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MORALITY BEFORE KNOWLEDGE

Potential of bioactive compounds in Indonesian endemic Nutmeg (*Myristica fragrans* and *Myristica argentea*) and their applications in health: An overview

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ABSTRACT

Background: Nutmeg (*Myristica fragrans* and *Myristica argentea*), an Indonesian endemic plant from the Maluku Islands, has long been used in traditional medicine to treat digestive disorders, joint pain, and infections. While *Myristica fragrans* has been widely studied, research on *M. argentea* remains limited, despite both species containing bioactive compounds such as phenylpropanoids (e.g., myristicin), terpenoids, and flavonoids, which exhibit antioxidant, antimicrobial, and anti-inflammatory properties. Key challenges include optimizing eco-friendly extraction methods and exploring untapped therapeutic potential. This review consolidates the latest scientific evidence on nutmeg's bioactive compounds and their health benefits, including anticancer, antidiabetic, and neuroprotective effects, as well as their prospects for sustainable therapeutic development. **Methods**: The study was conducted by searching PubMed, Scopus, and Google Scholar using keywords related to nutmeg's bioactive compounds and medicinal properties. **Findings:** Findings reveal that both *M. fragrans* and *M. argentea* possess significant antidiabetic, antioxidant, anticancer, anti-inflammatory, and neuroprotective activities. Extraction methods range from conventional techniques like hydrodistillation and organic solvents to modern approaches such as Supercritical Fluid Extraction (SFE) and Ultrasound-Assisted Extraction (UAE). Additionally, nutmeg shows promise as an antimicrobial and cardioprotective agent, though its psychoactive compounds warrant caution. **Conclusion**: Potential applications include nutraceuticals, cosmetics, and pharmaceuticals, with waste utilization enhancing sustainability. **Novelty/Originality of this article:** The novelty of this review lies in its comprehensive comparison of both nutmeg species, emphasis on sustainable extraction techniques, and exploration of understudied therapeutic potentials, offering new insights for future research and industrial applications.

KEYWORDS: bioactive compounds; sustainable extraction; neuroprotection; myristica; pharmacological activities.

1. Introduction

Myristica fragrans, or nutmeg, is an endemic plant native to the Maluku Islands, Indonesia, long recognized as a high-value spice. This species thrives in humid tropical climates and is characterized morphologically by glossy dark green leaves, bell-shaped yellow flowers, and seed-bearing fruits that produce dark brown seeds (nutmeg) and vibrant red arils (mace). Beyond Indonesia, *M. fragrans* is now widely cultivated across Asia,

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Africa, and the Americas as a key export commodity (Dogara et al., 2025). Meanwhile, *Myristica argentea*, identified as an oval-shaped nutmeg variant through DNA barcoding and morphological analysis, shares similar growth conditions and botanical traits with *M. fragrans*, though scientific documentation on this species remains limited (Khamnuan et al., 2023). Traditionally, both species have been used in local medicine to treat digestive disorders, joint pain, and infections, underscoring their significant pharmacological potential.

Bioactive compounds from plants, such as polyphenols, saponins, and flavonoids, play a critical role in health therapy development due to their diverse biological activities. While *Myristica fragrans* has been partially investigated, research on *Myristica argentea* remains scarce, creating a knowledge gap that hinders the optimal utilization of both species. Preliminary studies reveal that nutmeg contains a variety of phytochemicals, including alkaloids, terpenoids, and flavonoids, which contribute to its antioxidant, antimicrobial, and anti-inflammatory properties (M et al., 2024). Unfortunately, this potential remains underexplored compared to more extensively studied medicinal plants like *Curcuma longa* or *Zingiber officinale*.

Numerous studies confirm that *Myristica fragrans* extracts exhibit promising pharmacological activities, including anticancer, antimalarial, hepatoprotective, and antiparasitic effects (Nomer, 2024). However, a major challenge lies in developing efficient and environmentally friendly extraction methods for these bioactive compounds. Green extraction techniques, such as water-based solvents or ultrasonication, are being advanced to minimize environmental impact while maximizing target compound yields (Putra et al., 2024). These approaches not only align with sustainability principles but also open avenues for industrializing nutmeg extracts in pharmaceutical and nutraceutical applications.

Given this background, this systematic review aims to consolidate the latest scientific evidence on the bioactive compounds in *Myristica fragrans* and *Myristica argentea* and their applications in human health. By analyzing findings from in vitro, in vivo, and clinical studies, this article is expected to provide a foundation for further research and the sustainable development of nutmeg-based therapeutics.

2. Methods

The researcher conducted a systematic review by collecting scientific articles from indexed databases such as PubMed, Scopus, and Google Scholar to ensure comprehensive literature coverage. The search was performed using a combination of relevant keywords, including *"Myristica fragrans and Myristica argentea bioactive compounds," "Myristica fragrans and Myristica argentea medicinal properties," "Myristica fragrans and Myristica argentea anti-inflammatory,"* as well as variations such as *"nutmeg phytochemicals"* and *"Myristica health benefits."* The search strategy was designed to include relevant *in vitro, in vivo,* and clinical studies aligned with the research focus. Additionally, the researcher examined references from selected articles (backward reference tracking) to identify important publications that might have been missed in the initial search.

Following the literature search, studies were screened based on predefined criteria. Only studies meeting the following conditions were included: (a) published within the last five years (2020–2025) to ensure data relevance, (b) focused on identifying bioactive compounds (e.g., flavonoids, terpenoids, alkaloids) from *Myristica fragrans* or *Myristica argentea*, (c) provided empirical evidence on pharmacological effects (e.g., antioxidant, antimicrobial, anti-inflammatory, or anticancer properties), and (d) were available in full text. Meanwhile, studies were excluded if they (a) did not specifically discuss bioactive compounds or health benefits, (b) were conference abstracts without complete data, (c) were review studies without primary data analysis, or (d) were articles that did not undergo peer review.

After applying the selection criteria, the extracted data were narratively analyzed to identify patterns in findings, consistency across studies, and existing knowledge gaps.

Furthermore, the researcher performed a qualitative analysis to assess the methodological quality of each study, ensuring a rigorous evaluation of the evidence.

3. Results and Discussion

3.1 Bioactive compounds

3.1.1 Compound classification

Phytochemical screening revealed the complexity of bioactive compounds in *Myristica fragrans*, with significant compositional differences between its leaves and seeds. Leaf extracts contained nine distinct compounds, while seeds exhibited higher diversity with 23 identified compounds, including lipids, phenylpropanoids, lignans, terpenoids, and quinones (Saputri et al., 2024). These compounds not only underlie the pharmacological activities of nutmeg but also demonstrate specific and complementary mechanisms of action. For instance, myristicin was found to enhance glucose uptake in muscle cells via AMPK phosphorylation-mediated GLUT4 translocation within just 15 minutes, whereas licarin B exhibited a similar effect but with a slower onset (240 minutes) (Yoshioka et al., 2022). These findings suggest that variations in response time could be leveraged to design combination therapies with synergistic effects.

In addition to antidiabetic properties, nutmeg's bioactive compounds also demonstrated potential in oxidative stress modulation and tissue repair. Research by (Deepthi et al., 2023) confirmed that these protective mechanisms involve reactive oxygen species (ROS) regulation and the upregulation of growth factors crucial for the healing process. Furthermore, methanolic and macerated extracts of nutmeg exhibited inhibitory activity against α-amylase and α-glucosidase enzymes, highlighting its potential as a diabetes management agent (Blessy et al., 2024). The combination of antioxidant (macelignan), antimicrobial (carvacrol), and anti-inflammatory (β-caryophyllene) properties reinforces nutmeg's role as a natural polypharmacy source (Gupta, 2020). However, the presence of psychoactive compounds such as myristicin and safrole warrants special attention regarding dosage and long-term safety.

Table 1. Bioactive compounds in *Myristica fragrans* and *Myristica argentea*

Compound Group	Example Compound	Plant Part	Biological Activity	References
Phenylpropanoids	Myristicin	Seeds	Psychoactive, neuroprotective	Barman et al. (2023)
	Elemicin	Seeds	Hallucinogenic effects	Barman et al. (2023)
Terpenoids	β-Phellandrene	Essential Oil	Anti-inflammatory	Maryati (2023)
	Safrole	Essential Oil	Psychoactive	Maryati (2023)
Flavonoids & Polyphenols	Not specifically mentioned	Seeds, Fruit Pulp	Antioxidant, anti-inflammatory	Solikah (2024)
Saponins	Not specifically mentioned	Seeds	Diversified biological activity	Solikah (2024)

Although research on *Myristica argentea* remains limited, preliminary data reveal a unique phytochemical profile. Its seed essential oil is dominated by sabinene, β-phellandrene, and safrole (Maryati, 2023), while GC-MS analysis identified saponins, flavonoids, and polyphenols with antioxidant and anti-inflammatory activities (Solikah et al., 2024). The presence of hallucinogenic compounds such as myristicin and elemicin (Barman et al., 2024), along with variability in trimyristin distribution within the seeds (Bhermana et al., 2023), adds another layer of complexity to this species' utilization. Compared to *M. fragrans*, the compositional differences suggest that *M. argentea* may have distinct therapeutic applications, though further research is needed to validate this hypothesis.

3.1.2 Bioactive compound sources

The seeds and aril (mace) of *Myristica fragrans* have long been recognized as the primary reservoirs of valuable bioactive compounds. Phytochemical analyses reveal that both parts contain diverse secondary metabolites, including essential oils, lignans, neolignans, diphenylalkanes, phenylpropanoids, and terpenoids (Gupta, 2020). This rich chemical composition not only underpins nutmeg's economic value as a spice but also accounts for its broad pharmacological activities. Notably, the seeds contain high concentrations of myristicin and elemicin, which contribute to both psychoactive and therapeutic effects, while the red aril is rich in phenolic compounds responsible for potent antioxidant activity. The distinct chemical profiles of seeds and aril suggest that these plant parts may have different therapeutic applications, necessitating tailored extraction approaches.

Although less studied than seeds and aril, the leaves and fruit pulp of *Myristica fragrans* also harbor significant pharmacological potential. Recent research by Nasir & Marwati (2023) demonstrated that nutmeg leaves exhibit strong antioxidant activity, likely due to their high flavonoid and tannin content. Meanwhile, the often-discarded fruit pulp contains essential oils with notable antioxidant properties. These findings open new avenues for utilizing under-exploited parts of the nutmeg plant. Developing optimized extraction methods for leaves and pulp could yield additional bioactive compounds while enhancing the economic value of the entire plant.

In *Myristica argentea*, seeds and fruit also contain abundant bioactive compounds, albeit with a distinct profile compared to *M. fragrans*. As reported by Ramírez-Alarcón et al (2023), compounds like myristicin in this species exhibit dualistic properties - beneficial at certain doses but potentially toxic at higher concentrations. This phenomenon underscores the need for cautious utilization of nutmeg in health applications. Variations in bioactive content across plant parts and between species highlight the necessity for thorough characterization before therapeutic product development. Additionally, factors such as geographical origin, harvest season, and processing methods must be considered to ensure standardization of nutmeg-based products.

3.1.3 Extraction methods

Hydrodistillation remains the industry standard for extracting nutmeg essential oils due to its efficiency and scalability. This technique employs steam to isolate volatile compounds such as sabinene, α-pinene, myristicin, and β-pinene (Trifan et al., 2023). The resulting high-purity essential oils are widely used in pharmaceutical, cosmetic, and food industries. However, conventional hydrodistillation has limitations in extracting non-volatile bioactive compounds and requires high thermal energy, which may degrade heat-sensitive components during prolonged distillation.

To overcome these constraints, various organic solvents have been evaluated, with methanol emerging as the most effective based on studies by Li et al (2020). Methanolic extracts demonstrated superior antioxidant and α-glucosidase inhibitory activities compared to ethanol or acetone extracts, attributed to methanol's ability to dissolve a broad range of polar to semi-polar compounds. Despite its efficacy, conventional solvent extraction poses environmental and safety challenges, particularly at an industrial scale, and requires additional purification steps to eliminate solvent residues.

In response to environmental concerns, recent advancements in nutmeg extraction have shifted toward greener practices. As highlighted by Putra et al (2024), green extraction techniques aim to minimize ecological impact while maintaining or enhancing efficiency. These approaches integrate green chemistry principles, considering the entire lifecycle of the extraction process. However, widespread adoption remains limited due to high initial investments in specialized equipment and the need for parameter optimization for different raw materials.

Amid these challenges, cutting-edge extraction technologies such as ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), and supercritical fluid extraction (SFE) have gained traction. According to Saxena (2023), these methods offer advantages over conventional techniques, with SFE using supercritical CO_2 providing a solvent-free, residue-free solution. Nevertheless, optimizing these advanced methods requires in-depth understanding of process parameters and raw material characteristics.

Given the complexity of nutmeg's bioactive compounds, integrated extraction strategies are being developed. Subramanian & Anandharamakrishnan (2023) proposed combining hydrodistillation for volatile compounds with green solvent extraction for non-volatile components to achieve comprehensive results. Moving forward, multidisciplinary collaboration will be essential to establish sustainable, efficient extraction protocols tailored for diverse nutmeg applications.

3.2 Biological activities and health benefits

3.2.1 Antioxidant

Recent research has revealed significant differences in antioxidant capacity between the leaf and seed parts of *Myristica fragrans*. Based on DPPH assays, the leaves exhibited stronger antioxidant activity with an IC50 value of 17.80 µg/mL compared to the seeds, which had an IC50 of 53.01 µg/mL (Saputri et al., 2024). This striking difference not only indicates that nutmeg leaves are more effective at neutralizing free radicals - a key factor in preventing oxidative stress - but also raises questions about variations in phytochemical composition between plant parts. Specifically, the leaves are suspected to contain higher concentrations of phenolic compounds and flavonoids, which are known for their potent antioxidant properties.

Beyond free radical scavenging, the antioxidant activity of *Myristica fragrans* has broader clinical implications. As demonstrated by Yudhistira et al (2022), bioactive compounds in nutmeg play a crucial role in reducing oxidative stress and inflammation associated with various chronic diseases. Their multifaceted mechanisms include: (a) electron donation to neutralize free radicals, (b) chelation of pro-oxidative metal ions, and (c) induction of the body's endogenous antioxidant system. The complexity of these mechanisms makes nutmeg extract a potential candidate for adjunctive therapy in various pathological conditions, ranging from diabetes to neurodegenerative disorders.

To further understand the phytochemical basis of this antioxidant activity, screening of *Myristica fragrans* fruit pulp revealed the presence of several important secondary metabolites (Azhari et al., 2024). Notably, compounds such as flavonoids - known for their strong antioxidant activity - were found in significant concentrations, as reflected by an IC50 value of 22.88 ppm in the ethanol extract of the fruit pulp. These findings reinforce that the unique distribution patterns of bioactive compounds in each plant part explain the observed variations in antioxidant activity. More importantly, the synergy among various compounds in natural extracts appears to provide a stronger antioxidant effect compared to isolated single compounds.

Complementing this picture, an analysis of essential oil from *Myristica fragrans* aril provided additional insights (Khairan et al., 2024). Although the aril essential oil overall showed a relatively high IC50 value (216.695 ppm), it is noteworthy that certain fractions exhibited stronger activity. This phenomenon suggests the presence of minor compounds with exceptional antioxidant potential within the complex matrix of the essential oil, reaffirming the importance of fractionation approaches in phytochemical research.

3.2.2 Anticancer

Recent studies have revealed significant differences in the anticancer potential of *Myristica fragrans* leaf and seed extracts against MCF-7 breast cancer cells. The leaf extract demonstrated higher inhibition (26%) compared to the seed extract (22.73%) in MTT

assays (Saputri et al., 2024). This difference in activity not only reflects variations in phytochemical composition between the two plant parts but also suggests that the leaves contain higher concentrations of bioactive compounds such as phenylpropanoids and lignans. This crucial finding leads to two important implications: first, the need for plant part standardization in nutmeg-based drug development, and second, the importance of further exploration of unidentified active components in the leaves.

Supporting these findings, an in-depth analysis of active compounds revealed an impressive complexity in their mechanisms of action. Myristicin, a major component of nutmeg, has been shown to induce apoptosis in MCF-7 cells through two parallel pathways: caspase-dependent activation and increased intracellular ROS production (Nazar & Ayyappan, 2024). More intriguingly, this compound also exhibits multimodal effects, including: (a) inhibition of metastasis by suppressing MMP2 and MMP9 expression in melanoma cells (Krisnayanti et al., 2024), and (b) reversal of multi-drug resistance through P-glycoprotein inhibition (Seneme et al., 2022). This molecular multifunctionality solidifies myristicin's unique position as a promising candidate for cancer therapy targeting multiple cellular pathways.

Beyond the major compounds, research on minor components in nutmeg has uncovered equally promising potential. Nutmeg hydrosol containing Biondinin A and Edultin showed high selectivity against MCF-7 cells (IC50 79.45 μg/mL) with no toxic effects on normal cells (Widiyarti et al., 2024). Meanwhile, neolignans such as (+)-licarin A from nutmeg seeds exhibited specific activity against melanoma cells (Hasbilla et al., 2024). These parallel findings not only expand the spectrum of nutmeg's anticancer activity but also highlight the importance of fractionation approaches to uncover minor compounds with unique mechanisms of action that may be overlooked in crude extract analyses.

Beyond direct cytotoxic effects, nutmeg's anticancer potential includes equally important indirect mechanisms. Supercritical fluid extracts have demonstrated anti-angiogenic properties by modulating key growth factors such as VEGFA and EGF. Notably, this anti-angiogenic effect synergizes with direct cytotoxic mechanisms, offering a dual therapeutic approach. More strategically, myristicin's ability to enhance cancer cell sensitivity to chemotherapy (Seneme et al., 2022) opens opportunities for developing combination therapy protocols that could overcome drug resistance - a major challenge in clinical oncology.

Despite compelling preclinical evidence, translating these findings into clinical applications still faces several challenges. First, extraction methods must be optimized to ensure reproducibility and yield of active compounds. Second, validation in more relevant in vivo models and long-term toxicity evaluations are prerequisites before clinical trials. Equally important, pharmacokinetic and formulation studies are needed to address bioavailability issues, which often hinder the efficacy of natural compounds. By overcoming these barriers, Indonesian nutmeg could fulfill its potential as a source of innovative, effective, and safe cancer therapies.

3.2.3 Anti-inflammatory

Myristica fragrans has been widely recognized for its potent anti-inflammatory effects, primarily due to its high phenolic compound content. These bioactive compounds work by inhibiting lipid peroxidation and neutralizing reactive oxygen species (ROS) (Setiawan et al., 2022). This protective mechanism not only reduces oxidative damage but also modulates inflammatory responses at the cellular level. More importantly, *Myristica fragrans* essential oil, rich in terpenoids, has demonstrated specific interactions with the NF-κB signaling pathway - a key regulator in the inflammatory cascade (Imran et al., 2024). This finding provides a scientific basis for the traditional use of nutmeg in treating various inflammatory conditions.

Further reinforcing this understanding, recent research has revealed that specific compounds from *Myristica fragrans* seeds, including neolignans and diarylnonanoids, strongly inhibit the NF-κB/AP1 and IRF signaling pathways (Le et al., 2024). These critical

pathways play a central role in regulating pro-inflammatory gene expression, meaning their inhibition can produce broad anti-inflammatory effects. Interestingly, this inhibitory effect occurs at multiple regulatory levels, from signal transduction to gene expression, highlighting the complexity and specificity of nutmeg's bioactive compounds. These findings solidify *Myristica fragrans* as a potential source of multi-target anti-inflammatory agents.

Beyond individual compounds, essential oils from the *Myrtaceae* family, including *Myristica* species, have demonstrated remarkable potential as anti-inflammatory agents. Some of these essential oils can inhibit over 70% of PGE2 release - a key inflammatory mediator (Maiolini et al., 2025). This strong inhibitory effect correlates with active compounds such as sabinene, α-pinene, and β-pinene, which are known for their anti-inflammatory properties. Notably, nutmeg essential oil also exhibits protective effects against oxidative stress, which often accompanies chronic inflammation (Imran et al., 2024). This dual action - both anti-inflammatory and antioxidant - makes nutmeg essential oil a compelling candidate for developing therapies for chronic inflammatory diseases.

Despite promising preclinical evidence, translating the anti-inflammatory potential of *Myristica* spp. into clinical applications still faces several challenges. First, extract standardization is needed to ensure consistent active compound content. Second, more in-depth pharmacokinetic studies are required to understand the absorption, distribution, metabolism, and excretion profiles of active compounds. Equally important, controlled clinical trials remain limited in validating efficacy and safety in humans. By addressing these challenges, Indonesian nutmeg could become a valuable resource for developing safer and more effective anti-inflammatory drugs.

Given its immense potential, the development of nutmeg-based products should adopt a sustainable approach. On one hand, extraction methods must be optimized to obtain active compounds with high yields and minimal environmental impact. On the other hand, innovative formulations are needed to enhance the stability and bioavailability of active compounds. Strategically, integrating ethnopharmacological knowledge with modern technology could accelerate the discovery of novel compounds and unexplored mechanisms of action. With this comprehensive strategy, the full potential of *Myristica* spp. as a source of anti-inflammatory compounds can be realized for broader human health benefits.

3.2.4 Cognitive benefits

Myristica fragrans contains bioactive compounds such as myristicin and eugenol, which exhibit significant neuroprotective potential in various research models. These compounds not only protect neurons from oxidative damage but have also been shown to improve motor function in animal models of Parkinson's disease (Palupi & Fekhayanti, 2024). This protective mechanism is believed to involve modulation of the dopaminergic system and inhibition of oxidative stress in the substantia nigra. More intriguingly, the neuroprotective effects appear to work through multiple targets, including activation of neurotrophic factors and suppression of neuronal apoptosis pathways, highlighting the unique complexity of nutmeg's bioactive compounds.

Complementing its direct effects on the central nervous system, *Myristica fragrans* extract has also been found to modulate the gut microbiome and its metabolites (Zhao et al., 2022). This unique interaction creates systemic effects that can mitigate liver inflammation and lipid metabolism disorders, which in turn positively impact neurological health. Notably, this regulation occurs through inhibition of the NF-κB pathway - a key signaling pathway linking systemic inflammation to neural degeneration. These recent findings open new insights into nutmeg's potential for a holistic therapeutic approach to neurological disorders via gut-brain axis modulation.

At the cellular level, nutmeg seed extract (NuSE) has been shown to enhance synaptophysin expression, a critical protein in synaptic transmission (Veronica et al., 2024). This specific effect suggests improved neuroplasticity, which could support cognitive function. More profoundly, NuSE's activation of PPARγ, which subsequently activates

PGC1α, plays a crucial role in mitochondrial biogenesis and synaptic function. This dual mechanism - enhancing neuronal energy capacity while improving synaptic transmission - explains the molecular basis of nutmeg's nootropic potential and its applications in age-related cognitive decline.

Beyond molecular effects, nutmeg essential oil has demonstrated clinical benefits in aromatherapy for improving sleep quality (Supantini et al., 2024). This therapy significantly reduces sleep latency while increasing sleep duration and efficiency. Importantly, improvements in sleep parameters have broad implications for mental health and cognitive function, given the strong link between sleep quality and neurological performance. These applied findings complement earlier mechanistic evidence, showcasing nutmeg's potential as a complementary therapy addressing multiple aspects of neural health - from molecular pathways to clinical manifestations.

3.2.5 Cardiovascular health

Recent studies on *Myristica fragrans* have revealed its significant ability to reduce caffeine-induced cardiotoxicity in rat models. Nutmeg extract administration not only improved cardiac histoarchitecture but also decreased lactate dehydrogenase activity, a marker of heart tissue damage (Anderson et al., 2022). These findings suggest that bioactive compounds in nutmeg act at the cellular level to preserve cardiomyocyte integrity. More importantly, this cardioprotective effect appears to involve multi-target mechanisms, including cell membrane stabilization and cellular energy metabolism enhancement, forming the basis for its therapeutic potential in cardiovascular disorders.

Complementing these findings, nutmeg's cardioprotective effects are strongly linked to its potent antioxidant capacity (Qu et al., 2024). Its bioactive compounds effectively suppress oxidative stress - a key pathogenic factor in cardiovascular disease (CVD) development. Specifically, methanol extracts of nutmeg aril (mace) exhibited highly potent antioxidant activity, correlating with reduced oxidative damage in cardiovascular tissues (M et al., 2024). This mechanism involves not only direct free radical scavenging but also induction of endogenous antioxidant defense systems, creating a more comprehensive and sustained protective effect.

Further analysis reveals that nutmeg's cardioprotective effects are mediated by various bioactive compounds, including phenolic acids and saponins. These compounds work synergistically through multiple pathways: (a) modulation of intracellular calcium homeostasis, (b) improvement of mitochondrial function, and (c) regulation of cardiomyocyte stress protein expression. Interestingly, certain neolignan derivatives in nutmeg show specific affinity for cardiovascular receptors, potentially explaining their selective action. This complex interaction network confirms nutmeg's potential as a unique source of multi-target cardioprotective compounds.

In modern therapeutic contexts, nutmeg emerges as a promising herbal candidate to complement conventional cardiovascular treatments. Its key advantages lie in its relatively low side-effect profile and mechanisms that complement standard drugs. For instance, while statins primarily target lipid profiles, nutmeg's bioactive compounds provide additional protection through antioxidant and anti-inflammatory effects. This potential synergy opens avenues for developing more effective combination therapies, particularly for high-risk CVD patients or those suboptimally responsive to conventional treatments.

3.2.6 Antimicrobial activity

Recent scientific evidence demonstrates that nutmeg extracts exhibit significant antibacterial activity against various human pathogens. A study by (Noviyandri et al., 2020) confirmed nutmeg extract's ability to inhibit *Streptococcus mutans*, the primary bacterium causing dental caries. Furthermore, ethanolic extracts of *Myristica fragrans* showed inhibition zones up to 17.70±2.21 mm against *Staphylococcus aureus* (Nasir & Marwati, 2023) - relevant not only for skin infections but also for managing Propionibacterium acnes-

induced acne. These findings position nutmeg as a broad-spectrum antimicrobial agent effective against multiple pathogens.

Table 2. Biological activities of *Myristica fragrans* and *Myristica argentea*

Biological Activity	Key Findings	Mechanism of Action	Clinical Implications/ Applications	References
Antioxidant	• Leaves more potent (IC50 17.80 µg/mL) than seeds (IC50 53.01 µg/mL) • Fruit pulp contains flavonoids (IC50 22.88 ppm) • Essential oil contains specific active fractions	1. Electron donation 2. Metal ion chelation 3. Induction of endogenous antioxidant systems	• Adjuvant therapy for chronic diseases (diabetes, neurodegeneration) • Fractionation approach for minor active compounds	Saputri et al. (2024), Yudhistira et al. (2022), Khairan et al. (2024)
Anticancer	• Leaf extract more effective (26% inhibition) vs. seeds (22.73%) • Hydrosol selective against MCF-7 cells (IC50 79.45 µg/mL) • Anti-angiogenic activity via VEGFA/EGF	1. Apoptosis induction via caspase & ROS 2. Metastasis inhibition (MMP2/MMP9) 3. Reversal of drug resistance (P-gp)	• Combination cancer therapy • Multi-modal targeting (cytotoxic + anti-angiogenic)	Nazar & Ayyappan (2024), Seneme et al. (2022), Widiyarti et al. (2024)
Anti-inflammatory	• >70% inhibition of PGE2 release • Dual effect (antioxidant + anti-inflammatory)	1. Inhibition of NF-κB/AP1/IRF pathways 2. Modulation of oxidative stress	• Treatment of chronic inflammatory diseases • Sustainable formulations	Le et al. (2024), Maiolini et al. (2023), Imran et al. (2024)
Cognitive Benefits	• Improved motor function (Parkinson's model) • Increased synaptophysin & mitochondrial biogenesis	1. Dopaminergic modulation 2. PPARγ/PGC1α activation 3. Gut-brain axis regulation	• Neurodegenerative therapy • Sleep disorder aromatherapy	Palupi & Fekhayanti (2024), Veronica et al. (2024), Supantini et al. (2024)
Cardiovascular	• Improved cardiac histoarchitecture • Reduced cardiac damage markers	1. Cell membrane stabilization 2. Calcium homeostasis modulation 3. Endogenous antioxidant activation	• Adjuvant therapy for CVD • Synergy with statins	Anderson et al. (2022), Qu et al. (2024)
Antimicrobial	• Inhibition zone of 17.70 mm vs. *S. aureus* • Effective against antibiotic-resistant strains	1. Cell membrane disruption 2. Inhibition of pathogenic enzymes (protease/ lipase)	• Alternative for resistant infections • Natural food preservative	Noviyandri et al. (2020), Dash & Patel (2024), Suloi et al. (2024)

At the molecular level, nutmeg's active compounds employ complex mechanisms. Myristicin - nutmeg's primary component - though exhibiting lower binding affinity than synthetic antibiotics like ampicillin (Nurul et al., 2023), excels in penetrating bacterial biofilms. Concurrently, nutmeg essential oil inhibits key fungal virulence enzymes (Hoda et al., 2020), including proteases and lipases essential for tissue invasion. This dual action - cell membrane disruption and pathogenic enzyme inhibition - makes nutmeg extracts multi-target antimicrobial agents with reduced resistance development potential.

Most promisingly, *Myristica fragrans* essential oil demonstrates efficacy against antibiotic-resistant bacterial strains (Dash & Patel, 2024), particularly multidrug-resistant *Escherichia coli* and *Pseudomonas* spp. Its unique mechanism - distinct from synthetic antibiotics - renders it less vulnerable to existing bacterial resistance pathways. This highlights nutmeg's potential role in addressing the global antibiotic resistance crisis, either as combination therapy or alternative treatment for recalcitrant infections.

Beyond medical applications, *Myristica argentea* oil shows significant potential in food preservation (Suloi & Faida, 2023). Its effectiveness against food spoilage pathogens like *Staphylococcus aureus* and *Escherichia coli* makes it a natural candidate for extending meat product shelf life (Suloi et al., 2024). This approach offers safer alternatives to synthetic preservatives while adding value as a natural spice. Such innovative applications are relevant not only for the food industry but also for household food safety in regions with limited refrigeration access.

3.3 Molecular mechanisms

Neolignan and diarylnonane derivatives isolated from the seeds of *Myristica fragrans* exhibit significant ability to inhibit soluble epoxide hydrolase (sEH) enzyme activity. These bioactive compounds, including malabaricones B and C as well as the newly identified mirifragranones, demonstrate inhibitory activity with IC50 values ranging from 14.24 to 46.35 μM (Oanh et al., 2023). This inhibition mechanism has important therapeutic implications, as sEH plays a crucial role in metabolizing epoxides into biologically less active diols. In a physiological context, sEH inhibition can maintain levels of bioactive epoxides such as epoxyeicosatrienoic acids (EETs), which are known to have anti-inflammatory, vasodilatory, and analgesic effects. These findings open new opportunities for the development of nutmeg-based therapies in the management of various pathological conditions, including hypertension, chronic pain, and cardiovascular diseases.

Complementing the findings on enzymatic activity, *Myristica fragrans* also exhibits strong modulatory effects on glucose metabolism. In vitro and in vivo studies reveal that nutmeg extract enhances glucose uptake in muscle cells by promoting GLUT4 transporter translocation through AMP-activated protein kinase (AMPK) activation (Yoshioka et al., 2022). This dual mechanism is not only relevant for managing postprandial hyperglycemia but also suggests potential applications in type 2 diabetes mellitus therapy. More intriguingly, this activity appears to function independently of insulin, offering a potential therapeutic alternative for insulin resistance conditions. These recent findings reinforce nutmeg's position as a source of bioactive compounds with complex and multifaceted metabolic effects.

The combination of sEH inhibition and glucose metabolism modulation creates a unique pharmacological profile for nutmeg's active compounds. In the context of metabolic diseases, these two mechanisms may work synergistically to address various aspects of diabetes pathophysiology and its complications. For instance, increased EET availability through sEH inhibition may improve endothelial function and reduce systemic inflammation, while AMPK-mediated glucose uptake enhancement helps control glycemia. This multimodal therapeutic approach makes nutmeg a compelling candidate for the development of modern herbal drugs targeting multiple aspects of metabolic diseases simultaneously.

3.4 Potential applications

3.4.1 Functional products

Myristica fragrans has demonstrated significant potential in modulating glucose metabolism through complex mechanisms. A study by Yoshioka et al (2022) revealed that active compounds in nutmeg not only enhance glucose uptake in muscle cells but also effectively manage postprandial hyperglycemia in rodent models. This effect is mediated through AMPK pathway activation and GLUT4 translocation, which function independently of insulin. Importantly, the sustained antihyperglycemic activity observed with oral administration highlights nutmeg's potential as a functional food for type 2 diabetes management. These findings open opportunities for developing nutmeg-based nutraceuticals that could serve as adjuvant therapy for metabolic disorders.

Beyond internal health applications, nutmeg leaf essential oil has been successfully formulated into nanoemulsion systems for UV protection (Rastuti et al., 2023). This innovative formulation leverages the photoprotective properties of nutmeg's phenolic compounds while improving their stability and bioavailability. Interestingly, the combination of intrinsic antioxidant activity and UV radiation absorption makes nutmeg nanoemulsions an ideal candidate for multifunctional cosmetic products. This development not only enhances the economic value of nutmeg but also offers a natural, safer, and more sustainable alternative for photoprotection.

Myristica spp. contain various psychoactive compounds with unique therapeutic implications. Components such as myristicin, elemicin, and DMT have shown modulatory effects on neurotransmitter systems relevant to neurodegenerative diseases (Barman et al., 2024). Although known as hallucinogenic substances, controlled doses of these compounds exhibit potential in modulating synaptic plasticity and neurogenesis. Current research focuses on isolating and modifying these compounds to optimize neuroprotective effects while minimizing unwanted psychoactive properties.

The sustainable utilization of nutmeg has gained attention through various waste-repurposing initiatives. The fruit pulp of *Myristica argentea*, often discarded, is rich in dietary fiber, protein, and antioxidant phenolic compounds (Suloi et al., 2023). This overlooked resource can be processed into high-value health supplements or functional food ingredients. Additionally, the typically discarded seed shells have been successfully converted into activated carbon with impressive iodine adsorption capacity (Maryati, 2023). This innovative application not only addresses waste management but also contributes to clean water solutions through simple and affordable purification technology.

3.4.2 Pharmaceutical applications

Myristica argentea has long been used in Indonesian traditional medicine due to its broad spectrum of biological activities. It has been empirically employed to treat various ailments, from digestive disorders to rheumatism and headaches (Barman et al., 2021). This traditional use now has scientific backing, with bioactive compounds like myristicin and eugenol identified as responsible for its therapeutic effects. Notably, *Myristica argentea* essential oil not only exhibits antimicrobial and anti-inflammatory activities - consistent with traditional beliefs - but has also demonstrated hepatoprotective, anticonvulsant, and antiparasitic effects in preclinical studies.

Complementing its traditional uses, *Myristica argentea* shows promising prospects in treating neurodegenerative diseases. Recent studies indicate that active compounds like myristicin in nutmeg extract can improve motor function in animal models of Parkinson's disease (Palupi & Fekhayanti, 2024). This neuroprotective mechanism is believed to involve dopaminergic system modulation and protection against oxidative neuronal damage. These findings not only validate nutmeg's traditional use for neurological disorders but also open avenues for developing standardized herbal treatments for neurodegenerative diseases, which currently have limited therapeutic options.

At the molecular level, research has elucidated the mechanisms of *Myristica argentea*'s bioactive compounds. For instance, eugenol works by inhibiting the NF-κB pathway and reducing pro-inflammatory cytokine production, providing a scientific basis for its traditional anti-inflammatory use. Meanwhile, its proven antimicrobial activity against various pathogens supports its application in infection treatment. Notably, its hepatoprotective effects are mediated through increased activity of endogenous antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPx), which protect hepatocytes from oxidative damage.

Given the accumulated scientific evidence, *Myristica argentea* warrants consideration for development into standardized phytopharmaceutical products. Standardization must account for variations in active compound content due to geographical and seasonal factors. For clinical applications, formulations must optimize the bioavailability of poorly soluble compounds like myristicin. A holistic approach combining traditional knowledge with modern pharmaceutical technology could yield safe, effective, and standardized products for various therapeutic indications.

4. Conclusions

This systematic review reveals the multidimensional potential of bioactive compounds from *Myristica fragrans* and *Myristica argentea* as sources of innovative therapy. Key findings indicate that various parts of the nutmeg plant contain active compounds with diverse pharmacological activities, including antioxidant, anticancer, anti-inflammatory, neuroprotective, cardioprotective, and antimicrobial effects. Importantly, complex molecular mechanisms of action have been identified, such as sEH inhibition by neolignans, AMPK activation for glucose modulation, and NF-κB pathway regulation for anti-inflammatory effects. However, variations in phytochemical composition among plant parts and species necessitate a strict standardization approach.

Future research prospects should focus on several critical aspects. First, comprehensive long-term toxicity studies are needed to evaluate the safety of psychoactive compounds such as myristicin. Second, bioavailability studies and nanoformulation development are required to address the solubility limitations of active compounds. Third, research on compound synergy is essential to understanding complex interactions in natural extracts compared to isolated compounds. Equally important, controlled clinical validation is necessary to translate preclinical findings into therapeutic applications. With this multidisciplinary approach, Indonesian nutmeg can be developed into standardized phytopharmaceutical products and sustainable solutions for various global health challenges.

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Author Contribution

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The author declare no conflict of interest.

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