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Pharmacological insights into *Myristica fragrans* (Nutmeg): A systematic review on the therapeutic applications and bioactive compounds

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Abstract

Nutmeg (*Myristica fragrans*) is an aromatic spice derived from the seeds of an evergreen tree. It is treasured for its warm, slightly sweet flavour and its culinary, medicinal, and aromatic applications. This systematic review broadly examines the pharmacological properties of *Myristica fragrans* (nutmeg), focusing on their antimicrobial, anti-inflammatory, antioxidative, aphrodisiac and nootropic effects. Nutmeg's bioactive elements, including myristicin, polyphenols, terpenoids and alkaloids, contribute to its physiological and therapeutic possibilities. Following the PRISMA guidelines, this review makes findings from peer-reviewed studies published between 1972 and 2024, obtained from databases such as PubMed, Scopus, Web of Science and EBSCO, along with supplementary literature from Google Scholar. The analysis integrates *in vitro* and *in vivo* studies to estimate nutmeg's effectiveness across manifold health domains, including microbiology, pharmacology, neuroscience and traditional medicine. By consolidating existing evidence, identifying knowledge gaps and assessing procedural consistency, this review aims to provide a significant appraisal of nutmeg's pharmacological profile while informing future clinical applications and research priorities.

Keywords

anti-inflammatory; antimicrobial; antioxidant; aphrodisiac; cognition

Introduction

The scientific revolution in chemistry, led by A. Lavoisier in the late 18th century, introduced new insights into studying essential oils and phytochemicals. Early research focused mainly on turpentine, one of the oldest known essential oils. Over time, the usage of essential oils transformed from medicinal applications to perfumery, food flavouring and aromatics. However, traditional medicine, which relies on medicinal plants, remains vital to universal healthcare. According to the World Health Organization (WHO), around 80% of the worldwide population relies on plant-based remedies for primary healthcare needs. Remarkably, 80% of the 122 plant-derived drugs are still used for their original purposes in traditional medicine because of their safety, affordability, effectiveness and accessibility (1). Aromatic plants have been treasured since ancient times for their potential to preserve food, treat ailments and enhance flavours. Hippocrates, the 'father of medicine,' reinforced the use of fragrances for health benefits. Essential oils, which contribute to the healing properties of aromatic plants, were formally recognized in the 16th century when Paracelsus von Hohenheim coined the term 'essential oil' and emphasized their antimicrobial potential. Although essential oils exhibit antimicrobial properties,

they are not universally effective against all microbes. Traditionally, they have been used to treat urinary tract and genital infections due to their bactericidal properties. Additionally, certain essential oils aid in tissue repair, clear respiratory mucus and relieve gastrointestinal discomfort (2). By the mid-20th century, plant-derived essential oils were chiefly used in perfumery, cosmetics and food seasoning, with negligible importance in pharmaceutical applications. Comprising complex, multi-compound systems primarily consisting of terpenes and other non-terpene elements, essential oils are extracted from aromatic plants using procedures such as water or steam distillation, solvent extraction, pressure expression and supercritical or subcritical fluid techniques (3)

One such aromatic plant, *Myristica fragrans* (nutmeg), has been extensively used in traditional medicine for culinary and fumigation purposes due to its strong aroma and medicinal properties. Nutmeg possesses varying cultural significance, mainly in rituals and ceremonies, reflecting its versatility. It has been merged into traditional remedies for various therapeutic effects, including relief from stomach aches, analgesic properties, aphrodisiac effects and abortifacient potential (4). Because of its pleasant aroma and sweet flavour, nutmeg remains a commonly used spice in many countries (5). Wide-ranging research has been conducted on nutmeg's properties and chemical composition, indicating its benefits in gastronomy, healthcare and pharmaceuticals (6). However, despite its therapeutic potential, *M. fragrans* has often been ignored and misunderstood due to its toxic effects, with doses as low as 5 g being harmful to human beings (7). While nutmeg is valuable for drug development, its mechanism of action remains vague. The pharmacokinetic properties of *M. fragrans* stem from active metabolites such as myristicin, safrole and elemicin (8, 9) and these compounds undergo metabolic processes such as hydroxylation, demethylation and amination of the allyl group (10). According to Nagano (2009), nutmeg is a "well-rounded little nut" that improves food flavour, raises mood, enhances romantic experiences and induce vivid dreams. Once its full potential is fully identified, nutmeg can become a valuable and versatile asset in culinary and medicinal applications (11). This study aims to compile and synthesize scattered information on the pharmacological effects of *M. fragrans* to provide an in-depth understanding of its potential. This review covers taxonomic descriptions, traditional applications, bioactive compounds, chemical composition and therapeutic properties of *M. fragrans.*

Materials and Methods

A thorough search was conducted across a range of databases, precisely with a focus on accuracy and completeness. This meticulous keyword search was intended to identify relevant articles related to the active compounds and the pharmacological properties of *M. fragrans.*

Inclusion criteria : A systematic review of the pharmacological profile of *M. fragrans* was conducted, covering the period from 1972 to 2024 across multiple databases, including PubMed, Scopus, Web of Science, EBSCO and additional sources such as Google Scholar. From the 192 articles initially identified, 35 met the inclusion criteria, which focused on the bioactive elements and pharmacological and therapeutic properties of nutmeg. Relevant information on the specific topic was also incorporated from other reliable sources. For this review, only studies published in English were considered.

Exclusion criteria : The study excluded data from unreliable sources and discarded abstracts and full texts that did not exactly address the relevant properties of *M. fragrans.* Studies were also excluded if the tested extracts did not conspicuously feature nutmeg and its significant components. Moreover, articles such as letters, books and commentaries were not considered. To confirm the uniqueness of the information, duplicate papers were identified and removed through a combination of manual checks and software-assisted screening.

Search Strategy : For the systematic review, research papers were selected using the PRISMA guidelines, as illustrated in Fig. 1. Inclusion and exclusion criteria were applied to identify the most suitable papers. Various inquiries aligned with the therapeutic properties of nutmeg were collected from different databases using specific keywords.

Results and Discussion

These reviewed studies explore the active compounds, pharmacological and therapeutic properties and traditional uses of nutmeg seeds in treating several chronic diseases and ailments. Furthermore, they highlight its anti-inflammatory, antibacterial, antioxidant, aphrodisiac and memory-enhancing effects, as well as its appraisal in clinical trials. The data gathered from the selected articles are systematically analysed and emphasized.

History and Significance of M. fragrans

Myristica fragrans Houtt. (Magnoliales : Myristicaceae), commonly referred to as the nutmeg tree, is an evergreen spice tree originating from the Moluccas Islands of Indonesia but widely found across tropical Asia, including India, Singapore, Malaysia and Thailand (12). The aromatic evergreen tree *M. fragrans* is renowned for being a significant commercial source of mace (aril) and nutmeg (seed), both widely utilized in folk medicine as therapeutic agents to address diverse ailments. Moreover, different parts of *M. fragrans* have traditional applications in culinary practices. The fruit of *M. fragrans* comprises two essential parts: the shelled seed (nutmeg) and the red aril (mace) enveloping the seed. Because of its distinctive aroma and slightly sweet and warm flavour, both components are used as spices or flavouring agents (13). The nutmeg tree and its fruit, seed and aril are shown in Fig 2 and 3.

Active Compounds of M. fragrans

Research reveals that *M. fragrans* comprises a diverse range of phytochemicals, including lignans, neolignans, diphenyl alkanes, phenylpropanoids and terpenoids, with macelignan, meso-dihydroguaiaretic acid, myristicin and malabaricone C being largely powerful (14). Nutmeg comprises volatile and non-volatile elements that contribute to its pharmaceutical effects.

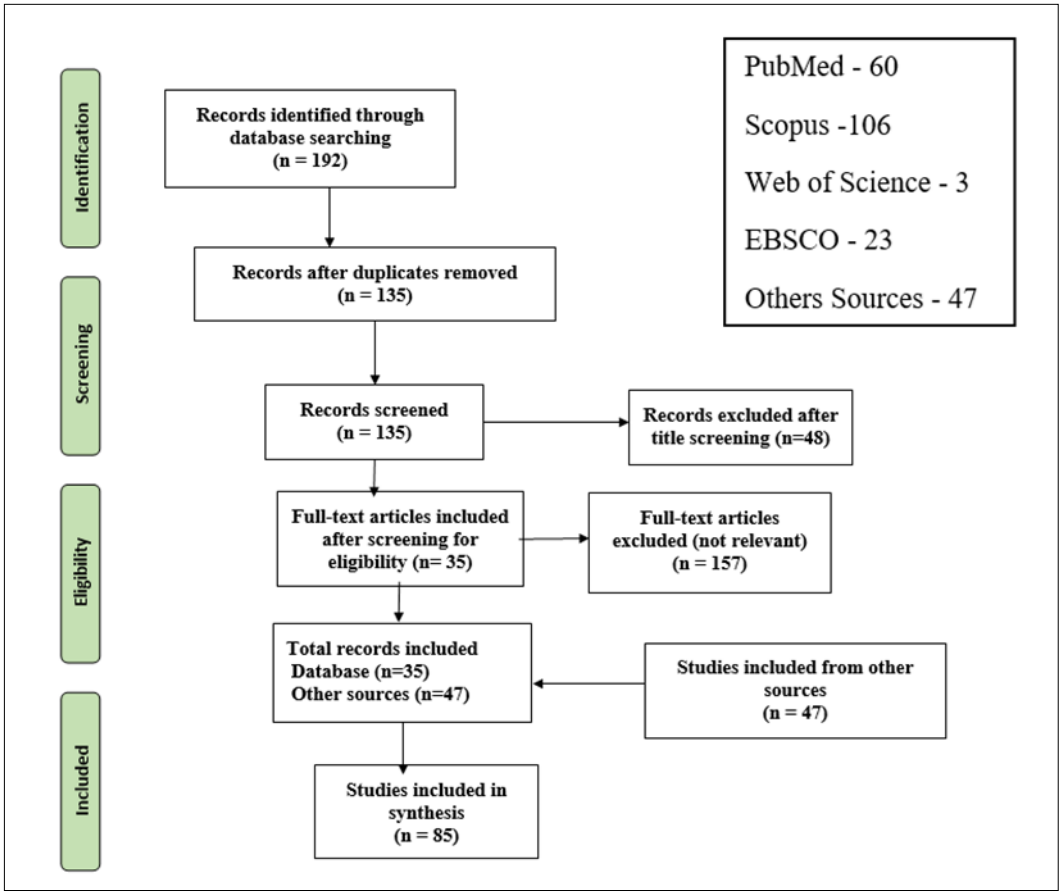

Fig. 1. PRISMA flowchart to find best suitable papers for the systematic review.

Fig. 2. *Myristica fragrans* (Nutmeg).

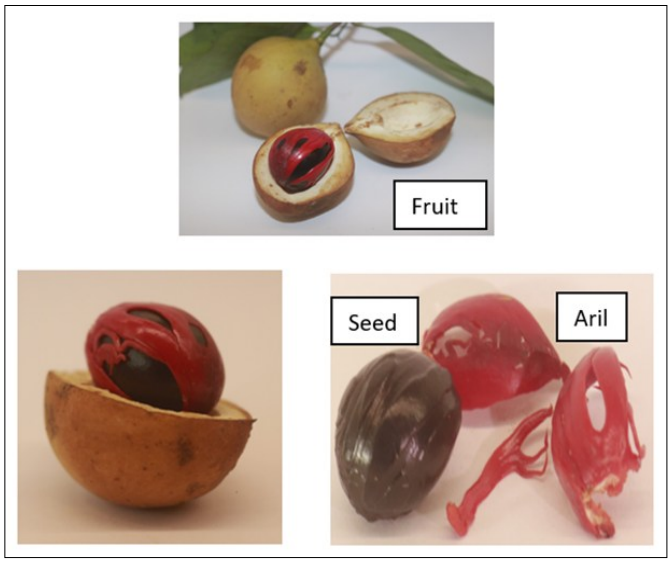

Fig. 3. Nutmeg fruit, seed and aril.

Volatile Phytochemicals of M. fragrans

Plant-derived essential oils are produced in specific glands and secretory organs of flowers, fruits, seeds, leaves, bark, bulbs and rhizomes. Essential oil analysis through SPE-C18 and GC/MS indicated it comprises 6.85% w/w, primarily containing sabinene (21.38 %), 4-terpineol (13.92 %) and myristicin (13.57 %). Nutmeg seeds possess chemicals like allyl benzene and propyl benzene derivatives, including myristicin, safrole and eugenol, which enhance their quality and potency (15). The bioactive compounds of nutmeg are provided in Table 1.

These secondary metabolites help plants to protect them from microbes, pests and diseases. It also helps the plants to reduce stress and to attract pollinators for reproduction and survival (16). Certain constituents such as sabinene, terpinene-4-ol, safrole, pinene, phellandrene, terpinene, terpinolene and thujene contribute to nutmeg's inhibitory effect on the linoleic acid system. This reducing power is possibly due to its hydrogen-donating ability (17). The phenolic groups present in nutmeg contribute to its antioxidant activity (18). Compounds like terpene-4-ol, methyl eugenol, trans-isoeugenol and trans-methyl eugenol in nutmeg essential oil and ethanol oleoresin are the main contributors to this effect. The volatile oil components display stronger antioxidant activity than oleoresins due to

Table 1. Bioactive compounds of nutmeg

Compounds	Percentage (%)	Compounds	Percentage (%)	Compounds	Percentage (%)	Compounds	Percentage (%)
α-Thujene	0.78	α-Terpineol	3.11	Trans-Sabinene Hydrate	0.03	Metoxy Eugenol	0.10
α-Pinene	10.23	Citronellol	0.77	Terpinolene	1.62	β-Asaron	0.03
Camphene	0.16	Linalyl Acetate	0.06	Linalool	0.75	Myristic Acid	0.11
Sabinene	21.38	Bornyl Acetate	0.24	Fenchyl Alcohol	0.05	Ethyl Myristate	0.04
α-Myrcene	2.38	Safrole	4.28	Cis-Sabinene Hydrate	0.06	Palmitic Acid	0.03
α-Terpinene	2.72	Methyl Eugenol	0.77	4-Terpineol	13.92	Ethyl Palmitate	0.07
Limonene	5.57	Isoeugenol	1.74	γ-Terpinene	3.98	Elemicin	1.42
β-Ocimene	0.03	Myristicin	13.57	-	-	-	-

their high phenolic content. Aromatic compounds with electron-donating groups, such as terpene-4-ol and eugenol, further heighten this activity (19). The coactive interaction of several elements amplifies the antioxidant properties of essential oils and oleoresins (20). Methyl eugenol, eugenol, trans-isoeugenol, trans-methyl eugenol and anisole (p-pentyl) in mace extract also contribute to the antioxidant properties of *M. fragrans*. Nutmeg contains 293 mg GAE/g of phenolic content, which significantly augments its antioxidant properties (21). Eugenol establishes notable antioxidant potential, inhibiting 96.7% of linoleic acid peroxidation at 15 µg/mL, beating standard antioxidants such as butylated hydroxyanisole, butylated hydroxytoluene, α-tocopherol and Trolox (22). According to the International Organization for Standardization (ISO), essential oils are plant-derived substances extracted without alternating their chemical structure, containing fragrant and odourless compounds stored in plant cell droplets (23).

Non-volatile phytochemicals of M. fragrans

In addition to the essential oil constituents, *M. fragrans* contains abundant non-volatile phytochemicals that contribute to its pharmacological properties. These compounds include lignans, neolignans, diphenyl alkanes, phenylpropanoids and terpenoids (24). Among these phytochemicals, macelignan and meso-dihydroguaiaretic acid are notable due to their potent biological activities, including anti-inflammatory, antimicrobial and antioxidant effects and the high phenolic content of *M. fragrans*, quantified at 293 mg GAE/g, emphasizes the plant's significant antioxidant capacity (25). Moreover, phenolic derivatives like malabaricone C and myristicin show strong neuroprotective and chemopreventive effects (26). Myristicin and eugenol play vital roles in free radical scavenging and lipid peroxidation inhibition, indicating the superior action of nutmeg compared to synthetic antioxidants (27). These non-volatile elements synergize with essential oils to enhance the therapeutic efficacy of *M. fragrans*, emphasizing its potential for pharmacological applications (28).

Pharmacological Evaluation of *Myristica fragrans*

Traditional Applications of Myristica fragrans **:** Seventeenth-century physicians supposed that several parts of *M. fragrans* could cure ailments such as the bloody flux and sweating sickness, later recognized as the Black Plague. Nutmeg is also recognized for its mild sedative effects, making it a general remedy for insomnia and anxiety. Because of all these effects, nutmeg has been incorporated into various preparations, including teas, wrappings and oils, to treat conditions ranging from cold symptoms to muscle pain (29). Traditionally, nutmeg has been extensively used for its therapeutic properties such as stimulating, antidiarrheal, carminative, stomachic, tonic and aphrodisiac effects. It has been widely used to relieve muscle and joint pain, headaches, nausea, diarrhoea, fever, stomach cramps and anxiety (30). The mace derived from *M. fragrans* has been utilized for centuries in Thai traditional medicine to alleviate stomach discomfort, peptic ulcers and nausea as a chief component in medicines targeting gastrointestinal issues. Both aqueous and ethanolic extracts of mace are beneficial in various traditional interventions. Furthermore, nutmeg is a main component of Ayurvedic formulations, such as pasupasi, weighing its significance in traditional Indian medicine (14).

In traditional Southeast Asian medicine, nutmeg has been valued for its antimicrobial properties. The oil extracted from nutmeg seeds was commonly used in topical ointments for treating infections, cuts and wounds. Additionally, nutmeg has been employed in treating respiratory issues such as coughs and asthma due to its expectorant properties. Its warming effects have also made it a popular component in traditional remedies for arthritis and rheumatic pain (24). Nutmeg is a rich source of bioactive compounds, particularly lignans such as macelignan, which exhibit numerous health benefits, including antibacterial, anti-inflammatory, anticancer, antidiabetic, liver-protective and brain-protective effects. Lignan-rich diets have also been linked to a reduced risk of obesity and cancer (31). The medicinal properties of nutmeg are ascribed to its varied constituents, including fixed oils (trimyristin and myristic acid) and volatile oils (terpenes, alkenyl benzene derivatives and 8 -11% myristicin). Phytochemical studies disclose that its pharmacological properties stem from phenylpropanoids, lignans, diphenyl alkanes, neolignans and terpenoids, which contribute to nutmeg's anti-inflammatory, antioxidant, antibacterial, antidiabetic and anticancer properties (32). Furthermore, nutmeg enhances cognitive function by inhibiting acetylcholinesterase activity, which supports memory and learning (33).

Insecticidal and Repellent Activity of M. fragrans : Beyond its medicinal applications, nutmeg also displays insecticidal and repellent properties, specifically against *Aedes aegypti* mosquitoes. The efficacy of nutmeg seed oil in killing mosquitoes is credited to the low volatility of its chemical components (34, 35). Furthermore, ethanolic extracts of nutmeg show strong repellent effectiveness against various insects, such as carpenter ants, mango mealybugs and red flour beetles, within just four hours of exposure. These findings specify nutmeg's potential as a natural, plant-based insect repellent with practical applications in pest control (36).

Anti-inflammatory Properties of M. fragrans : Inflammation is the immune system's response to foreign or internal non-infectious substances. Managing inflammatory diseases is of paramount significance and requires extra attention. Chronic inflammation and the resultant diseases are documented by the WHO as a significant global health issue. Considering these factors and the significance of discovering natural therapies while minimizing the adverse effects of anti-inflammatory drugs, various types of research have been undertaken to assess the efficacy of different nutmeg extracts in alleviating inflammatory responses (37).

As inflammation is a key factor in chronic diseases like cardiovascular disease, cancer and diabetes, the link between inflammation and cardiac health has driven research on natural anti-inflammatory agents. Eugenol, a phenolic compound in nutmeg, clove, cinnamon and bay leaf oils, displays strong anti-inflammatory properties by scavenging free radicals and inhibiting inflammatory mediators like prostaglandins, cytokines and chemokines. Various studies specify the strong anti-inflammatory potential of eugenol in arthritis, colitis and lung injury. The therapeutic properties of natural products stem from varied bioactive compounds, such as alkaloids, terpenoids, flavonoids and essential oils. The aromatic hydrocarbon terpenes, in particular, undergo modifications like oxidation and cyclization, enhancing their biological activity (38). Nutmeg is a commonly used spice in Ayurveda drug preparation because of its potential health benefits, including anti-inflammatory and antimicrobial effects (39, 40). Studies on nutmeg oil's effects in animals explain the anti-inflammatory properties in acute inflammation, analgesic effects along with antipyretic, antithrombotic and anti-diarrheal properties, although prolonged use may lead to gastric ulcers, indicating parallels to non-steroidal anti-inflammatory drugs (41).

Anti-bacterial Properties of M. fragrans : *M. fragrans* exhibits potent antibacterial properties, chiefly ascribed to its bioactive compounds. Nutmeg oil, rich in sabinene (39.12%) and alpha-pinene (11.96%), has confirmed significant antibacterial activity against pathogens like E. coli and Streptococcus aureus. The constituents of nutmeg disrupt bacterial cell membranes, reduce ATP concentrations and cause nucleic acid loss, thereby hindering DNA synthesis. These findings suggest that nutmeg possesses a natural antibacterial effect and is also useful in meat storage and preservation (42).

Another main antibacterial compound in *M. fragrans* is dehydrodiisoeugenol (DHIE), a neolignan first recognized in nutmeg bark in 1973. DHIE, also known as licarin A, shows a range of biological activities, including antibacterial, antiprotozoal, anticancer, antioxidant and anti-inflammatory effects. Nutmeg also holds neuroprotective properties by preserving antioxidant enzyme activity and scavenging reactive oxygen species, reducing oxidative stress-induced conditions like cancer, inflammation and neurodegenerative diseases. In addition, DHIE displays antimicrobial activity against specific Mycobacterium species and has potential benefits in treating neurological disorders due to its ability to cross the blood-brain barrier. It also possesses anti-diabetic and anti-obesity properties (43). Macelignan, a lignan derived from the seeds of nutmeg with antibacterial and antifungal properties effectively inhibits foodborne pathogens like *Bacillus cereus* and *Streptococcus mutans,* an oral carcinogenic bacterium associated with dental caries. Additionally, nutmeg's essential oils, fixed oils and other phytochemicals such as dihydroguaiaretic acid, elemicin, myristic acid and myristicin have beneficial effects on its medicinal and therapeutic applications (44).

Antioxidant Properties of M. fragrans : In the current era of novel interventions, there has been a surge in interest among health, food science researchers and medical professionals regarding antioxidants. Oxidative stress typically arises from the body's inability to neutralize reactive intermediates and free radicals effectively, resulting in systemic symptoms caused by reactive oxygen species (45). Free radicals disrupt the normal redox state of cells, posing harmful effects through the formation of peroxides that damage nucleic acids, proteins and lipids (46). Extracts from *M. fragrans* are reliable sources of antioxidants capable of scavenging free radicals due to the activity of their bioactive components. Myristicin improves the concentration and activity of antioxidant enzymes such as catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase while reducing lipid peroxidation levels. Research examining the nutmeg's essential oil with and without myristicin exposed that myristicin plays a crucial role in its antioxidant and sun-protective properties. Oils devoid of myristicin showed minimal protection, whereas myristicin-containing oils displayed moderate activity and isolated myristicin proved the highest protective and antioxidant potential. Additionally, higher concentrations of monoterpenes, carotenoids, vitamin C, vitamin E and phenolic compounds contribute significantly to the antioxidant activity of *M. fragrans* (47).

Nutmeg mace exhibits anti-*Helicobacter pylori* activity, validated through disc diffusion and agar dilution methods. With the anti-inflammatory properties of inhibiting nitric oxide production in cell lines, ethanolic mace extract possesses a wide range of therapeutic antioxidant benefits, even anticancer effects (48). Furthermore, myristicin impacts in vivo antioxidant activity by enhancing key enzymes and reducing oxidative damage (49). A study on the aqueous extract of *M. fragrans* seeds appraised its phytochemical constituents, anti-nutrients and antioxidant properties, displaying a high ascorbic acid value (100 mg/100 g), free radical scavenging activity (44%) and reducing power (0.6). However, histopathological examinations discovered erratic degrees of organ damage, including spleen lymphoid depletion, testicular germinal epithelial cell degeneration and kidney necrosis at higher doses. This advocates potential toxicity at prolonged high doses (400-500 mg/kg), likely because of metabolic activation of safrole and methyl eugenol in nutmeg (50). Apart from the antioxidant effect, nutmeg also exhibits antidiabetic effects. A 28-day study on 48 male *Wistar* rats proved that nutmeg extract significantly reduced blood glucose levels and increased serum insulin in diabetic rats. It also reduced oxidative stress and enhanced antioxidant activity in pancreatic tissue, signifying its β-cell protective effects (51). Steam-distilled essential oils of *M. fragrans* demonstrated extensive anti-angiogenic and antioxidant

properties (52). However, prolonged oral consumption (7-14 days) of nutmeg can induce liver toxicity, with effects depending on dosage and duration. This toxicity is associated with fluctuations in blood biochemistry and liver histopathology, indicating the susceptibility to liver damage and even cirrhosis of the liver (53).

Aphrodisiac Properties of M. fragrans : Upholding good sexual and reproductive health is key to happy families and strong self-esteem for both men and women. Infertility can sadly strain relationships. It is essential to approach sexual health positively, understanding the many factors that influence human sexual behaviour. Sound sexual health enhances fertility and sexuality is a vital part of being human, encompassing various aspects like gender, orientation, pleasure and reproduction. Human sexuality is shaped by biological, social and cultural factors. Sexual health involves a positive, respectful approach to relationships and ensuring safe, enjoyable experiences without pressure discrimination and violence (54).

Traditional medicine uses natural products to enhance sexual function and physical performance in men. Male impotence, often caused by cardiovascular disorders or diabetes, has been tackled for ages with natural remedies to enhance sexual desire and performance. Androgens, the chief hormone in male reproductive health, affect initiation and intercourse (55). Treatments for erectile dysfunction include psychotherapy, certain drugs and herbal aphrodisiacs. Ayurveda proposes spermatogenic and virility-enhancing remedies, classified into pharmacological (vajikarana) and non-pharmacological (rasayana) categories. In Ayurveda, herbs known as 'Vajikaran' or aphrodisiacs are extensively discussed for their potential to enhance male sexual potency. Aphrodisiacs are herbs with rejuvenating properties to improve sexual dynamics. Many Indian medicinal plants possess aphrodisiac properties, proposing remedies for sexual disorders like erectile dysfunction. By analysing historical accounts, biochemical studies and contemporary research, this review aims to unravel the enigmatic allure of nutmeg as a natural aphrodisiac (56).

An aphrodisiac, derived from the Greek goddess of love, Aphrodite, refers to any substance, whether from plants, animals, or minerals, that stirs sexual instinct, ignites desire and enhances pleasure and performance. Throughout human history, these substances have captivated man's passions (57). Even in the current scenario, man utilizes certain foods like strawberries and raw oysters, chocolate, coffee and honey, which possess aphrodisiac qualities, although scientific evidence supporting these claims is limited or absent. Even though in a recent study in Boston, 52% of men aged 40 to 70 reported some degree of erectile dysfunction (ED). Improved sexual function can contribute to heightened relationship satisfaction and self-esteem among individuals (58). The quest for effective aphrodisiacs has persisted across generations, with researchers expansively studying the roles of dopaminergic, adrenergic and serotonergic agents in human and animal studies to comprehend the neurophysiological processes involved in sexual arousal and exploring these drugs for treating sexual dysfunction (59).

Aphrodisiacs are divided into two major types, such as those that stimulate the senses (sight, touch, smell and sound) and those taken internally (food, drinks and love potions). They can also be categorized based on the mechanism of action, such as enhancing libido (desire and arousal), improving sexual potency (erection strength) and heightening sexual pleasure (60). Aphrodisiacs can induce relaxation of corpus cavernosum smooth muscle tissue in animals, enhance erection quality in humans and animals and augment sexual behaviour and satisfaction in both. Aphrodisiac effects can vary upon consumption or administration. They can exert psychological effects by amplifying sexual desire and pleasure through hallucinogenic or mood-stimulating properties (61). Aphrodisiacs can operate physiologically by augmenting erection through hormonal changes, increased blood flow and relaxation of smooth muscles (62). Synthetic aphrodisiac substances cause many side effects and can potentially interact dangerously with other medications. Furthermore, synthetic products do not fully address issues of libido. Hence, identifying natural substances with aphrodisiac potential that can enhance sexual experiences without adverse effects is beneficial (63).

ED is a significant medical and social concern, affecting a substantial portion of both men and women, characterized by the consistent inability to achieve or maintain an erection for satisfactory sexual activity and affecting particularly those with diabetes mellitus and atherosclerosis. Other contributing factors include hypertension, lipid disorders, diabetes and smoking (60). Endocrine disorders, pelvic trauma, surgeries, radiation therapies, anxiety, depression, stress, neurological conditions, penile disorders, systemic diseases, chronic alcohol consumption, smoking, age-related hormone decline and certain medications are all associated with ED (64).

In Unani medicine, the dried kernel of the broadly ovoid seeds of *M. fragrans* has been renowned for its potential to manage male sexual disorders. *M. fragrans* contains alkaloids and sterols and the nervous stimulating properties are responsible for the increased mating behaviour (65). Forensic toxicologists must cognize the potential toxicities of aphrodisiacs due to apprehensions about their misuse in drug-facilitated sexual assaults. Some common substances in aphrodisiacs, including phosphodiesterase inhibitors, steroid hormones, gamma-hydroxybutyric acid, bufo toad secretions, Spanish fly and horny goat weed, are known for their toxicity and ability to induce severe side effects and intoxication (66).

Traditionally, nutmeg has been cultivated for use as both an aphrodisiac and medicinal drug, with applications ranging from pain reduction to appetite enhancement and nerve stimulation. Despite its well-known historical use as an aphrodisiac, scientific studies on nutmeg are scarce and have only recently been conducted using animals. Nutmeg extract in various animal models displayed increased sexual activity with heightened mounting and intromission frequencies, reduced latency and improved penile reflexes. Nutmeg extract enhances libido and potency through nervous system stimulation, though the precise mechanism remains unclear, potentially involving changes in neurotransmitter levels or cellular actions. Elevated testosterone (an androgen) levels and the complex mix of biochemical compounds found in

nutmeg, such as myristicin, elemicin and safrole, have effects on the central nervous system and improve sexual behaviour. These elements influence neurotransmitter activity and neuroendocrine pathways related to sexual arousal and desire. Myristicin, with serotoninergic and dopaminergic properties, influences mood, motivation and libido. Nutmeg's trace elements and antioxidants contribute to its physiological effects, albeit with varying strengths and absorption rates (67).

Preliminary phytochemical analysis revealed the presence of sterols, phenols, alkaloids and amino acids in nutmeg, which contribute to its libido-enhancing effects. The observed effects of nutmeg on increasing sexual behaviour are attributed to its nerve-stimulating properties. Recently, scientists have researched the aphrodisiac properties of an ethanolic extract of nutmeg, on sexual activity in male rats and receptive female rats. Male rats given various doses of the extract for seven days showed improved sexual activity, particularly at a dose of 500 mg/kg, with increased mounting frequency, reduced latency and heightened penile reflexes, without adverse effects. The study suggests nutmeg's aphrodisiac properties are due to its nervous system-stimulating effects, increasing blood circulation and nerve activity (68). Certain research studied the effects of various plant extracts on sexual behaviour and established that the methanolic extract of nutmeg does not inhibit ROCK-II and the successive aqueous extract showed minimal inhibition. This suggests that nutmeg's aphrodisiac properties are not associated with ROCK-II inhibition. ROCK-II stands for Rho-Associated Coiled-Coil Kinase II, which is an enzyme involved in regulating various cellular processes, including smooth muscle contraction. In the context of sexual function, ROCK-II inhibition can affect penile smooth muscle relaxation, possibly swaying erectile function (69). A study administering varying doses (100, 250 and 500 mg/kg) of a 50% ethanolic nutmeg extract orally to male rats showed significant enhancement in sexual activity at 500 mg/kg. This is because of the increased mounting frequency, intromission frequency and decreased intromission latency, mounting latency and post-ejaculatory interval. No adverse effects or acute toxicity were exhibited by the extract. On the contrary, the effect of the extract elevated mounting frequency and penile reflexes under penile anaesthesia (70). This enhanced sexual functioning is attributed to compounds like myristin, myristic acid, pinene, sabinene, camphene, myristicin, elemicin, eugenol and safrole, known for their analgesic, anti-inflammatory and aphrodisiac effects. Additionally, nutmeg's nervous-stimulating action possibly contributes to its aphrodisiac effects (71).

A penile erection involves a balance between factors that contract and relax the smooth muscles in the corpus cavernosa, influenced by both the central and peripheral nervous systems, affecting blood flow to the genitals. The combined action of neurochemicals like norepinephrine, dopamine, serotonin, acetylcholine and histamine enhances sexual arousal. Aphrodisiacs can work through various mechanisms, including nitric oxide (NO) and androgen pathways. NO, a neurotransmitter, relaxes penile vasculature and smooth muscles and increases blood flow to the penis, causing engorgement and erection. Additionally, the cyclic adenosine monophosphate (cAMP) pathway, involving enzymes and proteins like prostaglandin and protein kinase G, also contributes to penile erections by relaxing smooth muscles and increasing blood flow in the cavernous tissues (72). Okukpe et al. (2012) investigated the impact of *M. fragrans* extract on sexual function in fifteen West African Dwarf Bucks (WAD) by administering subcutaneous doses of 0.01, 0.02 and 0.03 ml/kg body weight of the extract, with a control group receiving normal saline and a standard group receiving sildenafil citrate solution. Doses of 0.01 to 0.02 ml/kg of the extract increased sexual drive in the bucks, with signs of active sexual activity and mounting observed from the second day onwards. Nutmeg's aphrodisiac activity is linked with its nervous stimulating property, with phytochemical analysis revealing sterols, phenols, alkaloids and amino acids contributing to its sexual arousal effect. Serum testosterone levels also increased with nutmeg extract administration, supporting its potential as an aphrodisiac (73). Thus, these studies disclose the aphrodisiac functioning of *M. fragrans.*

Nootropic / Memory-Boosting Effect of M. fragrans : Many natural and herbal products are used for enhancing learning and memory, as well as to treat various cognitive illnesses, including memory loss. Memory loss can result from aging or various neurological disorders, *viz* Alzheimer's disease. Herbal medications with cognition-enhancing properties, known as nootropics, can help improve memory. Such herbal interventions strengthen memory, augment blood circulation and elevate acetylcholine levels in the brain (74). Nutmeg possesses significant central nervous system effects. Studies on nutmeg extracts have shown that their behavioural effects vary based on extract type and route of administration. Methanolic (ME), dichloromethane (DE) and hexane (HE) extracts evaluated via oral and intraperitoneal administration in mice revealed varied effects, with comparisons made to Delta 9-tetrahydrocannabinol, amphetamine and morphine (75).

The complexity of memory involves complex neural pathways and neurotransmitter systems within the brain. The study conducted by Milind et al, 2004, aimed to investigate the impact of *M. fragrans* seeds on learning and memory in mice. The n-hexane extract of *M. fragrans* was orally administered in three doses (5, 10 and 20 mg/kg p.o.) for three consecutive days to various groups of both young and aged mice. Learning and memory were evaluated by behavioural studies using elevated plus-maze and passive-avoidance apparatus. Additionally, the researcher also examined the effects of *M. fragrans* extract on scopolamine and diazepam-induced impairments in learning and memory. The results established that the lowest dose of *M. fragrans* extract (5 mg/kg p.o.) significantly enhanced learning and memory in both young and aged mice for three days. Moreover, the nutmeg extract reversed the impairments in learning and memory induced by scopolamine and diazepam in young mice. Overall, nutmeg extract improved the learning and retention capacities of both young and aged mice. It is explained that nutmeg's antioxidant, anti-inflammatory and procholinergic activity contribute to this observed effect (40).

Nutmeg offers cognitive benefits related to memory enhancement, antioxidant effects and anticonvulsant activity, because of bioactive compounds like eugenol, isoelemicin, isoeugenol, methoxyeugenol, myristic acid, myristicin,

saponins, lignin. Macelignan stimulates brain function by crossing the blood-brain barrier. In rats with Parkinson's disease, nutmeg seed extract significantly enhanced cognition, likely due to its neuroprotective qualities and inhibition of cholinesterase, an enzyme linked to cognitive decline (76). Macelignan shows anti-cholinesterase activity, suggesting its potential for elevating acetylcholine levels in the central nervous system, which is relevant to cognitive functioning. This specific bioactive compound derived from mace works as a therapeutic agent and is popular for its antibacterial properties and potential to address cognitive decline associated with Alzheimer's disease. Lignans also help in stress reduction and offer protection against various other neurodegenerative diseases (14).

Certain researchers evaluated nutmeg's neuroprotective properties against scopolamine-induced oxidative damage, inflammation and apoptosis in male rat cortical tissue. Pre-treatment with nutmeg methanolic extract for seven days lessened scopolamine-induced elevation of oxidative stress. Nutmeg's antioxidant, anti-inflammatory and antiapoptotic properties protect the brain's cortical tissues. Reducing oxidative stress is crucial for neuronal function and cognition and nutmeg's active compounds modulate apoptotic proteins, guarding against neuronal apoptosis, suggesting its potential as a natural neuroprotective agent, particularly in neurodegenerative diseases like Alzheimer's disease (77). In a study investigating the efficacy of *M. fragrans* extract on learning and memory enhancement, *Wistar* albino rats were administered 2mg/kg of the extract daily for 30 days. Neuromorphological analysis revealed that synaptic plasticity involves alterations in intrinsic excitability affecting action potential firing. The study demonstrated an increase in dendritic arborization of pyramidal neurons and thereby enhanced learning as well as memory. Dendrites are the chief determinants of integration and information processing of neurons and hence dendrites play a vital role in the functional properties of neuronal circuits. The functional architecture of the different parts of the brain is dynamic and can change in response to various experimental manipulations. After the formation of long-lasting functional enhancement of synapses in the hippocampal area, new spines appear on post-synaptic dendrites, whereas in control regions on the same dendrites, no significant spine growth occurs and thus the dendritic structural reorganization is the key feature in learning and memory. Nutmeg extract is also shown to enhance learning and memory by decreasing the activity of acetylcholine hydrolyzing enzyme, AChE. Plant-derived cholinesterases may provide sustained, long-term inhibition of AChE in the brain. The active principles of nutmeg cause prolonged increases in acetylcholine levels without significant adverse effects at therapeutic doses. The extract of *M. fragrans* improved learning and memory capacities in both young and aged mice, potentially due to its antioxidant, anti-inflammatory, or procholinergic properties. The impact of nutmeg on the central nervous system (CNS) is diverse, demonstrating both anticholinergic and CNS excitatory effects. The comparative brain cholinesterase inhibiting activity of *M. fragrans* within central cholinergic pathways significantly influences learning and memory processes (78). Phytochemical-based antioxidants are neuroprotective by reducing or reversing cellular damage and slowing down the progression of neuronal cell loss. Long-term memory storage mainly occurs in dendritic arbors of the cholinoceptive cells of the cerebral cortex, hippocampus and amygdala (79). The dendrites of cholinoceptive cells, which are prominently involved in memory, undergo restructuring during memory formation (80).

All these findings, along with previous studies and the current investigation, suggest that *M. fragrans* extract could serve as a promising source of natural anticholinesterase compounds, offering an herbal alternative for Alzheimer's disease treatment and cognitive enhancement. All the prominent properties of nutmeg are presented in Fig. 5.

Fig. 4. *Myristica malabarica* (False Nutmeg).

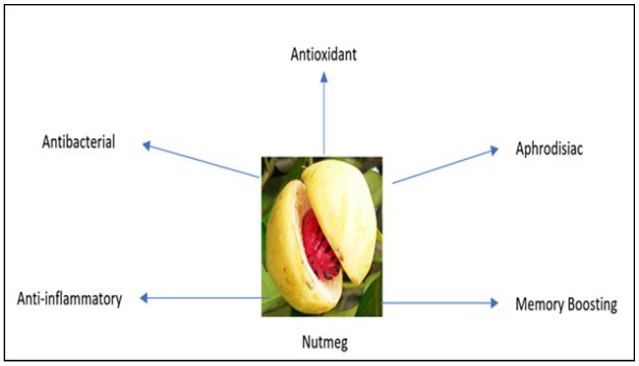

Fig. 5. Major therapeutic effects of Nutmeg.

Conclusion

Understanding the pharmacological effects of *M. fragrans* (nutmeg) is essential for its therapeutic potential in treating varied human ailments. Preclinical revisions using an effective dose of 2 mg/kg in *Wistar* albino rats recommend its cognitive-enhancing, anti-inflammatory, antimicrobial and antioxidative properties, with promising applications in neurodegenerative diseases, metabolic disorders and sexual dysfunction. However, standardized human-equivalent dosages, long-term safety and efficacy remain unclear. Clinical trials are necessary to confirm its benefits, address toxicity concerns and refine dosage through pharmacokinetic and pharmacodynamic studies. Establishing a safe standard dosage for human beings is essential and innovative pharmaceutical formulations, such as nanoemulsions, may improve the bioavailability. Interdisciplinary collaboration among researchers, clinicians and regulatory bodies is essential to integrate nutmeg into evidence-based remedies while ensuring safety and regulatory approval from agencies like the Food and Drug Administration (FDA).

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Authors' contributions

As I am the first and single author, I (DNP) carried out all aspects of the research, including the literature review, data analysis and manuscript drafting. I also conceived of the study, designed the work and performed the systematic review analysis.

Compliance with ethical standards

Conflict of interest: Do not have any conflict of interest.

Ethical issues: None

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