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Review

Phytochemical and Pharmacological Properties of *Myristica fragrans* Leaves Houtt.

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ABSTRACT. *Myristica fragrans* is a widely distributed plant that grows well in Indonesia. This plant, also known as nutmeg, has been used in various fields such as food, aromatherapy, and other industries. Research on nutmeg plants has been widely conducted, but most of it discusses the seeds and mace of nutmeg. However, research on nutmeg leaves is still limited, with only a few studies to be discussed in this review article. This article provides an overview of the chemical compounds, bioactivity, and toxic effects of essential oils and nutmeg leaf extracts collected from the latest literatures (2014–2024). This article aims to draw more attention to nutmeg leaf research to be developed into natural-based medicinal products. Some compounds contained in nutmeg leaves include dihydrokaempferol, myristicin, 1,1,3,3,5,5,7,7,9,9,11,11,13,13-tetradecamethylheptasiloxane, 2,2-dimethyl-1-decanol, bis(2-ethyl hexyl) phthalate, and 9-dodecane-1-al, gamma-terpinene; caryophyllene and others. In addition, nutmeg leaf compounds also have various interesting bioactivities such as antibacterial, antifungal, antioxidant, larvicidal, and good cytotoxic activity. Overall, nutmeg leaves show great potential as a raw material for medicine. The results of this study also show various types of secondary metabolites with interesting bioactivities that require further study.

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INTRODUCTION

As a mega biodiversity country, Indonesia has abundant natural resources, especially plants. These plants have various benefits, one of which is that they are a traditional medicine widely used by the community. This is because the side effects of traditional medicinal plants are relatively low, so they are considered safer for consumption than synthetic medicine (Nasim *et al*., 2022). Along with the development of science, research has been carried out to maximize the use of plants as medicine. Taking plant extracts to isolate pure active compounds is one effort to maximize the use of plants. One of the plants used in traditional medicine is *Myristica fragrans*, which is commonly called nutmeg. This species belongs to the Myristicaceae family and grows rapidly in tropical areas such as Indonesia. This plant is used as a medicine for diarrhea, flatulence, mouth ulcers, increasing appetite, joint pain, insomnia, and destroying kidney stones (Cao *et al*., 2015; Olaleye *et al*., 2006; Orabi *et al*., 2022). These benefits cannot be separated from the role of secondary metabolites contained in nutmeg plants.

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Secondary metabolites are compounds produced by plants that function to defend themselves from external attacks and interact with the surrounding environment. These metabolites have many benefits for humans, including benefits for medicine, the food industry, and agrochemicals. Various types of secondary metabolite compounds found in nutmeg include terpenoids, flavonoids, tannins, saponins, and phenylpropanoids. Phytochemical screening of water extracts of nutmeg seeds showed alkaloids, flavonoids, and anthraquinones (Ginting *et al*., 2021; Ha *et al*., 2020; Olaleye *et al*., 2006). Various parts of the nutmeg plant, such as seeds, mace, bark, leaves, and roots, have been used in traditional medicine for various purposes. For example, nutmeg is known for its essential oil, which is used as a body warmer, pain relief, and anti-inflammatory. Meanwhile, mace has health benefits such as antioxidants and antimicrobials (Assa *et al*., 2014; Naeem *et al*., 2016; Sulaiman and Ooi, 2012).

Nutmeg has various interesting bioactivities, especially the seeds and mace, but studies on nutmeg leaves are still very limited. Meanwhile, nutmeg leaves are particularly interesting because of their diverse natural chemical content, essential oils, and secondary metabolites. Several studies have shown that nutmeg leaves have potential bioactivity, including antioxidant, antimicrobial, anticancer, and larvicidal activities. Several studies have shown that nutmeg leaves have better bioactivity than nutmeg seeds (Thileepan *et al*., 2017). However, until now, no review article has specifically discussed the chemical content and bioactivity of nutmeg leaves. Therefore, this article aims to review the literature on the chemical content and bioactivity of nutmeg leaves to highlight the opportunities for developing nutmeg leaves as a natural ingredient with potential in natural-based medicine. This is expected to provide deeper insights regarding the pharmacological benefits of nutmeg leaves and the possibility of their future application as a natural and safe alternative medicine.

The approach used in this article review uses a narrative review to provide a comprehensive overview of the phytochemical and pharmacological properties of nutmeg leaves (Warsito, 2021). This review was obtained by searching for various relevant keywords such as "*Myristica fragrans* leaves", "nutmeg leaves", "pharmacology", "bioactivity", and "phytochemistry" on the Google search engine, Google Scholar and Science Direct. This review aims to obtain phytochemical data and pharmacological properties of nutmeg leaf extract and is limited to 2014 – 2024.

PHYTOCHEMICAL AND PHARMACOLOGICAL PROPERTIES

Botanical Description

The nutmeg tree consists of several parts, such as roots, stems, leaves, seeds, fruit flesh, and flowers. Nutmeg leaves are elliptical to oval with pointed tips and rounded bases. The leaves surface is dark green and shiny on the top, while the underside of the leaves is pale green and has a few fine hairs. Nutmeg leaves are generally about 5-15 cm long and 2 – 7 cm wide, depending on the growth conditions and age of the tree (Arumugam *et al*., 2019; Kuete, 2017). Nutmeg leaves have a distinctive aroma, although not as strong as that of nutmeg seeds and flowers. This is because nutmeg leaves contain essential oils, even in lower quantities than nutmeg seeds (Ashokkumar *et al*., 2021; Ashokkumar *et al*., 2022; Silalahi, 2021).

Chemical Composition

Every part of the nutmeg plant, including leaves, stems, seeds, fruit flesh, and mace, contains various secondary metabolites, some of which have interesting bioactivities. The literature review results show that nutmeg leaves contain various compounds in their extracts and essential oils. Thileepan *et al*. (2017) extracted nutmeg leaves and produced a methanol extract of 23.02 g/100 g and essential oil of 2 mL/100 g. This study also showed that nutmeg seeds' essential oil content was higher than nutmeg leaves, yielding 14 mL/100 g (Thileepan *et al*., 2017). Different methods also affect the results of the essential oil obtained. Nutmeg leaves essential oil with the hydrodistillation method produced a yield of 3.2% (v/w) and 0.7% with the steam distillation method.

As shown in Figure 1, the compound content is dominated by α-pinene (**1**), sabinene (**2**), β-pinene (**3**), δ-3-carene (**4**), limonene (**5**), β-phellandrene (**6**), α-terpinolene (**7**), linalool (**8**), safrole (**9**), and myristicin (**10**) (Ashokkumar *et al*., 2022; Carolina and Maman, 2016). In addition, the hydrodistillation method was also used to extract nutmeg leaves from the Western Ghats, India, which were identified using GC-MS analysis. Several compounds contained are divided into monoterpene groups with the main content of (**2**) (17.17%), (**3**) (6.44%), (**5**) (5.03%), and β-myrcene (4.74%). This is followed by the phenylpropenes group with the main content of

eugenol (**11**) (16.60%), and (**10**) (9.12%) and the sesquiterpene group consisting of caryophyllene (**12**) (8.82%), and germacrene D (**13**) (2.95%) (Ashokkumar *et al*., 2021).

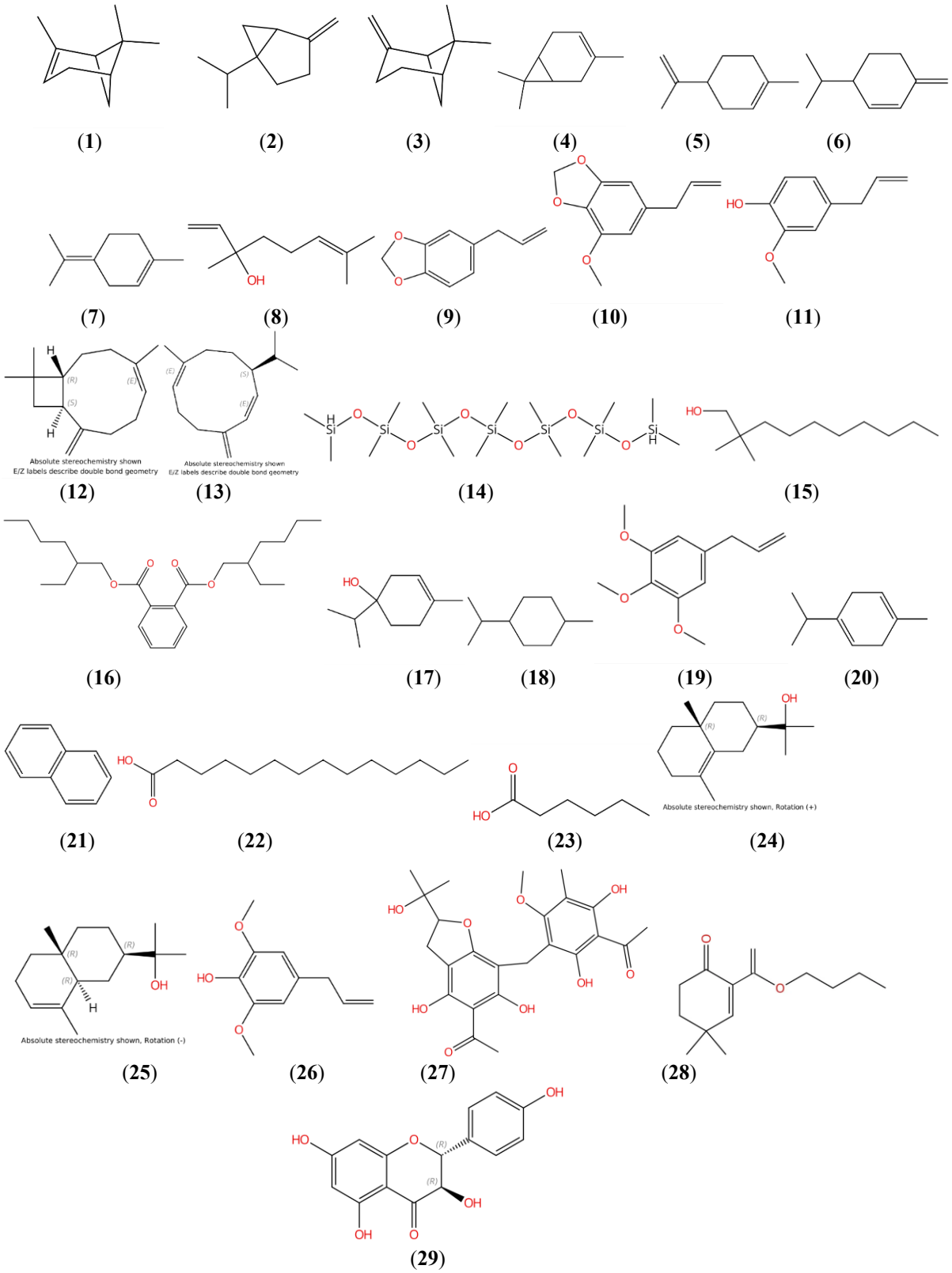

Figure 1. Structure of nutmeg leaves' compounds.

Meanwhile, Kapelle *et al*. (2022) used the steam water method to extract nutmeg leaves essential oil. This method yielded 0.26% with 20 identified compounds. The main composition of the essential oils includes (**10**) (15.92%), (**6**) (14.35%), (**6**) (11.20%), (**3**) (10.81%), and (**1**) (8.59%). Meanwhile, in the ethanol extract of nutmeg leaves with a yield of 29.01%, 37 components were identified. The main components of the extract include (**10**) (7.64%), 1,1,3,3,5,5,7,7,9,9,11,11,13,13-tetradecamethylheptasiloxane (**14**) (7.14%), 2,2-dimethyl-1-decanol (15) (7.12%), bis(2-ethylhexyl) and phthalate (16) (5.55%) (Kapelle et al., 2022). In addition, 50 other compounds were also identified in nutmeg leaves essential oil, such as 4-terpineol (**17**), phellandrene (**18**), caryophyllene (**12**), elemicin (**19**), and β-pinene (**3**) (Fernando and Senevirathne, 2021).

Extracting with acetone of nutmeg leaves shows the content of γ-terpinene (**20**), caryophyllene (**12**), naphthalene (**21**), myristic acid (**22**), hexanoic acid (**23**); γ-eudesmol (**24**) and α-eudesmol (**25**); phenol, 2,6-dimethoxy-4-(2-propenyl)- (**26**); isomallotochromanol (**27**) and 2-(1-butoxyvinyl)-4,4-dimethyl-2-cyclohexene-1-one (**28**) in the chromatogram of the results of the analysis using GC-MS (Adibuduge and Senevirathne, 2023). Isolation of n-hexane extract from nutmeg leaves produced seven mixed fractions of *Myristica fragrans* Heksana Daun (MFHD) 1 to 7. It was reported to have potential antioxidant activity (Ginting *et al*., 2017). In another study, Ginting *et al*. (2016) successfully isolated flavonoid group compounds from nutmeg leaf extract, namely dihydrokaempferol (**29**), and was proven to have potential antioxidant activity. In addition, tannins are another secondary metabolite reported to be contained in nutmeg leaves. Tannin is one of the secondary metabolites in nutmeg leaves; the phenolic group in tannin increases its ability to ward off free radicals, inhibit bacterial growth, and bind and protect proteins from microbial degradation in the rumen (Al-Qahtani *et al*., 2022; Antasionasti *et al*., 2021; Canadianti *et al*., 2020). Table 1 presents a comparison of the essential oil and crude extract of nutmeg leaves.

Table 1. Comparison of nutmeg leaves' essential oil and crude extract.

Extract	Essential Oil
Ethanol extract: myristicin (7.64%), 1,1,3,3,5,5,7,7,9,9,11,11,13,13-tetradecamethylheptasiloxane (7.14%), 2,2-dimethyl-1-decanol (7.12%), bis(2-ethyexyl) and phthalate (5.55%) (Kapelle *et al*., 2022).	α-pinene, sabinene, β-pinene, δ-3-carene, limonene, β-phellandrene, α-terpinolene, linalool, safrole, and myristicin (hydro distillation and steam distillation method) (Kapelle *et al*., 2022; Carolina *and* Maman, 2016).
Acetone extract: γ-terpinene compounds; caryphyllene; naphthalene; myristic acid, hexanoic acid, myristic acid, sucrose; γ- and α-eudesmol; phenol, 2,6-dimethoxy-4-(-2-propenyl)-; elemicin; isomallotochromanol and 2-(1-butoxyvinyl)-4,4-dimethyl-2-cyclohexene-1-one (Adibuduge *and* Senevirathne, 2023).	Monoterpene groups with the main content of sabinene (17.17%), β-pinene (6.44%), D-limonene (5.03%), and β-myrcene (4.74%). The phenylpropenes group with the main content of eugenol (16.60%) and myristicin (9.12%) and the sesquiterpene group consisting of caryophyllene (8.82%) and germacrene D (2.95%) (hydro distillation method) (Ashokkumar *et al*. 2021).
Flavonoid group compounds from extract: dihydrokaempferol (Ginting *et al*., 2016). Tannins compound (Canadianti *et al*., 2020).	Myristicin, β-phellandrene, limonene, β-pinene, and α-pinene (steam water method) (Kapelle *et al*., 2022).

Pharmacological Aspect

This nutmeg plant has various benefits, including adding flavor to food and as an ingredient in curry powder and jam. In the beverage industry, essential oils extracted from seeds and mace are used for soft drinks such as cola, beer, whiskey, and wine. Nutmeg is also used as raw materials for fragrance products such as making perfumes, colognes, aromatherapy candles, soaps, and lotions. These products produce a distinctive odor, namely a warm, sweet, and slightly cinnamon aroma. In addition, because of its analgesic properties, nutmeg essential oil is also widely used by people as a lubricant for sprained body parts, joint pain, and pulled muscles (Francis *et al*., 2019; Kumari *et al*., 2021; Nurjanah *et al*., 2017; Olaleye *et al*., 2006).

In the field of medicine, this plant is widely used as a medicine for diarrhea, treating flatulence, mouth ulcers, increasing appetite, treating joint pain, insomnia, and dissolving kidney stones (Cao *et al*., 2015; Olaleye *et al*., 2006; Orabi *et al*., 2022). However, consuming this plant in large quantities can also cause poisoning, which causes headaches, nervous system disorders, hallucinations, increased heart rate, and even death (Olaleye *et al*., 2006). Nutmeg has a variety of interesting bioactivities, especially the seeds and mace. However, several other studies have shown that the nutmeg leaves part also has interesting bioactivity. The study of the bioactivity of nutmeg leaves is still quite limited compared to the seeds, fruit, and mace. However, several studies comparing the bioactivity of the leaves and seeds show that nutmeg leaves have more potential than nutmeg seeds.

Antibacterial

A compound has antibacterial activity if it can inhibit the growth or kill bacteria. Antibacterial compounds are usually used to prevent or treat infections caused by pathogenic bacteria such as *P. aeruginosa, L. monocytogenes, S. enterica, E. coli, S. dysenteriae,* and others. Some methods used to test antibacterial activity include the disk diffusion method, well diffusion method, broth dilution, and agar dilution (Abdollahzadeh *et al*., 2021; Chandrasekaran *et al*., 2020; Erhonyota *et al*., 2023; Tacouri *et al*., 2013). Nutmeg leaves obtained from methanol extract has been shown to inhibit several strains of Methicillin-Resistant *S. aureus* (MRSA). The inhibition zone of *S. aureus* strain NCTC 6571 (control), MRSA strains 1 to 5 with inhibition values (mm) were sequentially 18 ± 0.0; 18 ± 0.0; 19 ± 0.0; 19 ± 0.0; 19 ± 0.0; 19 ± 0.0 (Table 2). Nutmeg leaves methanol extract is more potent in inhibiting the growth of *S. aureus* compared to nutmeg seed methanol extract. These data indicate that nutmeg leaves extract has better activity than nutmeg seeds. These results are also supported by data on the inhibition zone of nutmeg leaves essential oil, which is larger than that of nutmeg seed essential oil in the same study (Thileepan *et al*., 2017).

Table 2. Zone of inhibition of methanolic extract of nutmeg leaves (Thileepan *et al*., 2017).

Microorganism	ZOI (mm)
S. aureus NCTC 6571	18.0 ± 0.0
MRSA strain 1	18.0 ± 0.0
MRSA strain 2	19.0 ± 0.0
MRSA strain 3	19.0 ± 0.0
MRSA strain 4	19.0 ± 0.0
MRSA strain 5	19.0 ± 0.0

Nutmeg leaves essential oil has antibacterial activity against *S. enteritis, L. monocytogenes, S. dysenteriae, E. coli,* and *P. aeruginosa* strains. This is due to the inhibition zone formed in the five strains when tested using the agar disc diffusion method. However, this result is still half the size of the inhibition zone produced by the reference compound amoxicillin. Nutmeg leaves essential oil has the highest inhibition zone in sequence for *S. dysenteriae* strains (1.63 ± 0.04 cm), *L. monocytogenes* (1.37 ± 0.04 cm), *P. aeruginosa* (1.20 ± 0.07 cm), *E. coli* (1.17 ± 0.08 cm), and *S. enteritica* (1.03 ± 0.04 cm) (Fernando and Senevirathne, 2021). Kapelle *et al*. (2022) compared the antibacterial activity of essential oil and ethanol extract produced by nutmeg leaves against *S. aureus* and *S. aeruginosa* strains. The results showed that the ethanol extract of nutmeg leaves had a higher inhibition zone than nutmeg leaves essential oil against *S. aureus* with Zone of Inhibition (ZOI) of 23.56 and 20.31 (amoxicillin 45.31 mm), respectively. Meanwhile, in *S. aeruginosa* bacteria, the ethanol extract of nutmeg leaves had a smaller inhibition zone than nutmeg leaves essential oil with ZOI values of 8.86 and 11.79 (amoxicillin 39.64 mm).

Ethanol, acetone, chloroform, and hot water extracts from nutmeg leaves were tested for antibacterial activity against P. aeruginosa, L. monocytogenes, S. enterica, E. coli, and *S. dysenteriae* with the reference compound amoxicillin. The results showed that chloroform extract had the highest inhibition zone against *P. aeruginosa* bacteria, which was 0.97 ± 0.04 cm (ref 2.73 ± 0.01) compared to ethanol, acetone, and hot water extracts. Meanwhile, in *S. enterica* bacteria, ethanol extract had the highest inhibition zone, which was 0.98 ± 0.05 cm (ref 3.5 ± 0.01). *L. monocytogenes, E. coli,* and *S. dysenteriae* bacteria could be inhibited well by acetone extract with inhibition zones of 1.37 ± 0.11 (ref 3.1 ± 0.01); 1.27 ± 0.04 (ref 3.3 ± 0.01); 1.61 ± 0.04 (ref 3.7 ± 0.02) (Adibuduge and Senevirathne, 2023).

In addition to essential oils and nutmeg leaves extracts, several interesting studies are related to endophytic fungi isolated from nutmeg leaves. Four endophytic fungi were isolated from nutmeg leaves and characterized by *Myristica fragrans* Fungus (MYFRF) 1 to 4 (Table 3). The identification results showed that MYFRF 1 was *Colletotrichum sp*. with a colonization frequency of 2.77%; MYFRF 2 was *Pestalotiopsis sp.* (8.33%); MYFRF 3 was *Fusarium sp*. (1.38%); and MYFRF 4 was *Fusarium sp.* (4.16%). Antibacterial tests against *E. coli, K. pneumoniae,* and *S. aureus* showed potential results. In the test results against the *E. coli* strain, MYFRF 4 showed the same inhibition zone as the positive control, which was 19 mm. Meanwhile, in the *K. pneumoniae* and *S. aureus* strains, the largest inhibition zone was shown by MYFRF 3. The inhibition zone in both strains was 12 mm with a positive control of 17 mm (*K. pneumoniae*) and 12 mm with a positive control of 20 mm (*S. aureus*) (Deepthi *et al*., 2018).

Table 3. Inhibition zone of crude extract of endophytic fungi.

Name of endophytic fungi	Test organism (mm)		
	E. coli	***K. pneumoniae***	***S. aureus***
MYFRF 1	-	-	-
MYFRF 2	13	10	9
MYFRF 3	15	12	12
MYFRF 4	19	11	10
Positive control	19	17	20

Antifungal

Antifungal activity refers to the ability of an extract to inhibit the growth of or kill fungi. Extracts derived from plants, microorganisms, or chemical compounds can have properties that are effective in fighting fungal infections or preventing the growth of pathogenic fungal colonies. The process of testing antifungal activity is usually carried out through in vitro methods, where the extract is tested against various types of fungi, such as *A. niger, A. flavus*, and *A. ochraceous* (Hawar *et al*., 2022; Hsu *et al*., 2021; Meng *et al*., 2020).

Nutmeg leaves essential oil also can inhibit the development of *F. oxysporum* and *A. niger* with inhibition zones of 1.27 ± 0.18 and 0.57 ± 0.04 cm, respectively. However, when compared to the positive control captan, nutmeg essential oil has a lower inhibition zone, 3 times lower in both types of fungi (Fernando and Senevirathne, 2021). Myristicin is a compound that plays a role in antifungal activity in nutmeg essential oil. Myristicin from nutmeg essential oil was evaluated for its ability to protect food from aflatoxins produced by certain fungi. Nutmeg essential oil at a concentration of 0.1% inhibited the growth of *A. flavus* and *A. ochraceus* by 43% and 65%, respectively. Meanwhile, at a concentration of 0.3%, there was inhibition of 84% and 79%, respectively (Valente *et al*., 2014). In addition, antifungal activity against *A. niger* was tested using methanol, ethanol, acetone, chloroform, and hot-water extracts from nutmeg leaves. The results of this study showed that chloroform extract had the highest inhibition percentage (51.52 ± 3.71%) followed by acetone extract (49.92 ± 9.82%) and ethanol extract (40.00 ± 9.43%) (Adibuduge and Senevirathne, 2023).

Antioxidants

Antioxidants prevent oxidation processes or neutralize free radicals, such as reactive oxygen species/reactive nitrogen species (ROS/RNS) (Yashin *et al*., 2017). ROS/RNS can cause oxidative stress that triggers the development of age-related diseases, such as neurodegenerative diseases, kidney disorders, cardiovascular diseases, macular degeneration, gallbladder disease, cancer, chronic obstructive pulmonary disease, as well as sarcopenia and weakness. Spices and aromatic herbs are rich sources of chemical compounds with antioxidant properties, including nutmeg (Adiani *et al*., 2015; Gupta and Rajpurohit, 2011; Liguori *et al*., 2018; Yashin *et al*., 2017).

Adibuduge and Senevirathne (2023) tested the antioxidant activity of acetone extract from nutmeg leaves using various methods. From the study, the total phenolic content (TPC) test values were obtained (895.12 ± 44.24 mg gallic acid equivalent (GAE)/g of leaves), ferric reducing antioxidant power (FRAP) (715.78 ± 51.09 mg of Trolox/g of leaves), 2-2-diphenyl-1-picrylhydrazyl (DPPH) (65.56 ± 0.93 mg of Ascorbic acid/g of leaves), 2,2'-azinobis(3-ethybenzothiazoline-6-sulfonic acid (ABTS) (31.67 ± 0.49 mg of Trolox equivalent/g of leaves) and Ferrous Ion chelating (10.87 ± 1.85 mg of ethylenediaminetetraacetid acid (EDTA)/g of leaves). These data indicate that the acetone extract of nutmeg leaves has a high phenolic content, strong antioxidant potential, and the ability to ward off free radicals and bind iron ions. The methanol extract of nutmeg leaves also shows the same

potential leaves with an IC_{50} value of 36.31 ppm (ref Vit. C, IC_{50} = 3.657 ppm) using the DPPH method. From this study, several fractions were also obtained with stronger activity than the crude extract, namely fraction 4, fraction 3, and fraction 2, with IC50 values of 26.590 ppm, 27.239 ppm, and 29.639 ppm, respectively (Nurmilasari *et al*., 2017).

In addition to the extract, the fraction (MFHD 4) isolated from the *n*-hexane extract of nutmeg leaves has more potential antioxidant activity with a lower IC_{50} value than the reference (Vit. C), which is 0.729 ppm (ref. 7.875 ppm) (Table 4). This indicates that the fraction has better antioxidant activity than Vit. C, so it is interesting to develop further. The study is expected to produce a more effective and efficient free radical scavenging agent compared to several active compounds that have been used (Ginting *et al*., 2017). Endophytic fungi isolated from young nutmeg leaves also have potential antioxidant activity. Endophytic fungi from nutmeg leaves were identified as Phomopsis sp. with an IC_{50} value of 79.0 µg/mL in the antioxidant test using the DPPH method. These results are good enough to show the antioxidant activity of the endophytic fungi with an isolation result of 459.3 mg/200 ml Potato Dextrose Broth (PDB) (Rahmi *et al*., 2023). The compound dihydrokaempferol, a secondary metabolite of the flavonoid group, was successfully isolated from nutmeg leaf extract. The DPPH results show that the compound exhibits potent antioxidant activity with an IC_{50} value of 9.75 ppm (Ginting *et al*., 2016).

Table 4. IC_{50} values of n-hexane extract and fractions isolated from nutmeg leaves.

Samples	IC_{50} value (ppm)
n-hexane extract	96.676
MFHD 1	92.676
MFHD 2	96.716
MFHD 3	88.060
MFHD 4	0.729
MFHD 5	87.958
MFHD 6	114.95
MFHD 7	98.767
Vit. C (Ref)	7.875

Larvicidal

Larvicidal activity indicates the ability of a compound to kill or inhibit the growth of insect larvae or parasites. This test aims to control the spread of pests or diseases caused by insect vectors, such as malaria or dengue fever. Meanwhile, the adulticidal activity test aims to reduce the population of active adult insects to inhibit the spread of diseases transmitted by these insects (Ganesan *et al*., 2023; Manojkumar *et al*., 2023; Milugo *et al*., 2021). Essential oils from nutmeg leaves and fruits were tested for larvicidal activity against *Aedes aegypti* with concentrations of 50, 100, 150, and 200 µg/mL. The test results showed that essential oil from nutmeg fruit was more toxic than nutmeg leaves. This is indicated by the LC_{50} value of nutmeg fruit essential oil (110.1 µg/mL), which is lower than nutmeg leaves essential oil (133.8 µg/mL) (Carolina and Maman, 2016). The results of the larvicidal activity of aqueous extract from nutmeg leaves and zinc oxide nanorods synthesized using the nutmeg leaves extract showed significant differences against larvae (I, II, III, or IV instars) and pupae of *Aedes aegypti*. A comparison of LC_{50} and LC_{90} values as larvicidal in both samples can be seen in Table 5, while adulticidal activity is in Table 6 (Ashokan *et al*., 2017).

Table 5. Comparison of LC_{50} and LC_{90} (larvicidal activity) values of nutmeg aqueous leaves extract and green-synthesized ZnO nanorod against *Aedes aegypti* larvae and pupae (Ashokan *et al*., 2017)

Target	$LC_{50}(LC_{90})$ (ppm)	
	Nutmeg aqueous leaves extract	Green-synthesized ZnO nanorod
Larva I	162.03 (502.04)	3.44 (18.35)
Larva II	194.11 (542.56)	5.25 (30.37)
Larva III	240.1 (604.78)	8.02 (39.14)
Pupa	273.9 (660.96)	10.28 (44.07)

As shown in Table 6, the test results indicate that green-synthesized ZnO nanorods from nutmeg leaves extract are more effective as larvicidal and adulticidal agents than the crude extract (Ashokan *et al*., 2017).

Table 6. Comparison of LC_{50} and LC_{90} (adulticidal activity) values of nutmeg aqueous leaves extract and green-synthesized ZnO nanorod against *Aedes aegypti* larvae and pupae (Ashokan *et al*., 2017)

Treatments	$LC_{50}(LC_{90})$
Nutmeg aqueous leaves extract	180.26 (368.93)
Green-synthesized ZnO nanorod	15.004 (34.2)

Cytotoxic Assay

The cytotoxic test is one of the stages in drug development that determines the toxic dose and identifies a compound's anticancer potential. This test is done by measuring the ability of a compound to inhibit and stop the development of cancer cells. In addition, cytotoxic tests can also be used to evaluate a substance's safety before proceeding to the in vivo test stage on test animals. The method often used in this test is the methyl thiazolydiphenyl tetrabromide (MTT) assay, which measures the ability of test cells to reduce tetrazolium salts to formazan (Adan *et al*., 2016; Butler, 2004; Din *et al*., 2021; Ginting *et al*., 2020).

A cytotoxicity test against the human hepatic cell line HepG2 showed that ZnO nanorods had IC_{50} values of 22 and 20 µg/mL after 24 and 48 h, respectively. This study also found that the treatment of the samples (green-synthesized ZnO nanorod from nutmeg leaf extract) yielded significant results even though they came from the same source. The tiny size of the nanoparticles provides a vast surface area, thus increasing reactivity and efficiency in various applications (Ashokan *et al*., 2017; Hashemi *et al*., 2021; Khader *et al*., 2018; Perumalsamy and Krishnadhas, 2022).

Essential oils are generally studied as antibacterial, antifungal, and larvicidal. This is because essential oils have more concentrated active compounds and are lipophilic, such as α-pinene, sabinene, β-pinene, limonene, β-phellandrene, α-terpinolene, safrole, and myristicin (Abers *et al*., 2021; Carolina and Maman, 2016). This causes essential oils to penetrate the lipid membrane of microbial cells more effectively, while crude extracts have a variety of polar compounds that are not as efficient in penetrating microbial membranes (Abers *et al*., 2021;Mukurumbira *et al*., 2023).

Meanwhile, nutmeg extract has the potential as an antioxidant and has high cytotoxic activity. This is because crude extracts have a variety of bioactive compounds, including polar compounds such as flavonoids, polyphenol alkaloids, and tannins. These polar compounds effectively interact with cell membranes and hydrophilic cell components such as proteins and DNA. In addition, the diverse content in the crude extract can also cause compounds to work synergistically to increase antioxidant and cytotoxic activity (Awouafack *et al*., 2017; Lopez-Corona *et al*., 2022).

Table 7. Chemical composition and biological activities of nutmeg leaves.

Chemical composition	Bioactivity	Active compound	Results	References
Acetone extract	-	-	Gas Chromatography-Mass Spectrometry (GC-MS) γ-terpinene; caryophyllene; naphtalene; myristic acid, hexanoic acid, myristic acid; γ and α eudesmol; phenol,2,6-dimetheoxy-4-(2-propenyl)-; elemicin; isomallotochromanol; 2-(1-butoxyvinyl)-4,4-dimethyl-2-cyclohexene-1-one	(Adibuduge *and* Senevirathne, 2023)
-	Antibacterial (*P. aeruginosa*, *L. monooxygenases*, *S. enterica*, *E. coli*, *S. dysenteriae*)	Ethanol extract	ZOI (cm) = 0.56 ± 0.04; 1.26 ± 0.06; 0.98 ± 0.05; 1.27 ± 0.05; 1.56 ± 0.05	
		Acetone extract	ZOI (cm) = 0.57 ± 0.02; 1.37 ± 0.11; 0.61 ± 0.07; 1.27 ± 0.04; 1.61 ± 0.04	
		Chloroform extract	ZOI (cm) = 0.97 ± 0.04; 1.04 ± 0.02; 0.83 ± 0.04; 1.00 ± 0.07; 0.90 ± 0.07	
		Hot water extract	ZOI (cm) = 0.57 ± 0.02; 0.61 ± 0.01; 0.72 ± 0.05; 0.61 ± 0.02; 0.52 ± 0.003	
		Amoxicillin (Ref.)	ZOI (cm) = 2.73 ± 0.01; 3.1 ± 0.01; 3.5 ± 0.01; 3.3 ± 0.01; 3.7 ± 0.02	
	Antifungal (A. niger)	Methanol extract	ZOI (cm) = 38.10 ± 7.72	
		Ethanol extract	ZOI (cm) = 40.00 ± 9.43	
		Acetone extract	ZOI (cm) = 49.92 ± 9.82	
		Chloroform extract	ZOI (cm) = 51.52 ± 3.71	
		Hot water extract	ZOI (cm) = 33.75 ± 4.42	
	Antioxidant	Acetone extract	TPC 895.12 ± 44.24 mg GAE/g of leaves; FRAP 715.78 ± 51.09 mg of Trolox/g of leaves; DPPH 65.56 ± 0.93 mg of ascorbic acid/g of leaves; $ABTS^{+}$ 31.67 ± 0.49 mg of Trolox equivalent/g of leaves; Ferrous Ion chelating 10.87 ± 1.85 mg of EDTA/G of leaves	
Endophytic fungi from nutmeg young leaves		-	Fungal taxa = *Phomopsis sp.* (isolate extract 459.3 mg/200 mL	(Rahmi *et al*., 2023)
-	Antioxidant (DPPH)	*Phomopsis sp.*	IC_{50}= 79.0 µg/mL	

Chemical composition	Bioactivity	Active compound	Results	References
Nutmeg leaves	-	-	Yield 0.26% oil (steam-water distillation method)= 20 components with the main composition, namely myristicin (15.92%), β-phellandrene (14.35%), limonene (11.20%), β-pinene (10.81%), and α-pinene (8.59%) Yield 29.01% nutmeg leaf ethanol extract (extraction method) = 37 components with the main composition being myristicin (7.64%), 1,1,3,3,5,5,7,7,9,9,11,11,13,13-tetradecamethylheptasiloxane (7.14%), 2,2-dimethyl-1-decanol (7.12%) and bis-(2-ethylhexyl) phthalate (5.55%)	(Kapelle *et al*., 2022)
Nutmeg leaves oil	-	-	GC-MS = α-pinene (32.69%), β-pinene (26.68%), sabinene (8.23%), limonene (5.64%), and myristicin (8.59%)	(Azwar *et al*., 2022)
-	Antioxidant (DPPH)	Nutmeg leaves oil	IC_{50} (distillation at 125 ℃)= 2.03%	
Essential oils (EO) of leaves	-	-	A total of 51 compounds = myristicin (major compounds 14.19%), α-pinene, sabinene, 4-terpineol, phellandrene, caryophyllene, elemicin, and β-pinene	(Fernando *and* Senevirathne, 2021)
-	Antibacterial (*S. enteritica*, *L. monocytogenes*, *S. dysenteriae*, *E. coli*, *P. aeruginosa*	EO of leaves	ZOI (cm) = 1.03 ± 0.04; 1.37 ± 0.04; 1.17 ± 0.08; 1.20 ± 0.07	
	Antifungal (*F. oxysporum* and *A. niger)*		ZOI (cm) = 1.27 ± 0.18; 0.57 ± 0.04	
EO of leaves (hydrodistillation method)	-	-	Monoterpene hydrocarbons (48.16%), oxygenated phenylpropenes (28.61%), oxygenated monoterpenes (21.65%), and sesquiterpene hydrocarbons (16.76%). The main monoterpenes were sabinene (17.17%), β-pinene (6.44%), D-limonene (5.03%), and β-myrcene (4.74%). The phenylpropene group, represented primarily dominated by eugenol (16.60%) and myristicin (9.12%). The main sesquiterpene constituents of leaf oils were caryophyllene (8.82%) and germacrene (2.95%)	(Ashokkumar *et al*., 2021)

Chemical composition	Bioactivity	Active compound	Results	References
Endophytic fungi from nutmeg leaves (MYFRF 1–4)	-	-	MYFRF 1–4 (Colonization frequency) = *Colletrichum sp.* (2.77%); *Pestalotiopsis sp.* (8.33%); *Fusarium sp.* (1.38%); *Fusarium sp.* (4.16%)	(Deepthi *et al*., 2018)
-	Antibacterial (E. coli, *K. pneumoniae*, and *S. aureus*)	Endophytic fungi from nutmeg leaves (MYFRF 1–4)	Table 3	
Nutmeg leaves	-	-	Seven mixed fractions of MFHD 1 – 7	(Ginting *et al*., 2017)
-	Antioxidant (DPPH)	n-hexane extract from nutmeg leaves	Table 4	
Chloroform extract		-	Six fractions = (Myristica fragrans Metanol Daun) MFMD 1 – 6	(Nurmilasari *et al*., 2017)
-	Antioxidant	Methanol extract Chloroform extract MFMD 4 MFMD 3 MFMD 2 MFMD 6 MFMD 5 MFMD 1	IC_{50} = 36.310 ppm IC_{50} = 28.300 ppm IC_{50} = 26.590 ppm IC_{50} = 27.239 ppm IC_{50} = 29.639 ppm IC_{50} = 39.766 ppm IC_{50} = 55.436 ppm IC_{50} = 126.270 ppm	
Methanolic extract of leaves	-	-	Extract yield = 23.02 g/100 g	(Thileepan *et al*., 2017)
EO of leaves	-	-	EO yield = 2 mL/100 g	
-	Antibacterial (S. aureus NCTC 6571, MRSA strain 1–5)	Methanolic extract from leaves	Table 2	

Chemical composition	Bioactivity	Active compound	Results	References
-	Larvicidal and pupicidal (*Aedes aegypti*)	1. Nutmeg aqueous leaf extract	Table 5	(Ashokan *et al*., 2017)
	Adulticidal (*Aedes aegypti*)	2. Zinc oxide nanorods synthesized using the nutmeg leaf extract	Table 6	
	Cytotoxic assays (HepG2 cells)	Zinc oxide nanorods synthesized using the nutmeg leaf extract	IC_{50} after 24 h and 48 h = 22 and 20 µg/ mL	
EO of leaves	-	-	EO yield 0.66% (α-pinene sabinene, β-pinene, delta-3-carene, limonene, β-phellandrene, α-terpinolene, linalool, safrole, and myristicin	(Carolina *and* Maman, 2016)
-	Larvicidal	EO of leaves	IC_{50} = 133.8 µg/ mL	
Nutmeg leaves	-	-	A flavonoid compound = 3,5,7,4' tetrahydroflavanol or dihydrokaempferol	(Ginting *et al*., 2016)
-	Antioxidant (DPPH)	Dihydrokaempferol	IC_{50} value = 9.75 ppm	

CONCLUSION

This literature review summarizes the chemical content and bioactivity of nutmeg leaves from research conducted in 2014 – 2024. Nutmeg leaves have a diverse chemical composition in essential oils and extracts. Several components identified in nutmeg leaves essential oil include myristicin, eugenol, α-pinene, sabinene, β-pinene, δ-3-carene, limonene, β-phellandrene, α-terpinolene, linalool, safrole, β-myrcene, caryophyllene, and germacrene D with different percentages in each study. In nutmeg leaves extract, several secondary metabolites and compounds from the tannin and flavonoid groups, such as dihydrokaempferol, are used. In addition, several other compounds were also identified, such as myristicin, 1,1,3,3,5,5,7,7,9,9,11,11,13,13-tetradecamethylheptasiloxane, 2,2-dimethyl-1-decanol, bis(2-ethylhexyl) phthalate, γ-terpinene; caryophyllene; naphthalene; myristic acid, hexanoic acid, myristic acid; γ and α eudesmol; phenol, 2,6-dimethoxy-4-(2-propenyl)-; elemicin; isomallotochromanol and 2-(1-butoxyvinyl)-4,4-dimethyl-2-cyclohexene-1-one.

Essential oils and extracts of nutmeg leaves have various interesting bioactivities that have the potential to be studied further. Nutmeg leaves extract is known to have antibacterial activity against pathogenic bacteria such as *P. aeruginosa, L. monocytogenes, S. enterica, E. coli, S. dysenteriae, S. aeruginosa, K. pneumoniae,* both *S. aureus* and Methicillin-Resistant *S. aureus* (MRSA). In addition, nutmeg leaves compounds also have antifungal activity against *F. oxysporum, A. niger, A. flavus,* and *A. ochraceus*. In addition, antioxidant tests with various methods also showed good results in several other tests, such as larvacidal and cytotoxic assays. Overall, nutmeg leaves show great potential as raw materials for drugs. The results of this study also show various types of secondary metabolites with exciting bioactivities that need further study. The number of nutmeg plants spread across Indonesia is also huge and can be cultivated.

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CONFLICT OF INTEREST

The authors confirm that there is no conflict of interest concerning this work,

AUTHOR CONTRIBUTION

AS: Conceptualization, Manuscript Drafting; SF: Manuscript Review and Supervision; AHC: Conceptualization and Supervision.

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