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An update on the pharmacology, phytochemistry, and toxicity of *Myristica fragrans* Houtt. as a source of treatment: A scoping review

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ABSTRACT

Myristica fragrans (Houtt.) or nutmeg is reported to have many implementations in traditional medicine, and it possesses fragrance properties. 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 as per the scoping review guidelines. A total of 28 studies were identified, 2 of which are review studies. There were 15 studies on the pharmacology of different parts of the nutmeg plant; 5 studies focusing on nutmeg phytochemicals; 4 reports related to nutmeg toxicity, including studies presenting case reports; and 4 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.

INTRODUCTION

Traditional medicine has been widely used 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. Gas chromatography–mass spectrometry (GC-MS) analysis showed that nutmeg contains 37 metabolites, such as saccharides (monosaccharides and disaccharides), fats, amino acids, organic acids, alkaloids, and nonvolatile metabolites that explain nutmeg flavor as a spice (Farag *et al*., 2018). In addition, several carbazole alkaloids define nutmeg fragrance at maximum levels in the arillus (24%), followed by the seeds (7%) (Farag *et al*., 2018), which has analgesic, antinociceptive, and antidepressant activities (Hayfaa *et al*., 2013; Muchtaridi *et al*., 2010).

The chemical components of nutmeg include fats, proteins, starch, fixed oils, and essential oils (EOs) (Cao *et al*., 2020). Nutmeg EO (NEO) 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).

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In controlled laboratory studies, nutmeg was shown to have antioxidant and antimicrobial activities (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 analyzed (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 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 NEO rich in terpenes and phenylpropanoids and nutmeg containing nonvolatile lignan/neolignan type (Abourashed and El-Alfy, 2016). Other studies have reported chemical and pharmacological compounds, focusing on pure compounds (Ha *et al*., 2020). Previous reviews have not discussed nutmeg as the main topic but briefly discussed 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 aims to assess the landscape, map the published nutmeg phytochemical studies, and 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 10 years. The resulting findings are expected to inform the scientific community and facilitate decision-making about the future research direction in this area.

METHODS

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 does research on phytochemicals, pharmacology and nutmeg toxicity advance?" 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 Population, Intervention, Comparison, and Outcomes (PICO) framework was used to answer the research questions (Table 1).

Search strategy

The search was limited to full-text articles published in English for 10 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 (Fig. 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 the following 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).

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 3. Reports on toxicity, including adverse events, maybe related to using nutmeg. Secondary outcome: Reporting quality of indirect indicator toxicity and use of nutmeg for future life.

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. Moreover, 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). This 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 to 2020. A literature search found 2,110 articles, of which 1,315 have been deleted based on open-access journals, journals of the last 10 years, and journals of a research nature, leaving 792 articles. In total, 792 of those full-text articles were reviewed for notability based on inclusion criteria; 728 articles were removed because they were not eligible, and 67 remained. At least 39 articles were deleted because they were not related to the main topic. 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 three 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 its EOs' 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, which is 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 (CNS) disorders (Sivathanu *et al*., 2014). In addition, other studies agreed that myristicin is able to suppress the inflammatory response stimulated by low-density lipoprotein oxidation (ox-LDL) 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

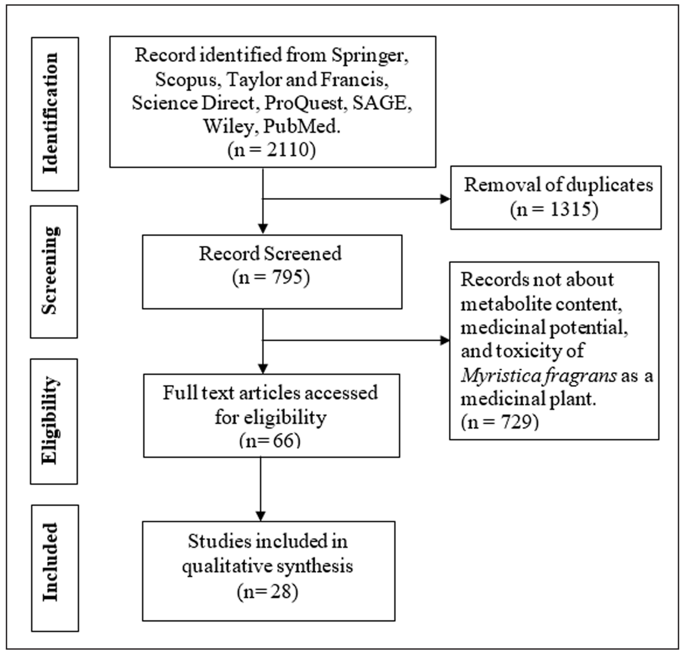


Figure 1. PRISMA flowchart illustrating the process of selecting articles for scoping review search.

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 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 antiallergic 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
Antimelanogenic	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

(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. 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 of 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 NEO. Various reports of nutmeg consumers showed toxicological side effects from myristicin compounds (Ehrenpreis *et al*., 2014). Side effects include phenytoin toxicity, which can affect the CNS and 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 antitumor, 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 (UV) radiation (and high temperatures) 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)**, 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

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 *K. parviflora* and NEO may affect neurotransmitter levels and the entire proteomic profile in the hippocampal of Sprague-Dawley Rats.	Thailand
2.	Li *et al*., 2021	The antitumor activity of DEH in colorectal cancer was investigated through cell-derived xenograft and patient-derived tumor xenograft models.	These findings suggest that 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 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 analyzing the underlying regulatory mechanisms.	Inhibition exerted by myristicin on the PI3K/Akt/mTOR signaling pathway may prevent the malignant biological behavior of liver carcinoma cells.	Myristicin of nutmeg	This research is preliminary *in vitro* study on the effects of myristicin on hepatocellular carcinoma, thus opening up opportunities for deeper research.	China
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 human umbilical vein endothelial cell 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

Continued

No.	References	Study aim	Study result	Plant part used	Implication	Country
9.	Zhang *et al*., 2016	Evaluating the combined effect of nutmeg oil on inflammation and pain.	Through the induction of complete Freund's adjuvant 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-negative oral pathogenic bacteria.	Demonstrate the potential effect of ethyl acetate and ethanol extracts from meat, seeds, and mace nutmeg as a new natural agent incorporated in oral care products.	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 antibacterial activity of the tested extracts.	Malaysia
11.	Iyer *et al*., 2017	To investigate the antifungal activity of nutmeg seed supercritical fluid extract against *C. 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 *C. albicans*, so it can be a strong candidate for antifungal molecules.	India
12.	Rizwana *et al*., 2021	Synthesized green AgNPs 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 AgNPs synthesized from nutmeg arillus and mace extract.	UAE
13.	Hoda *et al*., 2020	Explored the antimelanogenic effects of nutmeg extract on *A. fumigatus*.	Nutmeg extract combined with available antifungal drugs can increase the therapeutic efficacy of patients with *A. fumigatus* infection.	The nutmeg-dried spice	Inhibiting DHN-melanin biosynthesis by inhibiting the polyketide synthase gene 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-*Helicobacter 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 NEO against sunflower oil.	Three active compounds from NEO were identified using antioxidant activity-guided fractionation, including limonene, terpinolene, and geranyl acetate.	The nuts of nutmeg	Limonene from NEO is an antioxidant and has proven to have oxidative stability and a unique taste.	China
Phytochemicals						
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 pain, healing wounds and skin infections, and its use as a sedative agent	Kernel and mace of nutmeg	Analysis of extracts and pure compounds.	USA
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

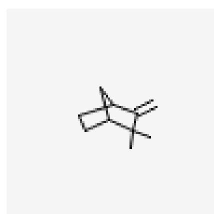
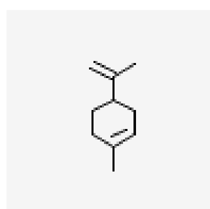
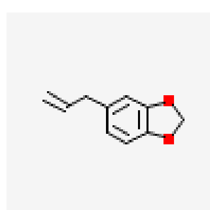
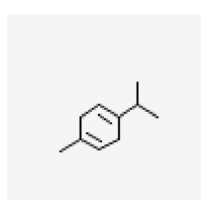
Continued

No.	References	Study aim	Study result	Plant part used	Implication	Country
3.	El-Sayed *et al*., 2022	Identify EOs' chemical composition and bio-efficacy (EOs) from *Anethum graveolens*, *Thymus vulgaris*, and nutmeg.	The analysis of the chemical components of 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.	NEO 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 nutmegs 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 1 or 2 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 NHE extracts of nutmeg seeds on liver and kidney status of rats.	Nigeria
2.	Reinholds *et al*., 2017	Analyzing the combination of multigrade 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 inductively coupled plasma mass spectrometry 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 spectroscopy, UV spectroscopy, X-ray diffraction, scanning electron microscopy, transmission electron microscopy, dynamic light scattering, and thermal gravimetric analysis, which will be examined for antimicrobial, antileishmanial, antidiabetic, antioxidant, antilarvicidal, and protein kinase inhibitory potential.	Pakistan

Continued

No.	References	Study aim	Study result	Plant part used	Implication	Country
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 EOs from Nutmeg seeds determined the qualitative and quantitative chemical composition of the obtained EOs and tested their antioxidant and antimicrobial activities.	NEO has the potential to be used in the pharmaceutical, chemical, and food industries as a natural antioxidant and antimicrobial agent.	Seed EO of nutmeg	The GC/MS and GC-flame ionization detector 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 nontoxic 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	MF	MW (g/mol)	Chemical structure	References
EO					
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

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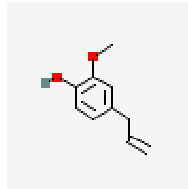
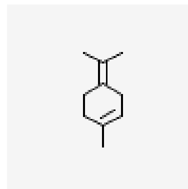
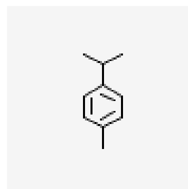
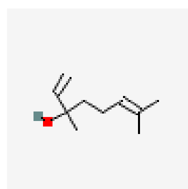
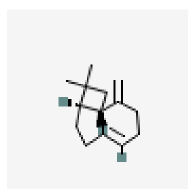
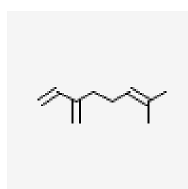
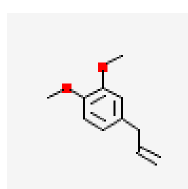
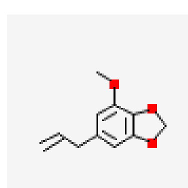
No.	Compound name	MF	MW (g/mol)	Chemical structure	References
5.	Eugenol	$C_{10}H_{12}O_2$	164.20		Abourashed and El-Alfy, 2016; El-Sayed *et al.*, 2022; Nikolic *et al.*, 2021; Plaingam *et al.*, 2017; Wang *et al.*, 2019
6.	Terpinolene	$C_{10}H_{16}$	136.23		El-Sayed *et al.*, 2022; Nikolic *et al.*, 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

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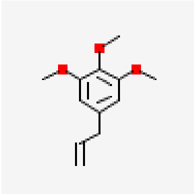
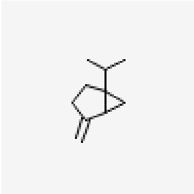
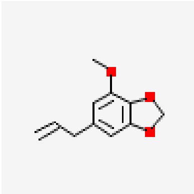
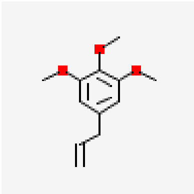
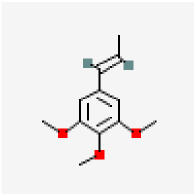
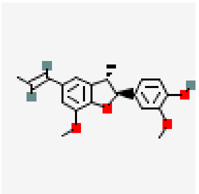
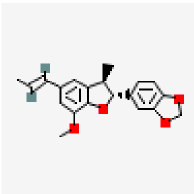
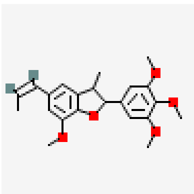
No.	Compound name	MF	MW (g/mol)	Chemical structure	References
13.	Elemicin	$C_{12}H_{16}O_3$	208.25		Abourashed and El-Alfy, 2016; El-Sayed *et al*., 2022; Wang *et al*., 2019; Zhang *et al*., 2016
14.	Sabinene	$C_{10}H_{16}$	136.23		Abourashed and El-Alfy, 2016; El-Sayed *et al*., 2022; Nikolic *et 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

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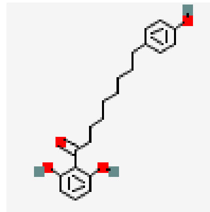
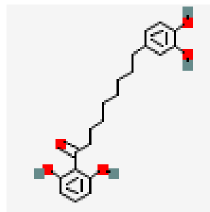
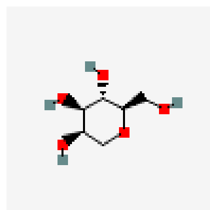
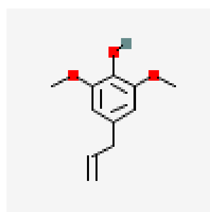
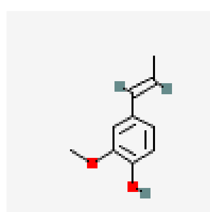
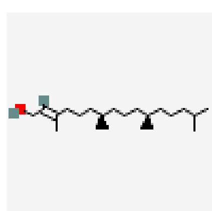
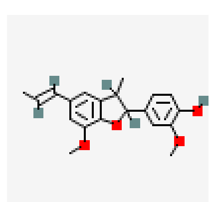
No.	Compound name	MF	MW (g/mol)	Chemical structure	References
7.	Malabaricone B	$C_{21}H_{26}O_4$	342.4		Chiu *et al*., 2016; El-Alfya *et al*., 2019
8.	Malabaricone C	$C_{21}H_{25}O_5$	358.4		Chiu *et al*., 2016; El-Alfya *et al*., 2019
			MeOH leaf extract of nutmeg		
1.	Styracitol	$C_6H_{12}O_5$	164.16		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.	DEH	$C_{20}H_{22}O_4$	326.4		Akinboro *et al*., 2012

Source: NCBI PubChem.

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 used for chronic inflammation and as a painkiller (Zhang *et al*., 2016). EOs 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). Furthermore, limonene in NEO 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 NEO 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 NEO 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 showed 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).

Antimelanogenic activities

Aging can be caused by an increase in the production of melanin pigmentation in response to damage caused by UV radiation (Oh *et al*., 2020). One of the studies concluded that nutmeg hexane extract has antimelanogenic 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). Furthermore, the study stated that combining with antifungal drugs will help many patients suffering from *Aspergillus fumigatus* infection.

Antifungal activities

One of the reasons for researching nutmeg as a plant is that it can reduce *Candida albicans* infection and antimicrobial resistance that humans are concerned about (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% ($p \leq 0.05$) 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 [Dehydrodiisoeugenol (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 treating 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 endoplasmic reticulum stress and 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). Li *et al*. (2019) stated that nutmeg could 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, it 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 effects 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 outcomes of the analysis revealed that ZnO nanoparticles synthesized from nutmeg could be used as potential candidates for biomedical and environmental applications that are environmentally friendly, nontoxicity, 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 NEO in maintaining oxidative stability in sunflower oil, and this proves that NEO 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 sulforhodamine B 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 excess alkaloids (5.1 g/kg), which caused slight toxicity and was nontoxic. Using nutmeg in high doses and for long periods is not recommended (Anaduaka *et al*., 2022). Similarly, other articles demonstrated 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), from January 2001 to December 2011, there were 32 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 was used in a suicide attempt, and another case 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, and 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's use as an alternative for various ailments has resulted in a massively popular effort to compare nutmeg to different extracts. The available nutmeg literature suggests that this medicinal plant is essential for use in biomedical and environmental applications, such as the treatment of neurodegenerative diseases, disorders of the CNS, 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 subsubjects of nutmeg chemical compounds were found to have significant potential as drug discovery agents. Studies have shown that multiple nutmeg extracts have a wide range of pharmacological activities, such as antioxidant, antibacterial, antimelanogenic, antifungal, anticancer, and cytotoxicity activities. 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, more in-depth research studies on this plant are warranted.

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AUTHOR 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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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL APPROVALS

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

DATA AVAILABILITY

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

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