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by Hilal Yaafi Elfia Susilo Susilo1*

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An Update on Pharmacology, Phytochemical, and Toxicity of *Myristica fragrans* Houtt. as the Source of Treatment: A Scoping Review

Hilal Yaafi Elfia[1] and Susilo Susilo[1*]

[1]Department of Biology Education, Faculty of Teacher Training and Education, Universitas Muhammadiyah Prof. DR. Hamka, Jakarta, Indonesia 13830

Abstract

Myristica fragrans (Houtt.) or nutmeg is reported to have many implementations in traditional medicine and the fragrance properties it possesses. The literature has recently shown scientific interest in health-promoting agents expected to make cost-effective therapeutic agents. This review aims to systematically review articles related to nutmeg's phytochemical, pharmacological, and toxicity activity. Information was collected by searching the Springer, Scopus, Taylor and Francis, ScienceDirect, ProQuest, SAGE, Wiley, and PubMed databases using Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) as per the scoping review guidelines. A total of 28 studies were identified, 2 of which included review studies. There were 15 studies on the pharmacology of different parts of the nutmeg plant; five studies focused on nutmeg phytochemicals; four reports related to nutmeg toxicity, including studies presenting case reports; and four studies discussing a combination of phytochemicals, pharmacology, and nutmeg toxicity. Overall, nutmeg is a medicinal plant that is claimed to help treat various diseases, including brain nerve disorders, cancer, psychological disorders, cancer, and digestive system disorders. However, further scientific studies are needed to explore individual chemical compounds' mechanisms of action and therapeutic effects.

Keywords: biological activity, nutmeg, phytochemistry, pharmacology, toxicity

INTRODUCTION

Traditional medicine has been widely carried out by people who use traditional plants, including plants from the Myristicaceae family. Myristicaceae grows considerably in tropical rainforests (Tallei and Kolondam, 2015), such as in Indonesia, China, Taiwan, Malaysia, India, Grenada, South America, and Sri Lanka (Naeem et al., 2016; Quigley et al., 2020). The use of nutmeg is widely used in parts of the world as a spice (Sharma and Armstrong, 2013) and as herbal medicine to overcome various diseases (Anaduaka et al., 2022). In addition, nutmeg is also commercially utilized in care products, active packaging of food (Pilevar et al., 2019), beverages, and antimicrobial agents in food preservation derived from trimyristin and its derivatives in nutmeg butter content, namely, myristic acid, myristyl alcohol, and glycerol (Bahrami et al., 2020; Singh, 2003).

The pharmaceutical importance of nutmeg lies in its capacity to produce a wide variety of secondary metabolites. GC-MS analysis showed that nutmeg contains 37 metabolites such as saccharides (monosaccharides and disaccharides), fats, amino, organic acids, alkaloids, and non-volatile metabolites that explain nutmeg flavor as a spice (Farag et al., 2018). In addition, several carbazole alkaloids define nutmeg fragrance at maximum levels in arillus (24%), followed by seeds (7%) (Farag et al., 2018), which has analgesic, antinociceptive, and antidepressant (Hayfaa et al., 2013; Muchtaridi et al., 2010).

The chemical components of nutmeg include fats, proteins, starch, fixed oils, and essential oils (Cao et al., 2020). Nutmeg essential oil has antimicrobial, antiseptic, antiparasitic, anti-inflammatory, and antioxidant properties (Matulyte et al., 2020; Muchtaridi et al., 2010). The main components of this oil are sabinene (21,38%), 4-terpineol (13,92%), and myristicin (13,57%). At the same time, the dominant compounds in nutmeg seeds are alkylbenzene and propylbenzene derivatives (pelican, safrol, eugenol, and its derivatives) (Muchtaridi et al., 2010).

In controlled laboratory studies, nutmeg was shown to have antioxidant and antimicrobial activity (Gupta et al., 2013; Nikolic et al., 2021). However, long-term use of nutmeg may cause degenerative changes in the kidneys, spleen, liver, heart, medial geniculate body, and superior colliculus trialed in albino rats (Olaleye et al., 2006). Nutmeg toxicity experiments in rats have also been carried out (Anaduaka et al., 2022). The results of the research above prove that information needs to be debated between the benefits and the impact. Some previous nutmeg reviews discussed chemical compounds, biological potentials, and toxic effects of nutmeg, which focused on nutmeg essential oil (NEO) content and compiled from the literature of 2000-2020 (Warsito, 2021).

Secondary metabolite content, pure compound extraction methods, and recent approaches to the total synthesis of several major components have also been reported, such as nutmeg essential oil rich in terpenes and phenylpropanoids and nutmeg containing non-volatile lignan/neolignan type (Abourashed and El-Alfy, 2016). Other studies have studied chemical and pharmacological compounds, focusing on pure compounds (Ha et al., 2020). A review does not make nutmeg the main discussion but briefly discusses chemical and pharmacological compounds such as ginger, turmeric, cumin, garlic, cinnamon, and vanilla (Johnson-Arbor and Smolinske, 2021; Mehmood et al., 2019). Although some nutmeg reviews have been widely reported, as far as we are concerned, it is still rare to provide a comprehensive review that focuses on the pharmacology, phytochemicals, and toxicity of nutmeg seeds. The increasingly developing chemical compound synthesis and analysis technologies allow identifying new compounds not discovered in previous research. As a varied source of metabolism with substantial as a prototyping agent in drug discovery, nutmeg requires greater attention within several limits, including the provision of sustainable bioactive through the development of analytical methods (Członka et al., 2020).

In line with this, there are possible scientific gaps in the phytochemical literature on nutmeg. Therefore, this study began to study the landscape, map the published nutmeg phytochemical studies, toxicological and pharmacological properties, and identify research gaps in this area. Scoping reviews are a practical methodology for understanding the breadth of research and knowledge gaps in a particular field (Peters et al., 2020). This review presents comprehensive data on nutmeg research using eight large databases for the last ten years. The resulting findings are expected to inform the scientific community and facilitate decision-making about the future research direction in this area.

METHOD

Research Design

This study employed a scoping review design. This review provides a preliminary assessment of the potential size and scope of the available research literature. It aims to identify the nature and extent of research evidence on a topic (Arksey and O'Malley, 2005; Grant and Booth, 2009). It is also a transparent method for mapping literature and answering broad research questions (Sarrami-Foroushani et al., 2015). Scoping reviews provide a comprehensive study to answer more general questions than a more specific systematic review of effectiveness or qualitative evidence (Peters et al., 2020). This methodology was chosen because it facilitates an efficient and detailed review of the scope, properties, and extent of nutmeg's phytochemicals, pharmacology, and toxicity. The Preferred Reporting Item guided this scoping review for Systematic Review and the Meta-Analysis extension for Scope Review (PRISMA-ScR) (Tricco et al., 2018).

Research Questions

This review is based on the main research question, "How is the utilization and development of phytochemicals, pharmacology, and toxicity in Nutmeg?" These key questions are further extended to secondary research questions, including the following:

1. What are the phytochemicals contained in nutmeg?
2. What are the pharmacological potentials of nutmeg?
3. What is the toxicity of the nutmeg content it has?

The following PICO (Population, Intervention, Comparison, and Outcomes) framework was used to answer the research questions **(Table 1).**

Search Strategy

The search was limited to full-text articles published in English for ten years (2011-2020). This study was conducted to find in-depth information on research topics tested using modern methods and technologies. During the search, articles were collected according to the research questions and filtered to select those that discuss relevant and promising results (**Figure 1**).

The literature search was conducted using the databases of Springer, Scopus, Taylor and Francis, ScienceDirect, ProQuest, SAGE, Wiley, and PubMed. The investigation used keywords and titles of the study subjects with search terms: *"secondary metabolite Nutmeg" or "metabolite Nutmeg", "pharmacology Nutmeg" or "pharmacology Myristica fragrans", and "potentiality Nutmeg" or "potentiality Myristica fragrans", "phytochemical Nutmeg" or "phytochemical Myristica fragrans", and "toxicity Nutmeg" or "toxicity Myristica fragrans".*

Exclusion and Inclusion Criteria

Studies were selected based on inclusion and exclusion criteria regarding research questions and PICO elements (**Table 1**). Studies were included when they (1) focused on the phytochemical, pharmacological, and toxicity activities of nutmeg; (2) had clear methodology; (3) were written in English; (4) were open access. Studies that did not contain clear or sufficient detailed methods or results were excluded. Specific inclusion and exclusion criteria were applied to each question to create an overall safety profile of nutmeg consumption (**Table 2**). It also allowed the most relevant data to be included in the study.

RESULTS AND DISCUSSION

Demographics of the study area

This work presents data on the pharmacological, phytochemical, and toxicity of nutmeg from 2011-2020. A literature search found 2110 articles, of which 1315 have been deleted based on open access journals, journals of the last ten years, and journals of a research nature, leaving 792 articles. Seven hundred ninety-two of those full-text articles were then reviewed for notability based on inclusion criteria; 728 articles were removed because they had no eligibility inclusion criteria, and 67 articles remained. At least 39 articles were deleted because they did not have nutmeg as the primary participant diagnosis. Thus, 28 articles were included for analysis and discussion (**Table 4**).

The studies included (**Table 3**) by categorizing them into pharmacology (n=15), phytochemicals (n = 5), toxicity (n=4), and combinations that included more than one variable (n = 4). All articles presented are characteristic of research variables. Most articles are randomized controlled trials on nutmeg pharmacology, with the USA as the leading country (21.42%). Three articles included a combination study type by investigating two to 3 variables and related nutmeg (10.71%). Studies of general and specific toxicity in rodents were published, with most reported by the UAE.

The scoping review results revealed a significant lack of studies to expand and deepen the knowledge of nutmeg. These included metabolites, phytochemicals, and pharmacology which will be discussed further in detail.

Phytochemistry

Nutmeg is one of the most commonly used spices due to essential oils' unique taste and aroma (Rizwana et al., 2021; Singh, 2003). Six active compounds were isolated by bioassay-guided fractionation, identified as eugenol, methyl eugenol, methyl isoeugenol, elemicin, myristicin, and safrole (Du et al., 2014). Myristicin and the active metabolite of nutmeg have psychoactive activity, mainly responsible for its toxicity (Seneme et al., 2021). However, this activity can also be explored as a potential therapeutic agent for treating central nervous system disorders (Sivathanu et al., 2014). In addition, other studies agree that myristicin is believed to be able to suppress the inflammatory response stimulated by ox-LDL (Low-Density Lipoprotein Oxidation) by regulating the signaling pathway PI3K/Akt/NF-κB in the development of atherosclerosis so that it can provide potential therapeutic targets that are useful for atherosclerosis (Luo et al., 2022).

Nutmeg hexane extracts showed the highest amounts of steroids, tannins, and terpenoids evaluated based on color production in phytochemical tests. In contrast, other extracts inhibited the formation of melanin at higher concentrations (Hoda et al., 2020). In addition, the phytochemical tests revealed the presence of steroids, carbohydrates, tannins, alkaloids, and terpenoids in nutmeg extract (Hoda et al., 2020). However, other studies reported the absence of terpenoids in its extract (Iyer et al., 2017). This variation was possible due to the plant source, climatic conditions, geographical origin, cultivation conditions, harvest season, and extraction methodology (Nikolic et al., 2021; Suhr and Nielsen, 2003). Another study revealed that nutmeg phytochemicals consist of various compounds that have been identified (Table 5).

Phenolic acids

The total phenolic content of 50% acetone and 80% methanol extract from each plant was determined using a Folin-Ciocalteu reagent (Yu et al., 2002). This result underlined testing the phenolic content in nutmeg, and the result obtained is that nutmeg's main antioxidant is less polar than other botanical materials under experimental conditions (Chatterjee et al., 2007). Nutmeg still shows a very significant and positive correlation between the content between total phenolics and antioxidant activity, especially in fresh fruits (Chatterjee et al., 2007). The tendency for phenolic content reported in nutmeg is acetone > ethanol > methanol > aqueous > butanol (Gupta et al., 2013).

Myristicin

Myristicin is the main component of nutmeg essential oil. Various reports of nutmeg consumers relate to toxicological side effects from myristicin compounds (Ehrenpreis et al., 2014). Side effects include phenytoin toxicity which can affect the central nervous system (CNS), gastrointestinal tract, vomiting, hypotension, and, very rarely, visual dysfunction (Ehrenpreis et al., 2014; Sivathanu et al., 2014). However, systematic follow-up research is still needed for further application of nutmeg.

Lignans

Lignans are a group of compounds derived from plants with various biological activities such as anti-tumor, antimitotic, antiviral, and antiatherosclerotic activities (Akinboro et al., 2011). It was identified in nutmeg seeds and flowers that lignans and neolignans were the most abundant secondary metabolites. They were proven on the mass spectral fragmentation pattern of individual peaks completed with GC-MS consisting of elemicin, erythro-neolignane, and their derivatives (Zálešák et al., 2019).

Flavonoids

Resistance to ultraviolet radiation (and high temperature) is associated with the chemical structure of nutmeg seeds containing extractive organics, such as polyphenols, quinones, or flavonoids (Członka et al., 2020). There are three flavonoids in nutmeg, including quercetin 3-*O*-α-L-rhamnopyranosyl-(1→6)-*O*-[α-L-rhamnopyranosyl-(1 → 2)]-*O*-*β*-D-galactopyranoside **(203)**, and which was found in aril 5,7-diacetyl chrysin **(204)**, catechins **(205)** (Morikawa et al., 2018).

Pharmacological evaluation of nutmeg compounds

Antioxidant activities

Ethanol extract in mace nutmeg has more significant antioxidant activity than aqueous extract (Suthisamphat et al., 2020). However, other studies evaluated nutmeg extract using the Allium cepa test, which was shown to have cytotoxic potential and antimutagenic effects on *A. cepa* chromosome division and cell partition (Akinboro et al., 2011). A temporary conjecture that nutmeg extract is quite promising in developing cancer therapeutic agents. In addition to nutmeg extract, nutmeg oil can potentially be chronic inflammation and painkiller (Zhang et al., 2016). Essential oils have been identified as having a more robust content of the chemical compound elemicin, but terpinen-4-ol has been shown to contribute the most to antioxidant activity (Nikolic et al., 2021). In addition, limonene in nutmeg essential oil was found to have an antioxidant effect when testing Chinese maye frying in sunflower oil (Wang et al., 2019). This fact showed that limonene in nutmeg essential oil was a safe and effective vegetable with oxidative stability and a unique taste.

Antibacterial activities

The presence of antibacterial activity in ethyl acetate and ethanol extracts in all parts of the dry sample (mesocarp, arillus, and seeds) indicated low antibacterial activity (Shafiei et al., 2012). On the other hand, a significant effect of nutmeg essential oil activity in inhibiting fungi is comparable to conventional nystatin antifungal drugs. The potential is beneficial in dentistry as an oral care product such as toothpaste and mouthwash (Sokmen et al., 2004). Another analysis performed against the antibacterial activity of arillus extracts and mace-mediated silver nanoparticles (AgNPs) from nutmeg shows that arillus-AgNPs are very effective in inhibiting bacterial test isolates and making them have good benefits for the agrochemical sector, industry, pharmaceuticals, and some biomedical applications (Rizwana et al., 2021).

Anti-melanogenic activities

Aging can be caused by an increase in the production of melanin pigmentation in response to damage caused by ultraviolet radiation (Oh et al., 2020). One of the studies concluded that nutmeg hexane extract has anti-melanogenic potential as evidenced by inhibition of melanin synthesis, loss of cell surface protrusion, formation of fine cell walls, and decreased ergosterol concentration and hydrophobicity of cell surfaces (Hoda et al., 2020). The study also stated that combining with antifungal drugs will help many patients suffering from *Aspergillus fumigatus* infection.

Antifungal activities

The antimicrobial resistance that humans worry about *Candida albicans* infection makes it one of the reasons to research nutmeg as a plant that can minimize the disease (Iyer et al. 2017). The study results show the high bioactivity of nutmeg extract to fungal pathogens and may be a potential candidate for a potent antifungal molecule. Nutmeg seed extract showed antimicrobial activity at a significant difference of 5% ($P \le 0.05$) during trials on nystatin. So nutmeg extract can meet the needs of developing effective and safe antifungal and antibacterial agents with few side effects (Abutaha et al., 2021).

Anticancer activities

Ehydrodiisoeugenol (DEH, CAS: 83377-50-8) is a benzofurane-type neolignan extracted from nutmeg that has long been prescribed in Chinese medicine (Lv et al., 2017). One of the studies has shown that DEH has a role in colorectal cancer that can represent a new treatment strategy with exceptional anticancer activity and low toxicity (Li et al., 2021). The part of DEH was obtained based on the research process by inhibiting cell growth and proliferation and inducing ERS-autophagy to exert an apparent anticancer effect on colorectal cancer cells (Li et al., 2021).

Myristicin can potentially be a therapeutic agent for liver carcinoma that can prevent the biological behavior of malignant liver carcinoma cells by inhibiting the signaling pathway PI3K/Akt/mTOR (Bao and Muge, 2021). F. Li et al. (2019) state that nutmeg can treat pathogenic bacteria associated with gastrointestinal diseases, reduce colon cancer, and improve metabolic disorders by regulating microbial metabolism in the gut, which can be a potential method to treat colon cancer. Other studies have shown that nutmeg leaf methanol extract induces cytotoxicity and mutagenesis at higher concentrations and indirectly inhibits the induction of mutagenic agents without significant mutagenesis; thus could be a promising candidate for cancer treatment therapy (Akinboro et al., 2012).

Neuroprotective effects

Nutmeg increased levels of serotonin (5-HT), norepinephrine, and dopamine in the hippocampus of rats. The data show that nutmeg can target and regulate multiple pathways involved in the underlying molecular therapy mechanisms, proving therapeutic effects in preventing and treating neurodegenerative diseases (Plaingam et al., 2017). A study reported the results of nutmeg on the endocannabinoid system on the tissues of complex neuromodulators involved in various physiological functions such as appetite, pain, reward, motoric control, memory, and cognition (El-Alfy et al., 2016).

Environmental applications

The antibacterial, antidiabetic, antioxidant, antiparasitic, and larvicidal properties of nutmeg have been evaluated before. The results of the analysis stated that ZnO nanoparticles synthesized from nutmeg could be used as potential candidates for biomedical and environmental applications that are environmentally friendly, non-toxicity, and biocompatibility (Faisal et al., 2021). Another study explored the use of nutmeg as vegetable oil. Vegetable oils have a fat composition that can cause the production of free radicals and eventually damage their oxidative (Aladedunye and Matthäus, 2014). More profound research was conducted on nutmeg essential oil in maintaining oxidative stability in sunflower oil, and this proves that nutmeg essential oil has antioxidant effects (Wang et al., 2019).

Toxicity activities

Extracts of arillus and ethanolic nutmeg show the presence of cytotoxic activity. Arillus extract has a selective cytotoxic effect in inducing apoptosis between cancer and normal cells, so arillus is a potential candidate as a potent chemotherapy agent (Rengasamy et al., 2017). Meanwhile, ethanolic extract in nutmeg showed significant cytotoxic activity against Kato III gastric cancer cells (IC_{50} = 26,06 g/ml) with the Sulphorhodamine B (SRB) Assay test (Suthisamphat et al., 2020). However, the study admitted that ethanolic extract in nutmeg could support the potential of arillus, which was used as a preparation component for treating gastrointestinal symptoms.

The treatment experiment was carried out on male and female rats given alkaloids on raw nutmeg and concluded that the administration of 4 g/kg or more exhibited abnormal behavior, including hypoactivity, unstable gait, or dizziness that lasted for several hours. The administration of 3 g/kg or less did not give rise to abnormal behavior (Hayfaa et al., 2013). However, the study agreed that the treatment did not lead to death and only in excess alkaloids (5.1 g/kg), which caused slight toxicity and was non-toxic. Using nutmeg in high doses and for long periods is not recommended (Anaduaka et al., 2022). Similarly, other studies stated that the lowest concentrations of toxic metals were found in nutmeg samples compared to plants of peppers, thyme, basil, oregano, and black paper (Reinholds et al., 2017). Such effects are associated with myristicin (Carstairs and Cantrell, 2011).

According to data from the Illinois Poison Center (IPC), it was known that from January 2001 to December 2011, there were thirty-two cases in children and adolescents of intentional or unintentional consumption of nutmeg (Ehrenpreis et al., 2014). Accidental cases are caused by a mixture of drugs containing nutmeg and consumed in excess, while in intentional cases, one is by consuming duloxetine, clonazepam, K2 (synthetic cannabinoids), and acetaminophen. Nutmeg as a suicide attempt and other cases involved a 16-year-old girl who reported consuming 25 g of nutmeg after reading that nutmeg was a “bowel cleanser” in a popular teen magazine. Overdose of nutmeg use provides serious effects, namely urinary retention, tremors, and seizures. The literature shows tremors in animals receiving toxic nutmeg doses associated with the anticholinergic effects of nutmeg attributed to myristicin and elemicin (Barceloux, 2009). Further research provides evidence that nutmeg extract works indirectly on the endocannabinoid system by inhibiting the enzymes FAAH and MAGL, which explains the cannabis-like effects of nutmeg (El-Alfya et al., 2019).

Finally, we must acknowledge the limitations of our study in using such an extensive research database. There are many phytochemical and biological studies on nutmeg outside our libraries. This famous spice plant has been proven to have many benefits that can be studied continuously. Seeing its wide distribution, we suggest further investigating this plant, for example, the phytochemical constituents of nutmeg and its pharmacological properties from different geographical areas or cultivation strategies to increase productivity which are still rare.

CONCLUSION

Nutmeg in its use as an alternative for various ailments, nutmeg resulted in a massively trendy effort to evaluate nutmeg with different extracts. The available nutmeg literature suggests this medicinal plant is essential for use in biomedical and environmental applications, such as neurodegenerative diseases, disorders of the central nervous system, atherosclerosis, cancer, chronic inflammation, and pain relief, *A. fumigatus* infections, gastrointestinal, oral care such as toothpaste including mouthwashes, and environmentally friendly vegetable oils. Alkaloids, tannins, carbohydrates, lignans, neolignans, diphenyl alkanes, phenylpropanoids, terpenoids, alkanes, fatty acids, fatty acid esters, and some minor constituents such as steroids, saponins, triterpenoids, and flavonoids are the main chemical constituents that have been proven in nutmeg. Various sub-subjects of nutmeg chemical compounds with significant potential as drug discovery agents, studies have shown that various nutmeg extracts have a wide range of pharmacological activities, such as antioxidant, antibacterial, anti-melanogenic, antifungal, anticancer, and cytotoxicity activities that support it. Nutmeg still has its toxic effects, although it tends to be low compared to the side effects of chemical drugs. Therefore, given its versatile usefulness, the improvement of more in-depth research studies on this plant needs to be improved.

AUTHORS' CONTRIBUTIONS

HYE and SS designed the study. HYE collected the data. SS analyzed the samples. All authors contributed to the drafting of the final manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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ETHICAL APPROVALS

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

DATA AVAILABILITY STATEMENT

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

INFORMED CONSENT STATEMENT

Not Applicable.

REFERENCES

Abourashed EA, El-Alfy AT. Chemical diversity and pharmacological significance of the secondary metabolites of nutmeg (Myristica fragrans Houtt.). Phytochem Rev 2016;15:1035–56. https://doi.org/10.1007/s11101-016-9469-x.

Abutaha N, Al-Keridis LA, Mohamed RAEH, AL-mekhlaf FA. Potency and selectivity indices of Myristica fragrans Houtt . mace chloroform extract against non - clinical and clinical human pathogens. Open Chem 2021:1096–107. https://doi.org/https://doi.org/10.1515/chem-2021-0097.

Akinboro A, Mohamed K Bin, Asmawi MZ. Antioxidants in aqueous extract of Myristica fragrans (Houtt .) suppress mitosis and cyclophosphamide-induced chromosomal aberrations in Allium cepa L . cells. J Zhejiang Univ B (Biomedicine Biotechnol 2011;12:915–22. https://doi.org/10.1631/jzus.B1000315.

Akinboro A, Mohamed K Bin, Asmawi MZ, Othman S, Ying TH, Maidin SM, et al. Mutagenic and antimutagenic assessment of methanol leaf extract of Myristica fragrans (Houtt.) using in vitro and in vivo genetic assays. Drug Chem Toxicol 2012;35. https://doi.org/10.3109/01480545.2011.638300.

Aladedunye F, Matthäus B. Phenolic extracts from Sorbus aucuparia (L.) and Malus baccata (L.) berries: Antioxidant activity and performance in rapeseed oil during frying and storage. Food Chem 2014;159:273–81. https://doi.org/10.1016/j.foodchem.2014.02.139.

Anaduaka EG, Okagu IU, Uchendu NO, Ezeanyika LUS, Nwanguma BC. Hepato-renal toxicity of Myristica fragrans Houtt. (Myristicaceae) seed extracts in rats. J King Saud Univ - Sci 2022;34:101694. https://doi.org/10.1016/j.jksus.2021.101694.

Arksey H, O'Malley L. Scoping studies: Towards a methodological framework. Int J Soc Res Methodol Theory Pract 2005;8:19–32. https://doi.org/10.1080/1364557032000119616.

Bahrami A, Moaddabdoost Baboli Z, Schimmel K, Jafari SM, Williams L. Efficiency of novel processing technologies for the control of Listeria monocytogenes in food products. Trends Food Sci Technol 2020;96:61–78. https://doi.org/https://doi.org/10.1016/j.tifs.2019.12.009.

Bao H, Muge Q. Anticancer effect of myristicin on hepatic carcinoma and related molecular mechanism. Pharm Biol 2021;59:1126–32. https://doi.org/10.1080/13880209.2021.1961825.

Barceloux DG. Nutmeg (Myristica fragrans Houtt.). Disease-a-Month 2009;55:373–9. https://doi.org/https://doi.org/10.1016/j.disamonth.2009.03.007.

Cao Z, Xia W, Zhang X, Yuan H, Guan D, Gao L. Biomedicine & Pharmacotherapy Hepatotoxicity of nutmeg : A pilot study based on metabolomics. Biomed Pharmacother 2020;131:110780. https://doi.org/10.1016/j.biopha.2020.110780.

Carstairs SD, Cantrell FL. The spice of life : An analysis of nutmeg exposures in California. Clin Toxicol 2011:177–80. https://doi.org/10.3109/15563650.2011.561210.

Chatterjee S, Niaz Z, Gautam S, Adhikari S, Variyar PS, Sharma A. Antioxidant activity of some phenolic constituents from green pepper (Piper nigrum L.) and fresh nutmeg mace (Myristica fragrans). Food Chem 2007;101:515–23. https://doi.org/10.1016/j.foodchem.2006.02.008.

Chiu S, Wang T, Belski M, Abourashed EA. HPLC-Guided Isolation, Purification and

Characterization of Phenylpropanoid and Phenolic Constituents of Nutmeg Kernel (Myristica fragrans). Nat Prod Commun 2016. https://doi.org/10.1177/1934578X1601100416.

Członka S, Strąkowska A, Kairytė A, Kremensas A. Nutmeg filler as a natural compound for the production of polyurethane composite foams with antibacterial and anti-aging properties. Polym Test 2020;86. https://doi.org/10.1016/j.polymertesting.2020.106479.

Du S, Yang K, Wang C, You C, Geng Z. Chemical Constituents and Activities of the Essential Oil from Myristica fragrans against Cigarette Beetle Lasioderma serricorne. Chem Biodivers 2014;11:1449–56.

Ehrenpreis JE, Deslauriers C, Lank P, Armstrong PK, Leikin JB. Nutmeg Poisonings : A Retrospective Review of 10 Y ears Experience from the Illinois Poison Center , 2001 – 2011. Toxicol Investig 2014:148–51. https://doi.org/10.1007/s13181-013-0379-7.

El-Alfy AT, Joseph S, Brahmbhatt A, Akati S, Abourashed EA. Indirect modulation of the endocannabinoid system by specific fractions of nutmeg total extract nutmeg total extract. Pharm Biol 2016;54. https://doi.org/10.1080/13880209.2016.1194864.

El-Alfya AT, Abourasheda EA, Patel C, Mazharib N, An H, Jeon A. Phenolic compounds from nutmeg (Myristica fragrans Houtt.) inhibit the endocannabinoid-modulating enzyme fatty acid amide hydrolase. J Pharm Pharmacol 2019;71:1879–89. https://doi.org/10.1111/jphp.13174.

El-sayed KK, Sherif RM, Kamal A. Chemical Composition and Bio-efficacy of Essential Oils Isolated from Seeds of Anethum graveolens L ., Leaves of Thymus vulgaris L ., and Nuts of Myristica fragrans Houtt . Against Callosobruchus maculatus (Fab .) (Coleoptera : Bruchidae). J Essent Oil Bear Plants 2022. https://doi.org/10.1080/0972060X.2021.2016498.

Faisal S, Jan H, Shah SA, Shah S, Khan A, Akbar MT, et al. Green Synthesis of Zinc Oxide (ZnO) Nanoparticles Using Aqueous Fruit Extracts of Myristica fragrans : Their Characterizations and Biological and Environmental Applications. ACS Publ 2021. https://doi.org/10.1021/acsomega.1c00310.

Farag MA, Mohsen E, El-Gendy AENG. Sensory metabolites profiling in Myristica fragrans (Nutmeg) organs and in response to roasting as analyzed via chemometric tools. LWT 2018;97:684–92. https://doi.org/10.1016/j.lwt.2018.08.002.

Grant MJ, Booth A. A typology of reviews: An analysis of 14 review types and associated methodologies. Health Info Libr J 2009;26:91–108. https://doi.org/10.1111/j.1471-1842.2009.00848.x.

Gupta AD, Bansal VK, Babu V, Maithil N. Chemistry, antioxidant and antimicrobial potential of nutmeg (Myristica fragrans Houtt). J Genet Eng Biotechnol 2013;11:25–31. https://doi.org/10.1016/j.jgeb.2012.12.001.

Ha MT, Vu NK, Tran TH, Kim JA, Woo MH, Min BS. Phytochemical and pharmacological properties of Myristica fragrans Houtt .: an updated review. Arch Pharm Res 2020;43:1067–92. https://doi.org/10.1007/s12272-020-01285-4.

Hayfaa AAS, Sahar AAMAS, Awatif MAS. Evaluation of analgesic activity and toxicity of alkaloids in Myristica fragrans seeds in mice. J Pain Res 2013;6:611–5. https://doi.org/10.2147/JPR.S45591.

Hoda S, Vermani M, Joshi RK, Shankar J, Vijayaraghavan P. Anti-melanogenic activity of

Myristica fragrans extract against Aspergillus fumigatus using phenotypic based screening. BMC Complement Med Ther 2020;20:67. https://doi.org/10.1186/s12906-020-2859-z.

Iyer M, Gujjari AK, Gowda V, Angadi S. Antifungal response of oral - associated candidal reference strains (American Type Culture Collection) by supercritical fluid extract of nutmeg seeds for geriatric denture wearers : An in vitro screening study. J Indian Prosthodont Soc 2017;17:267–272. https://doi.org/10.4103/jips.jips.

Johnson-Arbor K, Smolinske S. Stoned on spices: a mini-review of three commonly abused household spices. Clin Toxicol 2021;59:101–5. https://doi.org/10.1080/15563650.2020.1840579.

Li Changhong, Zhang K, Pan G, Ji H, Li Chongyang, Wang X, et al. Dehydrodiisoeugenol inhibits colorectal cancer growth by endoplasmic reticulum stress-induced autophagic pathways. J Exp Clin Cancer Res 2021;9:1–15. https://doi.org/https://doi.org/10.1186/s13046-021-01915-9.

Li F, Yang X, Krausz KW, Nichols RG, Xu W, Andrew D, et al. Modulation of Colon Cancer by Nutmeg. J Proteome Res 2019;14:1937–46. https://doi.org/10.1021/pr5013152.Modulation.

Luo L, Liang H, Liu L. Myristicin regulates proliferation and apoptosis in oxidized low-density lipoprotein-stimulated human vascular smooth muscle cells and human umbilical vein endothelial cells by regulating the PI3K / Akt / NF- κ B signalling pathway. Pharm Biol 2022;60:56–64. https://doi.org/10.1080/13880209.2021.2010775.

Lv Q-Q, Yang X-N, Yan D-M, Liang W-Q, Liu H-N, Yang X-W, et al. Metabolic profiling of dehydrodiisoeugenol using xenobiotic metabolomics. J Pharm Biomed Anal 2017;145:725–33. https://doi.org/https://doi.org/10.1016/j.jpba.2017.07.045.

Matulyte I, Jekabsone A, Jankauskaite L, Zavistanaviciute P, Sakiene V, Bartkiene E, et al. The Essential Oil and Hydrolats From Myristica Fragrans Seeds With Magnesium Aluminometasilicate as Excipient: Antioxidant, Antibacterial, and Anti-inflammatory Activity. Foods 2020;9. https://doi.org/10.3390/foods9010037.

Mehmood A, Zhao L, Wang C, Nadeem M, Raza A, Ali N, et al. Management of hyperuricemia through dietary polyphenols as a natural medicament: A comprehensive review. Crit Rev Food Sci Nutr 2019;59:1433–55. https://doi.org/10.1080/10408398.2017.1412939.

Morikawa T, Hachiman I, Ninomiya K, Hata H, Sugawara K, Muraoka O, et al. Degranulation inhibitors from the arils of Myristica fragrans in antigen-stimulated rat basophilic leukemia cells. J Nat Med 2018;72:464–73. https://doi.org/10.1007/s11418-017-1170-x.

Muchtaridi, Subarnas A, Apriyantono A, Mustarichie R. Identification of compounds in the essential oil of nutmeg seeds (Myristica fragrans Houtt.) that inhibit locomotor activity in mice. Int J Mol Sci 2010;11:4771–81. https://doi.org/10.3390/ijms11114771.

Naeem N, Rehman R, Mushtaq A, Ghania B. Nutmeg: A review on uses and biological properties. Int J Chem Biochem Sci 2016;9:107–10.

Nikolic V, Nikolic L, Dinic A, Gajic I, Urosevic M, Stanojevic L, et al. Chemical Composition, Antioxidant and Antimicrobial Activity of Nutmeg (Myristica fragrans Houtt.) Seed Essential Oil. J Essent Oil-Bearing Plants 2021;24:218–27. https://doi.org/10.1080/0972060X.2021.1907230.

Oh YS, Shin SY, Kim S, Lee KH, Shin JC, Park KM. Comparison of antiaging, anti-melanogenesis effects, and active components of Raspberry (Rubus occidentalis L.) extracts according to maturity. J Food Biochem 2020;44:1–10. https://doi.org/10.1111/jfbc.13464.

Olaleye MT, Akinmoladun AC, Akindahunsi AA. Antioxidant properties of Myristica fragrans (Houtt) and its effect on selected organs of albino rats. African J Biotechnol 2006;5:1274–8. https://doi.org/10.4314/ajb.v5i15.43113.

Peters MDJ, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. JBI Evid Synth 2020;18:2119–26. https://doi.org/10.11124/JBIES-20-00167.

Piaru SP, Mahmud R, Ismail S. Studies on the Phytochemical Properties and Brine Shrimp Toxicity of Essential Oil Extracted from Myristica fragrans Houtt . (Nutmeg). J Essent Oil Bear Plants 2013;5026. https://doi.org/10.1080/0972060X.2012.10644019.

Pilevar Z, Bahrami A, Beikzadeh S, Hosseini H, Jafari SM. Migration of styrene monomer from polystyrene packaging materials into foods: Characterization and safety evaluation. Trends Food Sci Technol 2019;91:248–61. https://doi.org/https://doi.org/10.1016/j.tifs.2019.07.020.

Plaingam W, Sangsuthum S, Angkhasirisap W. Kaempferia parvi fl ora rhizome extract and Myristica fragrans volatile oil increase the levels of monoamine neurotransmitters and impact the proteomic pro fi les in the rat hippocampus : Mechanistic insig. J Tradit Complement Med 2017;7:538–52. https://doi.org/10.1016/j.jtcme.2017.01.002.

Quigley DTG, MacNamara L, Gainey PA. First Records of Stranded Nutmegs Myristica Fragrans Houttuyn, 1774 (Magnoliales: Myristicaceae) on The Irish Coast and A Review of North Atlantic Records. Bull Irish Biogeogr Soc 2020;44:178–88.

Reinholds I, Pugajeva I, Bavrins K, Kuckovska G. Mycotoxins , pesticides and toxic metals in commercial spices and herbs. Food Addit Contam Part B 2017;10:5–14. https://doi.org/10.1080/19393210.2016.1210244.

Rengasamy G, Venkataraman A, Veeraraghavan VP, Jainu M. Cytotoxic and apoptotic potential of Myristica fragrans Houtt . (mace) extract on human oral epidermal carcinoma KB cell lines. Brazilian J Pharm Sci 2017:1–8. https://doi.org/http://dx.doi.org/10.1590/s2175-97902018000318028 Article.

Rizwana H, Bokahri NA, Alkhattaf FS, Albasher G, Aldehaish HA. Antifungal, Antibacterial, and Cytotoxic Activities of Silver Nanoparticles Synthesized from Aqueous Extracts of Mace-Arils of Myristica fragrans. J Mol 2021. https://doi.org/https:// doi.org/10.3390/ molecules26247709.

Sarrami-Foroushani P, Travaglia J, Debono D, Clay-Williams R, Braithwaite J. Scoping Meta-Review: Introducing a New Methodology. Clin Transl Sci 2015;8:77–81. https://doi.org/10.1111/cts.12188.

Seneme EF, Carla D, Marcela E, Silva R, Edwirges Y, Franco M, et al. Pharmacological and Therapeutic Potential of Myristicin : A Literature Review. J Mol 2021:1–15. https://doi.org/https://doi.org/10.3390/molecules26195914.

Shafiei Z, Shuhairi NN, Md Fazly Shah Yap N, Harry Sibungkil CA, Latip J. Antibacterial activity of Myristica fragrans against oral pathogens. Evidence-Based Complement Altern Med 2012:825362,. https://doi.org/10.1155/2012/825362.

Sharma M V., Armstrong JE. Pollination of Myristica and other nutmegs in natural populations.

Trop Conserv Sci 2013;6:595–607. https://doi.org/10.1177/194008291300600502.

Singh RH. The Nutmeg and Spice Industry in Grenada : Innovations and Competitiveness. Sci Technol 2003. https://doi.org/https://www.researchgate.net/publication/275771715.

Sivathanu S, Sampath S, David HS. Myristicin and phenytoin toxicity in an infant. Case Rep 2014:2013–5. https://doi.org/10.1136/bcr-2013-203000.

Sokmen A, Gulluce M, Akpulat HA, Daferera D, Tepe B, Polissiou M, et al. The in vitro antimicrobial and antioxidant activities of the essential oils and methanol extracts of endemic Thymus spathulifolius. Food Control 2004;15:627–34. https://doi.org/10.1016/j.foodcont.2003.10.005.

Suhr KI, Nielsen P V. Antifungal activity of essential oils evaluated by two different application techniques against rye bread spoilage fungi. J AppliedMicrobiology 2003:665–74.

Suthisamphat N, Dechayont B, Phuaklee P, Prajuabjinda O, Vilaichone R, Itharat A, et al. Anti-Helicobacter pylori, Anti-Inflammatory, Cytotoxic, and Antioxidant Activities of Mace Extracts from Myristica fragrans. Evidence-Based Complement Altern Med 2020. https://doi.org/10.1155/2020/7576818.

TALLEI TE, KOLONDAM BJ. DNA Barcoding of Sangihe Nutmeg (Myristica fragrans) using matK Gene. HAYATI J Biosci 2015;22:41–7. https://doi.org/10.4308/hjb.22.1.41.

Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. Ann Intern Med 2018;169:467–73. https://doi.org/10.7326/M18-0850.

Wang D, Dong Y, Wang Q, Wang X, Fan W. Limonene, the compound in essential oil of nutmeg displayed antioxidant effect in sunflower oil during the deep-frying of Chinese Maye. Food Sci Nutr 2019;8:511–20. https://doi.org/10.1002/fsn3.1333.

Warsito MF. A Review on Chemical Composition , Bioactivity , and Toxicity of Myristica fragrans Houtt. Essential Oil. Indones J Pharm 2021;32:304–13.

Yu L, Perret J, Davy B, Wilson J, Melby CL. Antioxidant properties of cereal products. J Food Sci 2002;67:2600–3. https://doi.org/10.1111/j.1365-2621.2002.tb08784.x.

Zálešák F, Bon DJYD, Pospíšil J. Lignans and Neolignans: Plant secondary metabolites as a reservoir of biologically active substances. Pharmacol Res 2019;146:104284. https://doi.org/10.1016/j.phrs.2019.104284.

Zhang WK, Tao S, Li T, Li Y, Li X, Cong R, et al. Nutmeg oil alleviates chronic inflammatory pain through inhibition of COX-2 expression and substance P release in vivo. Food Nutr Res 2016;6628. https://doi.org/10.3402/fnr.v60.30849.

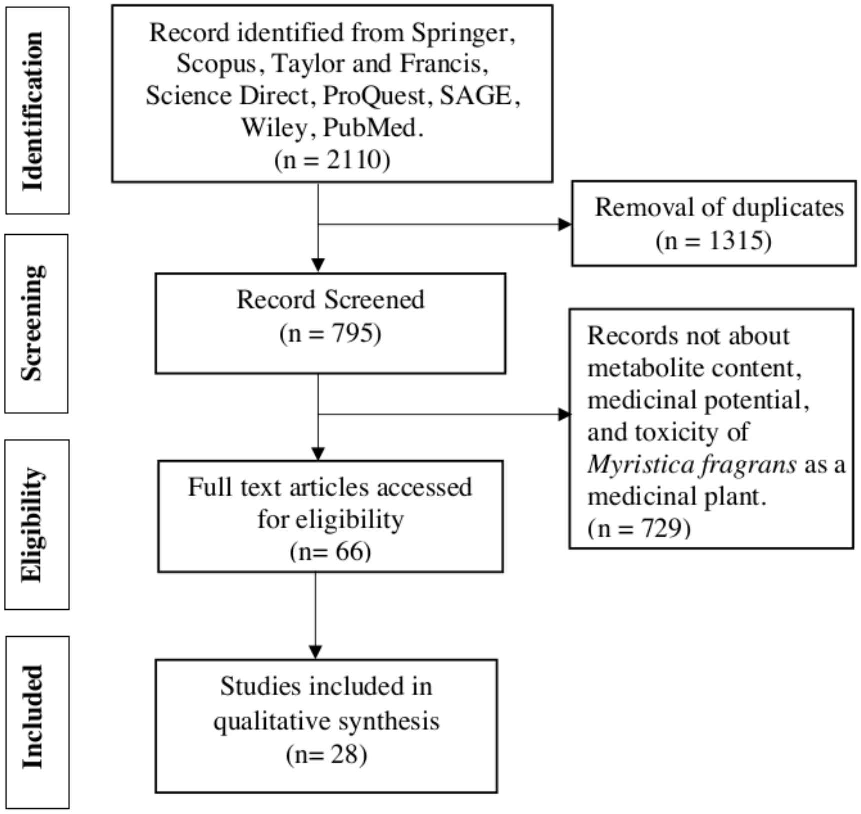


Figure 1. PRISMA flowchart illustrating the process of selecting articles for scoping review search

Table 1. PICO framework

Elements	Details
Population	1. Phytochemical of nutmeg 2. Pharmacology activities of nutmeg 3. Toxicity of nutmeg
Intervention	Nutmeg as herb medicine, only studies that discuss the chemical content, pharmacological activity, and evidence of the toxicity of the nutmeg plant are included.
Comparison	Comprehensive review, three variables, no treatment
Outcomes	Primary outcome: 1. Phytochemical data of nutmeg. 2. Pharmacology data of nutmeg, including indirect use it. 3. Reports on toxicity, including adverse events, may be related to using nutmeg. Secondary outcome: Reporting quality of indirect indicator toxicity and use of nutmeg for future life.

Table 2. Inclusion and exclusion criteria	
Phytochemical studies	
Inclusion criteria	a) Research articles on nutmeg of phytochemistry; b) Articles that investigated nutmeg as an intervention in all types of phytochemistry compounds; c) Articles of phytochemistry that included nutmeg in it; d) Articles published in English; e) The types of articles used are research articles, experiments, and reviews;
Exclusion criteria	a) They were published as literature reviews; b) They did not provide clear information; c) A full text was not available;
Pharmacology studies	
Inclusion criteria	a) Research articles on nutmeg of pharmacology; b) Articles that investigated nutmeg as an intervention in all types of pharmacology formulation; c) Articles published in English; d) Articles of pharmacology that included nutmeg in it;
Exclusion criteria	a) They were published as literature reviews; b) They did not provide clear information; c) A full text was not available;
Toxicity studies	
Inclusion criteria	a) Research, reviews, and reports articles on nutmeg toxicity; b) Articles that investigated nutmeg as an intervention in all types of toxicity compounds; c) Articles published in English;
Exclusion criteria	a) They were published as literature reviews; b) They did not provide clear information; c) A full text was not available;

Table 3. Demographics of included articles

Demographic categories	Frequency (n)	Percentage (%)
***Type of article* (n = 28)**		
Advanced research	3	10.71
Randomized controlled trial	11	39.28
True experiment trial	9	32.14
Review article	2	7.14
Quasi experimental trial	2	7.14
Case report	1	3.57
***Type of study* (n = 28)**		
Pharmacology	15	53.57
Phytochemical	5	17.85
Toxicity	4	14.28
Combination	4	14.28
***Indication* (n = 28)**		
Neuroprotective effects	1	3.57
Anti-inflammatory and anti-allergic effects	1	3.57
Antioxidants and anticancer	1	3.57
Anticancer	3	10.71
General biomedical	6	21.42
Atherosclerosis	1	3.57
Anti-inflammatory	1	3.57
Antibacterial	1	3.57
Antifungal	1	3.57
Anti-melanogenic	1	3.57
Antioxidant	1	3.57
Animal experiment	1	3.57
Eos	3	10.71
Kernel	1	3.57
Specific toxicity	2	7.14
General toxicity	3	10.71
***Country* (n = 28)**		
Thailand	2	7.14
Nigeria	1	3.57
China	5	17.85
Malaysia	4	14.28
USA	6	21.42
Pakistan	1	3.57
UAE	2	7.14
Egypt	1	3.57
Serbia	1	3.57
Latvia	1	3.57
India	3	10.71
Iraq	1	3.57

Table 4. General study characteristics

No.	References	Study aim	Study result	Plant part used	Implication	Country
			Pharmacology			
1.	(Plaingam et al., 2017)	Investigating the effects of *Kaempferia parviflora* and nutmeg on levels of monoamine neurotransmitters (norepinephrine, serotonin, and dopamine).	The results showed that nutmeg increased serotonin, norepinephrine, and dopamine in the hippocampus of rats	Volatile oil	Determine whether and how ethanol extracts of *Kaempferia parviflora* and nutmeg essential oil may affect neurotransmitter levels and the entire proteomic profile in the hippocampal of Sprague Dawley Rats (SD).	Thailand
2.	(Li et al., 2021)	The anti-tumor activity of DEH in colorectal cancer was investigated through cell-derived xenograft (CDX) and patient-derived tumor xenograft (PDX) models.	These findings suggest that Dehydrodiisoeugenol (DEH) extracted from nutmeg enables a promising therapeutic drug for treating colorectal cancer.	The Seed of nutmeg	It clarifies the anticancer effects of DEH on colorectal cancer and its mechanism of action.	China
3.	(Akinboro et al., 2011)	Examines the efficacy of phytochemical constituents in preventing the development of cancer and the development of cancer chemotherapy agents.	Nutmeg freeze-dried aqueous extract is promising in developing cancer therapeutic agents, although further investigation is required.	The freeze-dried water extract from the leaves of nutmeg	Evaluated the effectiveness of aqueous extracts from nutmeg leaves in suppressing cyclophosphamide (CP)-induced cytotoxicity and chromosomal damage in *A. cepa* cells.	Malaysia
4.	(Li et al., 2019)	Investigating metabolic shifts in colon cancer induced by mutations in the Adenomatous Polyposis Coli (APC) gene using nutmeg.	The reduction in colon cancer with antimicrobial nutmeg treatment supports the idea that inflammation and metabolic disturbances associated with colon cancer result from alterations in gut microbial metabolism	The dried ripe seeds of nutmeg	Revealing the antimicrobial and antioxidant potential of nutmeg.	USA
5.	(Bao and Muge, 2021)	Myristicin nutmeg's anticancer effects on liver carcinoma and	Inhibition exerted by myristicin on the PI3K/Akt/mTOR signaling	Myristicin of nutmeg	This research is preliminary in vitro study on the effects of myristicin on	China

		analyzing the underlying regulatory mechanisms.	pathway may prevent the malignant biological behavior of liver carcinoma cells.		hepatocellular carcinoma, thus opening up opportunities for deeper research.	
6.	(Luo et al., 2022)	This study aimed to reveal that myristicin inhibits atherosclerosis by inactivating the PI3K/AKT/NF-B signaling pathway.	Myristicin suppresses the inflammatory response and may be a promising therapeutic target for ox-LDL-stimulated immune inflammation in atherosclerosis.	Myristicin of Nutmeg	Describing the role of myristicin in bovine LDL-induced hVSMC and HUVEC during the pathogenesis of atherosclerosis.	China
7.	(El-Alfy et al., 2016)	Evaluating nutmeg's binding capacity to various CNS receptors and potential interaction with the endocannabinoid system.	This study stated that none of the nutmeg fraction results showed significant binding to CNS receptors and provided evidence that nutmeg targets the endocannabinoid system, indirectly explaining that the mechanism has a cannabis-like effect.	Whole nutmeg kernels	Understand the full spectrum of nutmeg's neurological activity.	USA
8.	(Akinboro et al., 2012)	Determine the potential anticancer properties of nutmeg methanol leaf extract.	The ability of nutmeg MeOH leaf extract to inhibit the mutagenicity of indirect mutagens without being significantly mutagenic.	Fresh leaves of nutmeg	Nutmeg methanol leaf extract Sustainability for mutagenic and antimutagenic potential through in vitro assays as a preliminary test to be supplemented with in vivo tests.	Malaysia
9.	(Zhang et al., 2016)	Evaluating the combined effect of nutmeg oil on inflammation and pain.	Through the induction of CFA injection, allodynia and heat hyperalgesia in rats showed that nutmeg oil has the potential to reduce joint swelling and allow nutmeg oil to be a potent chronic, inflammatory, and pain reliever.	Nutmeg oil from dried seeds of nutmeg	A mouse inflammatory pain model was used in this study, and three different evaluation methods have been introduced to test the anti-inflammatory and analgesic effects of nutmeg oil.	China
10.	(Shafiei et al., 2012)	Investigating the antimicrobial activity of ethyl acetate and ethanol extracts of nutmeg flesh, seeds, and mace against Gram-positive and Gram-	Demonstrate the potential effect of ethyl acetate, and ethanol extracts from meat, seeds, and mace Nutmeg as a new natural	The fresh flesh, mace, and seed of the nutmeg	Potential antibacterial activity of crude extracts. Hence reference strains were used instead of clinical isolates to investigate the	Malaysia

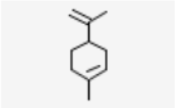
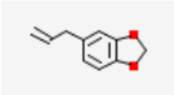
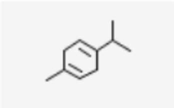
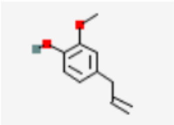
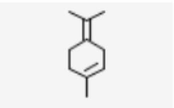
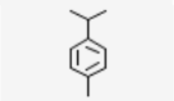
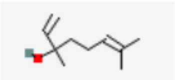
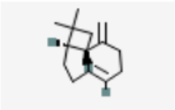
		negative oral pathogenic bacteria.	agent incorporated in oral care products.		antibacterial activity of the tested extracts.	
11.	(Iyer et al., 2017)	To investigate the antifungal activity of nutmeg seed supercritical fluid extract against *Candida albicans* species.	The high bioactivity of nutmeg against fungal pathogens could be an excellent potential for potent antifungal molecules.	Nutmeg seeds	Research confirms that plant products such as nutmeg can interfere with the growth and metabolism of Candida albicans, so it can be a strong candidate for antifungal molecules.	India
12.	(Rizwana et al., 2021)	Synthesized green silver nanoparticles using Nutmeg aril and evaluated their cytotoxic and antimicrobial activity against various pathogenic microorganisms.	Antibacterial, antifungal, and cytotoxic activities are present in mace-AgNPs.	Mace and arillus of Nutmeg	Antifungal and antibacterial activity of silver nanoparticles synthesized from nutmeg arillus and mace extract.	UAE
13.	(Hoda et al., 2020)	Explored the anti-melanogenic effects of nutmeg extract on *Aspergillus Fumigatus*.	Nutmeg extract combined with available antifungal drugs can increase the therapeutic efficacy of patients with *Aspergillus fumigatus* infection.	The nutmeg-dried spice	Inhibiting DHN-melanin biosynthesis by inhibiting the PKSP gene/gene product can be considered a new drug target.	India
14.	(Suthisamphat et al., 2020)	Further analyze the pharmacological activity of mace nutmeg.	The ethanolic mace extract has anti-H. Pylori, anti-inflammatory, antioxidant, and anticancer activities.	Dried arils of Nutmeg (Mace)	Research supports the use of mace nutmeg in gastrointestinal medicine, but the synergistic effect of the herbal combination must be considered.	Thailand
15.	(Wang et al., 2019)	Explore the antioxidant potential of nutmeg essential oil against sunflower oil.	Three active compounds from nutmeg essential oil were identified using antioxidant activity-guided fractionation, including limonene, terpinolene, and geranyl acetate.	The nuts of nutmeg	Limonene from nutmeg essential oil is an antioxidant and has proven to have oxidative stability and a unique taste.	China
			Phytochemical			
1.	(Abourashed and El-Alfy, 2016)	Provides an overview of secondary metabolites isolated from nutmeg and mace seeds.	The traditional use of nutmeg in reducing gastrointestinal disorders, overcoming rheumatic	Kernel and mace of nutmeg	Analysis of extracts and pure compounds.	USA

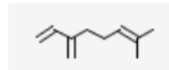
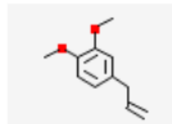
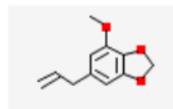
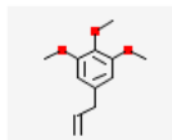
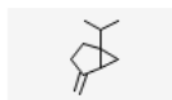
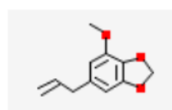
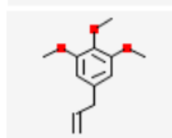
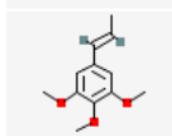
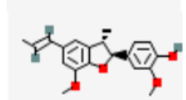
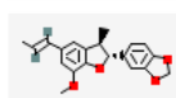
			pain, healing wounds and skin infections, and its use as a sedative agent.			
2.	(El-Alfya et al., 2019)	Identify nutmeg compounds that interact indirectly with the endocannabinoid system.	This study provides further evidence that nutmeg extract targets the endocannabinoid system indirectly by inhibiting the FAAH and MAGL enzymes.	Whole nutmeg kernels	Characterizes FAAH inhibitory activity and offers a plausible explanation for nutmeg's longstanding reputation as an inferior cannabis substitute.	USA
3.	(El-sayed et al., 2022)	Identify essential oils' chemical composition and bio-efficacy (EOs) from *Anethum graveolens*, *Thymus vulgaris*, and nutmeg.	The analysis of the chemical components of essential oils (EOs) using nutmeg showed that nutmeg showed good insecticidal activity, making it very attractive to be used as a potential source of natural protective agents.	Dried nuts of nutmeg	Catatherizing EO and evaluating the bioefficacy of nutmeg against the main pest of adult insects *Callosobruchus maculatus*.	Egypt
4.	(Piaru et al., 2013)	Knowing the nature of phytochemicals and their cytotoxic activity.	Nutmeg essential oil exhibits various phytochemical properties and low toxicity activity.	The fresh fruits of the nutmeg	Determining the phytochemical properties and cytotoxicity of nutmeg oil obtained from the fruit parts by qualitative phytochemical screening methods and toxicity tests of brine shrimp.	Malaysia
5.	(Chiu et al., 2016)	Developed a reproducible procedure for preparing specific extracts and isolating the main phenolic constituents in nutmeg seeds.	The availability of compounds in nutmeg allows the development of specific, accurate, and pharmacokinetic studies to have exciting potential.	Six nutmeg in the whole kernel or powdered	Developed and optimized qualitative HPLC method to guide the isolation/purification process.	USA
			Toxicity			
1.	(Anaduaka et al., 2022)	To determine the effect of giving high doses of Nutmeg seeds for one or two weeks on serum markers of kidney and liver rats.	This study shows that long-term administration of high doses of the extract causes hepato-renal toxicity.	N-hexane (NHE) extracts of the nutmeg seed	Evaluating the constituents of oral administration of high-dose methanol and n-hexane extracts of Nutmeg seeds on liver and kidney status of rats.	Nigeria

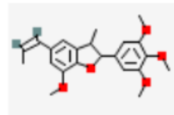
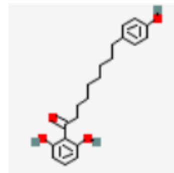
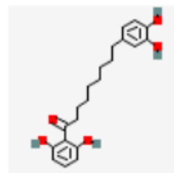
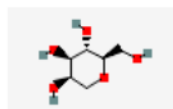
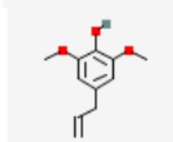
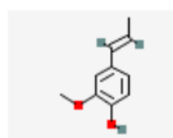
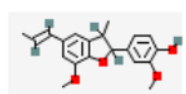
2.	(Reinholds et al., 2017)	Analyzing the combination of multi-grade pesticide residues, conventional mycotoxins, and toxic metal elements in nutmeg.	Nutmeg leaf extract inhibits the mutagenicity of indirect mutagens without being significantly mutagenic.	Ground herb of nutmeg	Using HPLC-QqQ-MS/MS and ICP-MS to evaluate the occurrence of contaminants in the nutmeg.	Latvia
3.	(Rengasamy et al., 2017)	Evaluating the cytotoxicity and apoptotic induction potential of mace extract of nutmeg.	Mace extract functions as a broad-spectrum anticancer agent in human cancer cells by blocking the cell cycle and triggering apoptosis through an intrinsic pathway with a slightly more normal cytotoxic effect on cells.	The authenticated sample of the dried mace of nutmeg	Demonstrated potential apoptotic activity of mace extract on oral cavity carcinoma cell lines.	India
4.	(Ehrenpreis et al., 2014)	Analyzing and comparing Illinois data with the literature and looking for trends in nutmeg poisoning when the study was conducted.	Studies show an unexpected percentage of accidental exposure in adolescents under 13 years of total nutmeg exposure.	Nutmeg extract	Further intervention in adolescents is needed regarding the mixing of nutmeg in medicine.	USA
			Combination			
1.	(Faisal et al., 2021)	Report on synthesizing vegetable zinc oxide nanoparticles using Nutmeg fruit water extract.	The biogenic ZnO-NP using nutmeg's juicy fruit extract is used for various diseases, cosmetics, and cancer research.	Extracts of Nutmeg	The synthesized green nanoparticles will be characterized using modern techniques such as Fourier transform infrared (FTIR) spectroscopy, ultraviolet (UV) spectroscopy, X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), dynamic light scattering (DLS), and thermal gravimetric analysis (TGA), which will be examined for antimicrobial, antileishmanial, antidiabetic, antioxidant, antilarvicidal, and protein kinase inhibitory potential.	Pakistan

2.	(Abutaha et al., 2021)	Assessed the antimicrobial, toxicity, and phytochemical profile of Nutmeg extracts.	Research studies provide scientific support for using nutmeg as a traditional medicine because of its proven bioactivity.	Mace of Nutmeg	Different solvent extracts were tested for antimicrobial activity against clinical and reference microbial strains using disc diffusion assays, wells, and microdilution techniques.	UAE
3.	(Nikolic et al., 2021)	Isolated essential oils from Nutmeg seeds determined the qualitative and quantitative chemical composition of the obtained essential oils and tested their antioxidant and antimicrobial activities.	Nutmeg essential oil has the potential to be used in the pharmaceutical, chemical, and food industries as a natural antioxidant and antimicrobial agent.	Seed essential oil of nutmeg	The GC/MS and GC/FID methods determined the chemical composition. The antioxidant activity of the oil was examined using the DPPH test, and the antimicrobial activity using the disc diffusion method.	Serbia
4.	(Hayfaa et al., 2013)	Knowing the identity of the active constituents responsible for analgesic activity	Nutmeg seeds are rated slightly toxic and practically non-toxic on acute toxicity.	Dried Nutmeg seeds	Examined the analgesic effect of alkaloids in Nutmeg seeds in a rat model of acetic acid-induced visceral pain.	Iraq

Table 5. The Compound contents of nutmeg

No.	Compound name	M.F.	M.W. (g/mol)	Chemical structure	Perpustakaan
Essential oil					
1.	Camphene	$C_{10}H_{16}$	136.23		(Plaingam et al., 2017; Zhang et al., 2016)
2.	Limonene	$C_{10}H_{16}$	136.23		(Abourashed and El-Alfy, 2016; Chiu et al., 2016; El-sayed et al., 2022; Nikolic et al., 2021; Plaingam et al., 2017; Wang et al., 2019; Zhang et al., 2016)
3.	Safrole	$C_{10}H_{10}O_2$	162.18		(Abourashed and El-Alfy, 2016; El-sayed et al., 2022; Nikolic et al., 2021; Plaingam et al., 2017; Wang et al., 2019; Zhang et al., 2016)
4.	γ-Terpinene	$C_{10}H_{16}$			(Abourashed and El-Alfy, 2016; El-sayed et al., 2022; Nikolic et al., 2021; Plaingam et al., 2017; Wang et al., 2019; Zhang et al., 2016)
5.	Eugenol	$C_{10}H_{12}O_2$	164.20		(Abourashed and El-Alfy, 2016; El-sayed et al., 2022; Nikolic et al., 2021; Plaingam et al., 2017; Wang et al., 2019)
6.	Terpinolene	$C_{10}H_{16}$	136.23		(El-sayed et al., 2022; Nikolic et al., 2021; Wang et al., 2019; Zhang et al., 2016)
7.	p-Cymene	$C_{10}H_{14}$	134.22		(El-sayed et al., 2022; Nikolic et al., 2021; Plaingam et al., 2017)
8.	Linalool	$C_{10}H_{18}O$	154.25		(Nikolic et al., 2021; Wang et al., 2019; Zhang et al., 2016)
9.	(E)-Caryophyllene	$C_{11}H_{24}$	204.35		(El-sayed et al., 2022; Nikolic et al., 2021; Plaingam et al., 2017; Wang et al., 2019)

10.	Myrcene	$C_{10}H_{16}$	136.23		(El-sayed et al., 2022; Nikolic et al., 2021; Plaingam et al., 2017; Wang et al., 2019)
11.	Methyl eugenol	$C_{11}H_{14}O_2$	178.23		(Abourashed and El-Alfy, 2016; El-sayed et al., 2022; Nikolic et al., 2021; Plaingam et al., 2017; Zhang et al., 2016)
12.	Myristicin	$C_{11}H_{12}O_3$	192.21		(Abourashed and El-Alfy, 2016; El-sayed et al., 2022; Nikolic et al., 2021; Plaingam et al., 2017; Wang et al., 2019; Zhang et al., 2016)
13.	Elemicin	$C_{12}H_{16}O_3$	208.25		(Abourashed and El-Alfy, 2016; El-sayed et al., 2022; Wang et al., 2019; Zhang et al., 2016)
14.	Sabinene	$C_{10}H_{16}$	136.23		(Abourashed and El-Alfy, 2016; El-sayed et al., 2022; Nikolic et al., 2021; Zhang et al., 2016)
Kernel of nutmeg					
1.	Myristicin	$C_{11}H_{12}O_3$	192.21		(Chiu et al., 2016; El-Alfya et al., 2019)
2.	Elemicin	$C_{12}H_{16}O_3$	208.25		(Chiu et al., 2016; El-Alfya et al., 2019)
3.	Isoelemicin	$C_{12}H_{16}O_3$	208.25		(Chiu et al., 2016; El-Alfya et al., 2019)
4.	Licarin A	$C_{20}H_{22}O_4$	326.4		(Chiu et al., 2016)
5,	Licarin B	$C_{20}H_{20}O_4$	324.4		(Chiu et al., 2016; El-Alfya et al., 2019)

6.	Licarin C	$C_{22}H_{26}O_5$	370.4		(Chiu et al., 2016)
7.	Malabaricone B	$C_{21}H_{26}O_4$	342.4		(Chiu et al., 2016; El-Alfya et al., 2019)
8.	Malabaricone C	$C_{21}H_{25}O_5$	358.4		(Chiu et al., 2016; El-Alfya et al., 2019)
MeOH leaf extract of nutmeg					
1.	Styracitol	$C_6H_{12}O_5$	164.16		(Akinboro et al., 2012)
2.	Methoxyeugenol	$C_{11}H_{14}O_3$	194.23		(Akinboro et al., 2012)
3.	Isoeugenol	$C_{10}H_{12}O_2$	164.20		(Akinboro et al., 2012)
4..	Phytol	$C_{20}H_{40}O$	296.5		(Akinboro et al., 2012)
5.	Dehydrodiisoeugenol	$C_{20}H_{22}O_4$	326.4		(Akinboro et al., 2012)

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