyl</td>
<td>De Colmenares et al. (1998), Jayakumar et al. (2021)</td>
</tr>
<tr>
<td>Sesquiterpenes alcohol</td>
<td>nerolidol, and α-bisabolol</td>
<td>De Colmenares et al. (1998)</td>
</tr>
<tr>
<td>Sesquiterpenoid</td>
<td>carophyllene oxide, globulol, calarene</td>
<td>Noor et al. (2021),</td>
</tr>
<tr>
<td>Monoterpenoid</td>
<td>1,8 cineole</td>
<td>De Colmenares et al. (1998), Susanto et al. (2003)</td>
</tr>
<tr>
<td>Ester</td>
<td>methyl benzoate</td>
<td>De Colmenares et al. (1998)</td>
</tr>
<tr>
<td>Alkane and alkene</td>
<td>bicyclo[2.2.1]heptane, 2,2,3-trimethyl</td>
<td>Jayakumar et al. (2021)</td>
</tr>
<tr>
<td>Phenylpropanoid</td>
<td>eugenol, methyleugenol</td>
<td>Noor et al. (2021)</td>
</tr>
</tbody>
</table>

**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 CₙH₂ₙ₊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 (LC₅₀) and lethal concentration for 95% population (LC₉₅) 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 LC₅₀ 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 LC₅₀ 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 (LC₃₀), while it decreased by about 13.6% at LC₅₀ (Jayakumar et al., 2021). At the same time, the activity of acetylcholinesterase was increased in both LC₃₀ and LC₅₀ up to 9.7%, and 11.4%, respectively (Jayakumar et al., 2021). Besides that, the activity of alpha carboxylesterase was increased in both LC₃₀ and LC₅₀ up to 7.5% and 11.4%, while the activity of beta carboxylesterase was also increased in both LC₃₀ and LC₅₀ up to 22.5% and 15.2% (Jayakumar et al., 2021).

Moreover, the activity of glutathione-s-transferase was increased significantly (p≤0.05) in the LC₅₀ 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
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 (KT50) or knockdown-time values in 95% of the population (KT95) were obtained (Bakar et al., 2009). At concentrations of 5%, the KT50 values for *Ae. albopictus* and *Ae. aegypti* were more than 7,000 minutes when exposed for five seconds, while for 10 seconds, the KT50 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 KT50 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/cm², 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-terpinene, 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-cineole, caryophyllene, limonene, terpineolene, α-terpeneol, 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**

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<th>Pharmacology</th>
<th>Method used</th>
<th>Mechanism of action</th>
<th>References</th>
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<td>Contact toxicity</td>
<td>Coptotermes curvignathus Holmgren termites, Tribolium castaneum and Stilophilus zeamais</td>
<td>The presence of chemical compositions (quinone, flavonoids, terpenoids, and fatty acids) that cause contact toxicity.</td>
<td>(Roszaini et al. 2013) Ko et al. (2009)</td>
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<td></td>
<td>Rhyzopertha dominica</td>
<td>The fumigant toxicity effect was mediated by the alteration of acetylcholinesterase, carboxylesterase and glutathione-s-transferase activities</td>
<td>Jayakumar et al. (2021)</td>
</tr>
<tr>
<td>Repellence activity</td>
<td>Tribolium castaneum and Stilophilus zeamais</td>
<td>The repellent activity might be caused by the chemical composition of MCEO (α-pinene, limonene, α-terpinene and α-terpinol)</td>
<td>Ko et al. (2009)</td>
</tr>
<tr>
<td></td>
<td>Coptotermes curvignathus Holmgren termites</td>
<td>The repellent activity occurs due to the presence of chemical compositions such as quinone, flavonoids, terpenoids and fatty acids</td>
<td>Roszaini et al. (2013)</td>
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<tr>
<td>Repellence activity</td>
<td>Ae. albopictus, Ae. aegypti, Cx. quinquefasciatus, An. dirus, Ae. aegypti and Ae. albopictus</td>
<td>The repellent activity occurs due to the presence of chemical compositions such as flavonoids and terpenoids</td>
<td>Tawatsin et al. (2006)</td>
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<td></td>
<td>Ae. aegypti and Ae. albopictus</td>
<td>Exerted larvicidal and adulticidal effects might be due to the presence of chemical compositions such as 2-propenonic acid carophyllene</td>
<td>Bakar (2020)</td>
</tr>
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<td>Repellence activity</td>
<td>Ae. aegypti and Ae. albopictus</td>
<td>Repellent activity might be due to the presence of phytochemical compounds such as β - carophyllene, carophyllene, citral, α- pinene, linalool, terpene-4-ol, chavicol, γ-terpine, limonene, α-terpineol, myrcene, p-cymene and 1,8-cineole</td>
<td>Zainon et al. (2019)</td>
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<td>Repellence activity</td>
<td>Trogoderma granarium</td>
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<td>Antibacterial</td>
<td>Streptococcus pyogenes</td>
<td>Presence of monoterpenes, monoterpenic alcohols, flavonoids and sesquiterpenes</td>
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<td>Staphylococcus aureus</td>
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<td>Escherichia coli, Bacillus cereus and Staphylococcus aureus</td>
<td></td>
<td>Musta et al. (2022)</td>
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<td>Escherichia coli and Staphylococcus aureus</td>
<td>Initiating bacteriostatic activity</td>
<td>Wibowo et al. (2021)</td>
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<td>Acinetobacter baumannii, Candida albicans, Escherichia coli, Enterococcus faecalis, Klebsiella pneumonia, Pseudomonas aeruginosa, Salmonella typhimurium, Serratia marcescens, Staphylococcus aureus and Aeromonas sobria</td>
<td></td>
<td>Zainon et al. (2019)</td>
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<td>Antibacterial</td>
<td>Acinetobacter baumannii, Candida albicans, Escherichia coli, Enterococcus faecalis, Klebsiella pneumonia, Pseudomonas aeruginosa, Salmonella typhimurium, Serratia marcescens, Staphylococcus aureus and Aeromonas sobria</td>
<td></td>
<td>Hammer et al. (1999)</td>
</tr>
<tr>
<td>Antibacterial</td>
<td>Staphylococcus epidermidis, Staphylococcus aureus, MRSA CI strain, MRSA, VRE CI strain, VRE, Streptococcus pyogenes, Bacillus subtilis Streptococcus agalactiae, Streptococcus oralis, Acinetobacter baumannii, Klebsiella pneumonia, Escherichia coli, Pseudomonas aeruginosa,</td>
<td>The presence of monoterpenes (1,8-cineole, carophyllene, limonene, terpineolene, α-terpineol, α- carophyllene 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</td>
<td>Hamoud et al. (2012)</td>
</tr>
</tbody>
</table>

*References to the studies mentioned in the table.*
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 cajuput candy and non-sucrose cajuput 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).

### Table 2. Continued

<table>
<thead>
<tr>
<th>Pharmacology</th>
<th>Method used</th>
<th>Mechanism of action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibacterial</strong></td>
<td><em>Streptococcus mutans</em> and <em>Candida albicans</em></td>
<td>Streptococcus mutans is inhibited by preventing it from forming insoluble glucan, and Candida albicans is inhibited by preventing the yeast from forming hyphae</td>
<td>Septiana et al. (2019)</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em> strains (Mtb-15, Mtb-13, Mtb-12, Mtb-11, Mtb-10, Mtb-9 and Mtb-1) and non-tuberculous mycobacteria (<em>Mycobacterium abscessus-1, Mycobacterium abscessus-2 and Mycobacterium simiae</em>)</td>
<td><em><strong>Streptococcus mutans</strong></em></td>
<td>Reduced the expression of DNA in <em>S. mutans</em> and increased pyruvate oxidase mRNA expression, which lead to an increase in hydrogen peroxide production and <em>S. sanguinis</em> colonisation</td>
<td>Wijaya et al. (2020)</td>
</tr>
<tr>
<td><strong>Antifungal</strong></td>
<td><em>Candida parapsilosis, Candida albicans</em> and <em>Candida glabrata</em></td>
<td>The presence of monoterpenes (1,8-cineole, 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</td>
<td>Hamoud et al. (2012)</td>
</tr>
<tr>
<td><em>Candida albicans</em> resistant strains (S7/1, U6/2, U15/1, and U8/1)</td>
<td><em>Streptococcus mutans</em></td>
<td>Initiating fugal activity and lowering the expression of the MDR1 efflux-pump gene</td>
<td>Keereedach et al. (2020)</td>
</tr>
<tr>
<td><strong>Antiparasite</strong></td>
<td><em>Trichomonas vaginalis</em></td>
<td>Exercising cytotoxicity effect</td>
<td>Trinh et al. (2021)</td>
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<tr>
<td>Acetycholineserine inhibition inhibitor</td>
<td>Acetycholinesterase inhibition assay</td>
<td>The presence of chemical constituents such as α-pinene</td>
<td>Pettrachaavan et al. (2019)</td>
</tr>
<tr>
<td><strong>Antivirus</strong></td>
<td>SARS-CoV-2</td>
<td>Inhibition of angiotensin-converting enzyme 2 protein and PDB6LU7 due to the presence of phytochemical compounds</td>
<td>My et al. (2020)</td>
</tr>
</tbody>
</table>

MCEO was found to be cytotoxic to *Trichomonas vaginalis* after 24 hours (MIC value = 0.03 to 0.25%) and 48 hours (MIC value
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 anticonora 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 (Richburt 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, anti-diabetic 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 phytochemicals 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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