

Myristicin: From its biological effects in traditional medicine in plants to preclinical studies and use as ecological remedy in plant protection

Karina Ramírez-Alarcón¹  | Miquel Martorell^{1,2,3}  | Eda Sönmez Güler⁴ |
 Ismail Laher⁵ | Hei-Long Lam⁶ | Ebtihal Abdalla M. Mohieldin⁷ |
 Ali Mahoumd Muddathir⁸ | Muhammad Akram⁹ | Mehwish Iqbal¹⁰ |
 Hamda Shafique⁹ | Gerardo Leyva-Gómez¹¹ | Shabnum Shaheen¹² | Manoj Kumar¹³ |
 Javad Sharifi-Rad¹⁴  | Ryszard Amarowicz¹⁵ | Monica Butnariu¹⁶

¹Department of Nutrition and Dietetics, Faculty of Pharmacy, University of Concepción, Concepción, Chile

²Centre for Healthy Living, University of Concepción, Concepción, Chile

³Unidad de Desarrollo Tecnológico, UDT, Universidad de Concepción, Concepción, Chile

⁴Department of Pharmacognosy, Faculty of Pharmacy, Sivas Cumhuriyet University, Sivas, Turkey

⁵Department of Anesthesiology, Pharmacology and Therapeutics, Faculty of Medicine, The University of British Columbia, Vancouver, British Columbia, Canada

⁶LKS Faculty of Medicine, University of Hong Kong, Hong Kong, China

⁷Faculty of Pharmacy, University of Science and Technology, Omdurman, Sudan

⁸Department of Horticulture, Faculty of Agriculture, University of Khartoum, Shambat, Khartoum North, Sudan

⁹Department of Eastern Medicine, Government College University Faisalabad, Faisalabad, Pakistan

¹⁰Institute of Health Management, Dow University of Health Sciences, Karachi, Pakistan

¹¹Departamento de Farmacia, Facultad de Química, Universidad Nacional Autónoma de México, Ciudad de México, Mexico

¹²Department of Plant Sciences, LCWU, Lahore, Pakistan

¹³Chemical and Biochemical Processing Division, ICAR—Central Institute for Research on Cotton Technology, Mumbai, India

¹⁴Facultad de Medicina, Universidad del Azuay, Cuenca, Ecuador

¹⁵Department of Chemical and Physical properties of Food, Olsztyn, Poland

¹⁶University of Life Sciences “King Michael I” from Timisoara, Calea Aradului, Timis, Romania

Correspondence

Miquel Martorell, Centre for Healthy Living,
University of Concepción, Concepción 4070386,
Chile.

Email: mmartorell@udec.cl

Manoj Kumar, Chemical and Biochemical
Processing Division, ICAR—Central Institute
for Research on Cotton Technology, Mumbai-
400019, India.

Email: drmanojpuniya@gmail.com

Javad Sharifi-Rad, Facultad de Medicina,
Universidad del Azuay, 14-008 Cuenca,
Ecuador.

Email: javad.sharifirad@gmail.com

Abstract

Myristicin is an allylbenzene and a major key constituent of many plant species, such as *Myristica fragrans* Houtt. (nutmeg), *Foeniculum vulgare* Mill. (fennel), and *Petroselinum crispum* (Mill.) Fuss (parsley). Their plant parts have been used in traditional medicine and as a flavoring seasoning for cooking but, and as biopesticides with natural compounds. Myristicin has been related with several biological effects, such as anticarcinogenic, anti-inflammatory, antimicrobial, antioxidant, antidiabetic, analgesic, and hepatoprotective. The traditional uses include the treatment of complications related to gastrointestinal tract, respiratory system, and gynecological disorders. However, several studies have been reported contraindications associated to high dose consumption of

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Monica Butnariu, University of Life Sciences
 “King Michael I” from Timisoara, Calea
 Aradului 119, Timis, 300645, Romania.
 Email: monicabutnariu@yahoo.com

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myristicin. This review summarizes the biological activities of myristicin and myristicin-rich plants, toxicological effects along with its bioavailability, and metabolism. In addition, their traditional uses and their role as ecological remedy in plants protection has been reviewed. Nutmeg is the myristicin-rich plant with more pharmacological effects reported but also with most contraindication and toxically reports.

KEYWORDS

green ecology, myristicin, nutmeg, parsley, phytotherapy, toxicity, traditional medicine

1 | INTRODUCTION

Myristicin [C₁₁H₁₂O₃] is methoxysafrole meaning an allyl-benzene (Figure 1) and a major key constituent of many species, like, *Myristica fragrans* Houtt. (nutmeg), *Foeniculum vulgare* Mill. (fennel), *Anethum graveolens* L. (dill weed), *Petroselinum crispum* (Mill.) Fuss (parsley), *Apium nodiflorum* (L.) Lag. (Water celery), and *Echinophora spinosa* L. Myristicin or 5-allyl-1-methoxy-2,3-methylenedioxybenzene is a metabolite of the phenylpropenes family, a subclass of phenylpropanoids. It is present in certain essential oils (EOs) and is especially present in nutmeg and to a lesser extent in other herbs, such as parsley, dill, and carrots. Structure and visual appearance of various sources of myristicin are presented in Figure 1.

The biosynthetic pathway leading to myristicin has the possible precursors methyl eugenol (Nishizawa et al., 1989) and shikimic acid (Yu et al., 1997). Myristicin is the most important aromatic constituent found in the EOs isolated from the dried ripened seed of *M. fragrans* (Ashokkumar et al., 2022) and is usually isolated from natural EOs by using fractional distillation. It is used as a fragrance in the cosmetic industry and as a flavouring agent in food (Slameňová et al., 2009). Plants and spices rich in myristicin have been used in traditional medicine to treat cholera, stomach cramps, nausea, diarrhea, and anxiety, however, several studies have reported contraindication effects (Castleman, 2009, Chap. 5; Grover et al., 2002; Martins et al., 2011; Motilal & Maharaj, 2013; Seneme et al., 2021).

In contrast, myristicin acts as a serotonin receptor antagonist and as a hallucinogenic compound (Dawidowicz & Dybowski, 2013) so is often used as a cheap hallucinogenic intoxicant (Forrester, 2005; Rahman et al., 2015). The structure of myristicin closely resembles that of amphetamine compounds and is capable of producing psychotropic effects similar to *N*-methyl-1-(3,4-methylenedioxyphenyl) propan-2-amine (MDMA) compounds. Because of this, it can be used in synthetic synthesis to create amphetamine derivatives and to create designer drugs such as 5-methoxy-3,4-methylenedioxymethamphetamine that are similar in structure and effect to MDMA. *M. fragrans* is the most commonly used plant to isolate myristicin to exploit its effects as recreative drug. A mild cerebral stimulation in human brains is caused with 400 mg myristicin doses (6–7 mg/kg body weight), equivalent to 15 g of

M. fragrans powder (Stein et al., 2001). However, myristicin doses of 1–2 mg/kg body weight, equivalent to 5 g of *M. fragrans*, are toxic and can lead to organ damages and impact on the cardiovascular systems (Hallström & Thuvander, 1997; Rahman et al., 2015).

The aim of the present review is to highlight the traditional uses and pharmacological activities of myristicin-rich plants along with their potential as ecological remedy in plant protection and contraindications. In addition, the mechanisms of action of myristicin as a single chemical entity have been reviewed along with its bioavailability and metabolism.

2 | TRADITIONAL USES AND PRECLINICAL PHARMACOLOGICAL ACTIVITIES

In the current section major sources of the myristicin-rich plants are discussed with specific reference to their traditional and preclinical pharmacological activities.

The traditional and pharmacological activities of plants rich in myristicin, such as *M. fragrans*, *F. vulgare*, *A. graveolens*, *P. crispum*, *A. nodiflorum*, and *E. spinosa*, are summarized in Table 1 whereas contraindications associated with the consumption of myristicin is shown in Figure 2. Myristicin is present in the EOs of some edible plants, however the concentration is not likely to have toxic effects for normal doses used in the kitchen. Of the common spices that contain myristicin, nutmeg has the highest relative concentration of the compound.

2.1 | *Petroselinum crispum* (Mill.) Fuss (parsley)

This culinary herb, also known as cilantro, has many pharmaceutical applications. It contains several important phytochemical constituents such as carotenoids, coumarins, and EOs containing the significant concentrations of myristicin and apiol compounds (Foudah et al., 2022; Tunali et al., 1999). Various studies have revealed that consumption of *P. crispum* exhibits strong antimicrobial activity against urinary tract infections. It is also used in traditional medicine for the treatment of bronchitis, asthma, anorexia, and uterine problems (Yarnell, 2002).

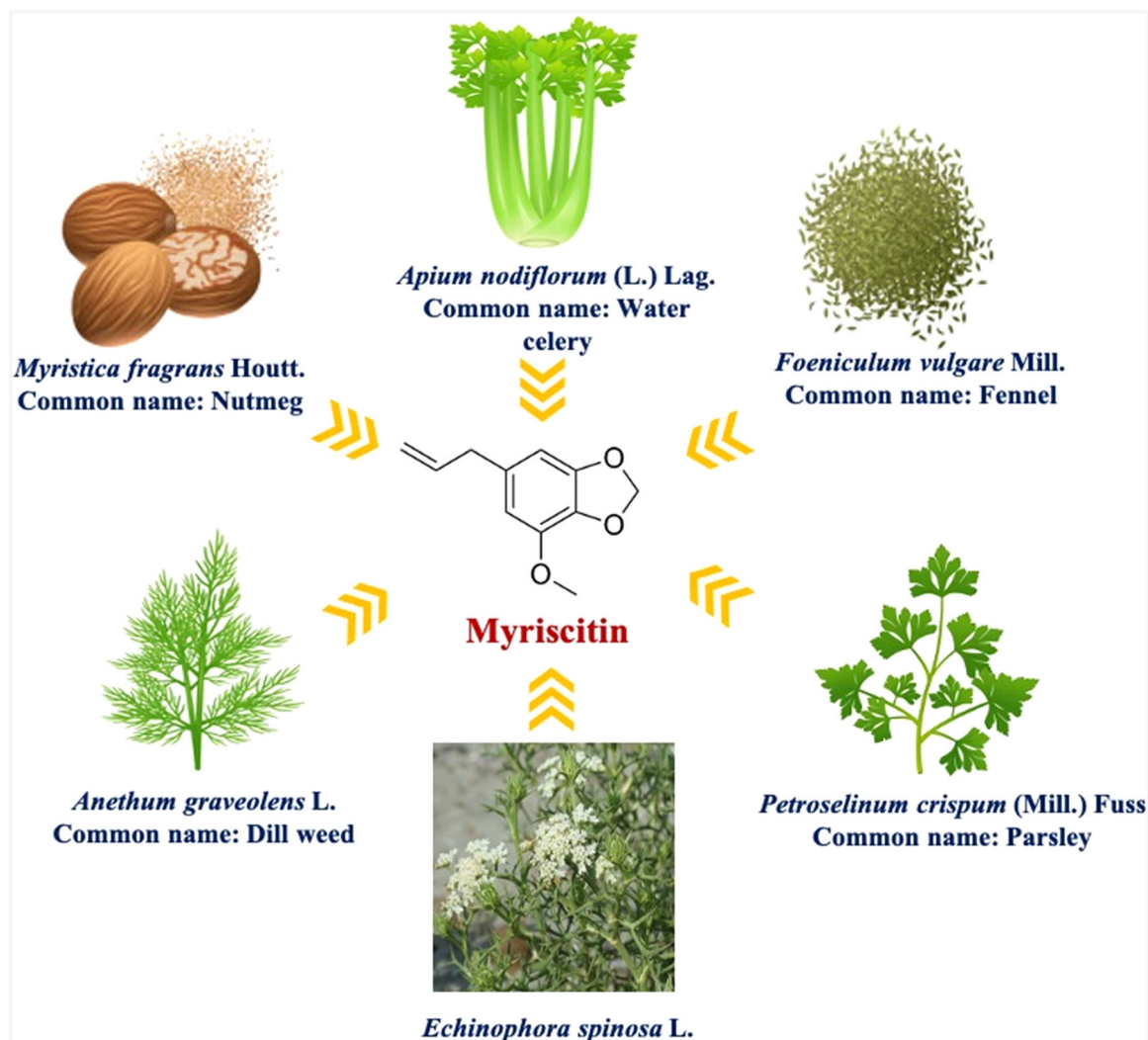


FIGURE 1 Chemical structure and visual appearance of major sources of the myristicin.

Two main components, myristicin and apiol, extracted from EOs of *P. crispum* are known to exhibit antioxidant activity (Badr et al., 2021; Bruneton, 1999). Myristicin is known to stimulate glutathione S-transferases, in mice and it also regresses carcinogenesis that is produced by benzo[a]pyrene in the lungs of mice (Ahmad et al., 1997). However, apiol, a phenylpropene, is accountable for the abortion-inducing properties of *P. crispum*, and the drug may be consumed to manage menstrual aches (Castleman, 2009, Chap. 5). In Middle Ages, wine simmered amid *P. crispum* was advised as a management for chest pain and arthritis. Infusions of *P. crispum* were employed to manage and control menstrual ache by Colombian migrants in London (Ceuterick et al., 2008).

P. crispum has also been accounted as useful herb for postmenopausal women. The utilizations of both *P. crispum* juice and *P. crispum* seed powder have been applied for provocation of hair growth when it is applied to the scalp, and also used for the prevention and management of bug bites (Peter, 2004). *P. crispum* was accounted to guard cells by inhibiting the process of ageing because of its

antioxidant properties, amid the chief contributors to its activity against free radicals being myristicin and apiol (Badr et al., 2021; Chevallier, 1996; Taiz & Zeiger, 1998, Chap. 13).

In addition, *P. crispum* has been traditionally utilized for the management of hypersensitivity reactions, chronic inflammatory and autoimmune disorders (Yousofi et al., 2012).

Tissue injuries, neuropathological ailments, and autoimmune diseases may alter the immune system, and myristicin contained in EOs from *P. crispum* can decrease the immune inflammation by reducing nitric oxide (NO), cytokine production, and the discharge of inflammatory proteins (Lee & Park, 2011).

2.1.1 | *Petroselinum crispum* (Mill.) Fuss contraindications

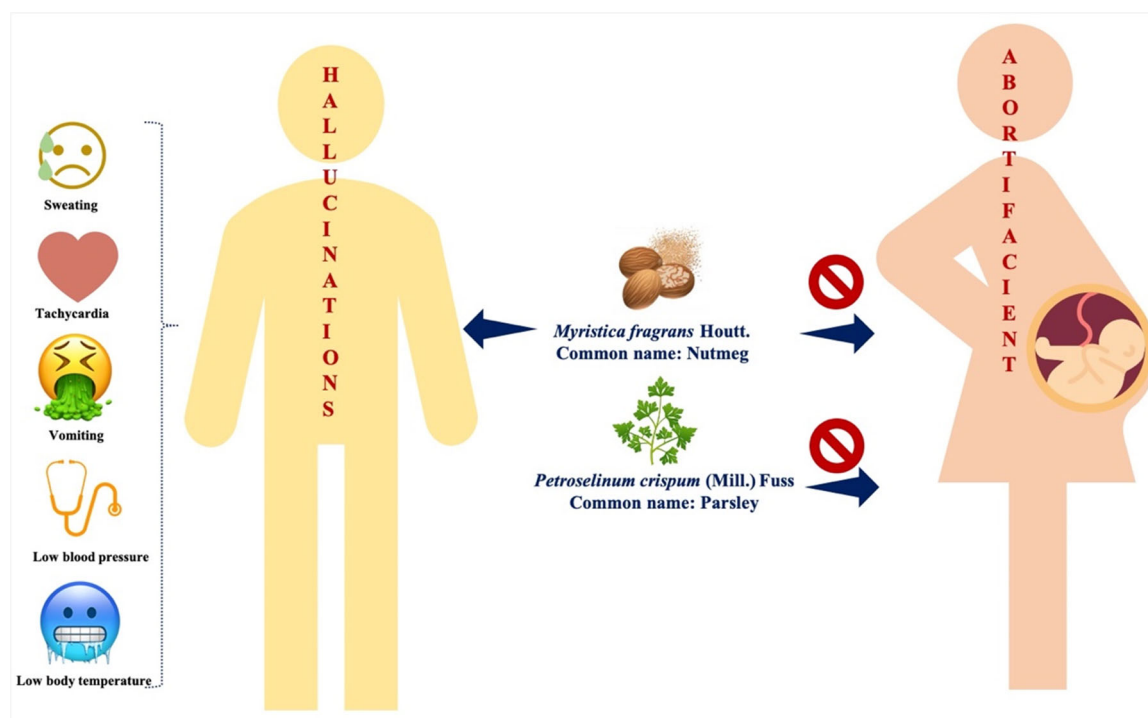
Parsley should be pre-eminently avoided by pregnant women as its apiol and myristicin content may excite the uterus. The accessibility of these constituents in the

TABLE 1 Traditional uses and preclinical pharmacological activities of myristicin-rich plants.

Plant	Traditional use/pharmacological activity	References
<i>Petroselinum crispum</i> (Mill.) Fuss	Diuretic and antimicrobial against urinary tract infections	Yarnell (2002)
	Antioxidant	Bruneton (1999), Chevallier (1996), and Taiz and Zeiger (1998, Chap. 13)
	Anticarcinogenesis	Ahmad et al. (1997)
	Manage and control menstrual ache	Castleman (2009, Chap. 5) and Ceuterick et al. (2008)
	Prevention and management of bug bites	Peter (2004)
	Anti-inflammatory and immune modulator	Lee and Park (2011) and Yousofi et al. (2012)
<i>Foeniculum vulgare</i> Mill.	Analgesic and carminative agents	Rahimi and Ardekani (2013)
	Antioxidant	Sultana et al. (2007)
	Antispasmodic	Rahimi and Ardekani (2013) and Ruberto et al. (2000)
	Increase milk production in feeding mothers	Shahat et al. (2011)
	Antibacterial	Jazani et al. (2009), Parejo et al. (2004), and Sultana et al. (2007)
	Anti- <i>Helicobacter pylori</i> and anti- <i>Campylobacter jejuni</i>	Cwikla et al. (2010) and Mahady et al. (2005)
	Antifungal	Rahimi and Ardekani (2013)
	Anti-inflammatory	Choi and Hwang (2004) and Rahimi and Ardekani (2013)
	Management of stress and anxiety	Koppula and Kumar (2013) and Mesfin et al. (2014)
	Anticonvulsant, anticramp, and antiemetic herb	Kaur and Arora (2010)
<i>Anethum graveolens</i> L.	Analgesic, anti-inflammatory, and gastric muscle relaxant	Ishikawa et al. (2002)
	Antimicrobial	Ishikawa et al. (2002) and Stavri and Gibbons (2005)
<i>Myristica fragrans</i> Houtt.	Anti-inflammatory	Bennett et al. (1974), Lee and Park (2011), Morita et al. (2003), Ozaki et al. (1989), and Rasheed et al. (1984a)
	Antioxidant	Kareem et al. (2013) and Moinuddin et al. (2012)
	Carminative	Oliver-Bever (2010)
	Antimicrobial	Dhingra and Sharma (2006) and Smith-Palmer et al. (2002)
	Hypolipidemic	Dhingra and Sharma (2006) and Smith-Palmer et al. (2002)
	Antirheumatism	Gomathi et al. (2016, Chap. 69) and Oliver-Bever (2010)
	Anticarcinogenic	Dhingra and Sharma (2006), Miller et al. (1983), and Smith-Palmer et al. (2002)
	Platelet antiaggregatory activity	Rasheed et al. (1984b) and Venton et al. (1991)
	Liquefy renal calculi's	Essam and Maytham (2012) and Sanghai-Vaijwade et al. (2011)
	Pain-relieving and antipyretic	Vane (1971)
	Anticholera	Gomathi et al. (2016, Chap. 69)
	Hepatoprotective	Kareem et al. (2013), Moinuddin et al. (2012), and Morita et al. (2003)
	Diuretic and decongestant of kidneys and urinary tract	Allen and Hatfield (2004)
<i>Apium nodiflorum</i> (L.) Lag.	Laxative	Viegi et al. (2001)
	Antiarthritis	Marc et al. (2008)

TABLE 1 (Continued)

Plant	Traditional use/pharmacological activity	References
<i>Echinophora spinosa</i> L.	Aarasiticide agent	Viegi et al. (2001)
	Antifungal activity	Maxia et al. (2012)
	Insecticide activity against <i>Trichoplusia ni</i>	Heshmati Afshar et al. (2017)
	Anti- <i>Helicobacter pylori</i>	Menghini et al. (2010)
	Ameliorate osteoporosis symptoms in Wistar rats	Tsakova et al. (2015)
	Antimicrobial	Fraternale et al. (2013)
	Larvicidal activity against <i>Culex quinquefasciatus</i>	Pavela et al. (2018, 2020)

FIGURE 2 Contraindications of *Petroselinum crispum* (Mill.) Fuss and *Myristica fragrans* Houtt.

stalks, leaves, and roots is less than in the EOs of seed, so these are harmless to use. The individuals with hypersensitivity to the plants of the Apiaceae family should keep away from every constituent of *P. crispum* (Castleman, 2009, Chap. 5).

2.2 | *Foeniculum vulgare* Mill. (fennel)

F. vulgare is a plant belonging to the Apiaceae family. Every component of *F. vulgare*, for instance, leaves, roots, fruit (dry seed), and particularly its seeds is consumed worldwide (Moura et al., 2005).

Seeds of *F. vulgare* contain 42.3% carbohydrates, 18.5% fibers, 13.4% minerals, 10% fats, 9.5% protein, and

6.3% water (Rather et al., 2016). The leaves of *F. vulgare* contain minerals and vitamins, for instance, sodium, phosphorus, calcium, potassium, iron, Vitamin B1, Vitamin B2, Vitamin B3, and Vitamin C (Miguel et al., 2010).

There are over 30 varieties of terpenes complexes in the indispensable EOs of *F. vulgare*, the most significant of them are 50%–80% trans-anethole, 8% of fenchone, and 5% of limonene (Salehi, 2006). This plant also has phenolic compounds, for instance, tannin, coumarin, phenolic acids, and hydroxycinnamic acids (Rahimi & Ardekani, 2013). It has been used in traditional herbal medicines for decades due to its pharmacological properties. *F. vulgare* seeds are commonly used as anti-inflammatory, antispasmodic, analgesic, and carminative

agents. Lately, there has been substantial obsession on the antioxidant capability and antimicrobial activities of extracts from *F. vulgare* seeds and its EOs (Sultana et al., 2007).

F. vulgare fruit has 1%–3% EOs, exhibiting strong anti-inflammatory activity majorly on respiratory and digestive systems. Also it shows an antispasmodic effect on smooth muscle (Ruberto et al., 2000).

The EOs content of this plant is used to treat menstrual problems, like, menorrhagia, dysmenorrhea, and gynecological problems, like, uterine fibroids. It is also used to cure stomach ache, flatulence, and bloating due to its carminative action. Besides, it helps increase milk production in feeding mothers (Shahat et al., 2011).

EO of *F. vulgare* has antimicrobial effect on all strains of bacteria so its extract can be utilized to control several antibiotic-opposing microbes (Jazani et al., 2009). EO of *F. vulgare* has also antifungal activity against a range of fungal species, for instance, dermatophytes, *Candida albicans* and species of *Aspergillus* (Rahimi & Ardekani, 2013).

The herb also has favorable effects on the management of stress and anxiety (Mesfin et al., 2014).

2.3 | *Myristica fragrans* Houtt. (nutmeg)

M. fragrans is an evergreen aromatic herb commonly known as nutmeg plant and Jaifal Javetri in India and Pakistan. *M. fragrans* has a characteristic, strong smell and a warm, somewhat sweet taste (Ashokkumar et al., 2022; Gomathi et al., 2016, Chap. 69). It is therapeutically utilized as a stomachic, stimulant, carminative in addition also treats diarrhea, colic, intestinal catarrh, headaches, emesis, nausea, pyrexia, halitosis, to arouse appetites and to control flatulence. Furthermore, it is utilized for its anti-inflammatory properties and an agent to enhance sexual desire and pleasure. *M. fragrans* is also claimed as psychoactive plant (Duarte et al., 2019; Orwa et al., 2009). The major phytoconstituents of this plant are myristicin, myristic acid, terpenes, and trimyristin (Jaiswal et al., 2009).

Nutmeg is the dried seed of the plant that is used in spices and has many pharmacological activities. The seeds are brown in color, and have an aromatic odor and bitter taste (Olajide et al., 2008). Its EOs is useful to liquefy renal calculi's and useful in treating diseases associated with kidney, additionally it plays a crucial role in the management of diarrhea (Essam & Maytham, 2012; Sanghai-Vaijwade et al., 2011), cholera and rheumatism (Gomathi et al., 2016, Chap. 69). Topically, the indispensable EOs from *M. fragrans* is utilized as a carminative and putted on locally for treatment of rheumatism (Oliver-Bever, 2010). The drug is a gentle sleep-inducing agent, and the constituent accountable for this activity is myristicin (Iwu, 1993).

Nutmeg accommodates 5%–15% of EOs, holding camphene, sabinene, elemicin, myristin, isoelemicin, isoeugenol, eugenol, safrole, methoxyeugenol, diametric phenylpropanoids, neolignans, and lignans (Gomathi et al., 2016, Chap. 69). The indispensable EOs segregated from the seeds of *M. fragrans* produced in Nigeria was established to have sabinene (49.09%), α -pinene (13.19%), α -phellandrene (6.72%), and γ -terpinol (6.43%) as chief components (Ogunwande et al., 2003). In another study, it was observed that *M. fragrans* encompasses ~10% of EOs, which principally contains camphene and pinene. The insignificant constituents include terpinolcymene, safrole, myristicin, elemicin, eugenol, methyleugenol, and isoeugenol. The plant also contains elemicin and safrole (Gottlieb, 1979; Iwu, 1993).

M. fragrans reduces prostaglandins and associated endo-chemicals made in the colon of human beings (Bennett et al., 1974; Rasheed et al., 1984a). Bennett et al. (1974) stated that the medicine minimizes the contractions of prostaglandin E2 on mice gastric strips. A platelet antiaggregatory activity of *M. fragrans* was also reported by Rasheed et al. (1984b) and Venton et al. (1991).

The antiaggregatory outcome was ascribed to eugenol and isoeugenol. Safrole from *M. fragrans* has been established to be carcinogenic in rats (Miller et al., 1983). Pain-relieving and antipyretic outcomes were also demonstrated by *M. fragrans* EOs. These properties of *M. fragrans* EOs appear to signify that the EOs works like NSAIDs, for instance, indomethacin and aspirin. These remedies create anti-inflammatory, pain relieving, and antifever effects possibly by restraining the biosynthesis of prostaglandins (Vane, 1971). *M. fragrans* has previously been revealed to be an inhibitor of prostaglandins in the colon of human being (Bennett et al., 1974; Rasheed et al., 1984a).

In a study conducted by Ozaki et al. (1989), the anti-inflammatory activity of *M. fragrans* was observed and was noticed that the activity was almost equivalent to that of induced in the case of indomethacin.

Myristicin present in *M. fragrans* is liable for anti-inflammatory action. Myristicin shows significant anti-inflammatory activity and this is believed that this activity of myristicin may be due to the suppression of inflammatory cytokines, chemokines, and growth factors in RNA-stimulated macrophages through the calcium channel pathway (Lee & Park, 2011). Similar to the nonsteroidal anti-inflammatory drugs (NSAIDs), *M. fragrans* caused ulceration in the stomach mucosa of rats. The NSAIDs cause gastric sores by reducing the biosynthesis of prostaglandin (Ivey, 1986). This research also confirms the bioequivalence antiplatelet aggregating property of *M. fragrans* EOs. *M. fragrans* has been demonstrated to be a strong inhibitor of platelet aggregation (Rasheed et al., 1984b; Venton et al., 1991). NSAIDs, for instance, aspirin, generate antiplatelet

aggregating effects by inhibition of the biosynthesis of thromboxane A₂ in thrombocytes (Warner et al., 2011).

In an experimental study, EOs extracted from nutmeg showed a significant reduction in the production of protein listeriolysin in infection caused by *Listeria monocytogenes* (Smith-Palmer et al., 2002).

Myristicin in *M. fragrans* has significant importance due to its hepatoprotective activity because of the inhibitory effect on tumor necrosis factor (TNF)- α from macrophages (Morita et al., 2003). Along with the hepatoprotective and antioxidant activity, *M. fragrans* also has antidepressant (Iwata et al., 2022; Moinuddin et al., 2012), antimicrobial, hypolipidemic, and anticarcinogenic activity (Dhingra & Sharma, 2006).

2.3.1 | *Myristica fragrans* Houtt. contraindications

Myristicin, the chief constituent of *M. fragrans*, has been associated to have the subsequent unfavorable effects, like, distancing from reality, low blood pressure, confabulation, rapid heartbeat, numbness, drowsiness, emesis, flushing, gagging, painful obstruction of ileum, paresthesia, blurred vision, low body temperature, and sweating (Grover et al., 2002). The noxious effects of *M. fragrans* have been claimed to be due primarily to myristicin EOs (Ehrenpreis et al., 2014). In a case statement, it was emphasized that *M. fragrans* can cause critically toxic outcomes, for instance, status epilepticus. In fact, a progressively growing normal new-born had recurred incidents of afebrile status epilepticus after intake of nutmeg (Sivathanu et al., 2014).

A retrospective study on human exposure to toxic substances between 2008 and 2018 covering the French Mediterranean coast identified 31 cases of nutmeg intoxication, nine of which were excluded due to insufficient data (Reynoard et al., 2019). Clinical effects included neuropsychiatric disorders (hallucinations, blurred vision, and agitation), gastrointestinal disorders (abdominal pain and diarrhea), sore throat, dry mouth, feeling faint, and tachycardia. Another retrospective study from the Illinois Poison Center conducted between 2001 and 2011 showed similar clinical effects (Ehrenpreis et al., 2014), with one notable case of respiratory depression. However, this patient was attempting to commit suicide, and consumed nutmeg along with duloxetine, clonazepam, K2 (a synthetic cannabinoid), and acetaminophen. Therefore, the evidence for the association between *M. fragrans* overdose and respiratory depression remains insufficient. Two other case reports from as early as 1970 and 1992 also reported similar clinical effects, such as hallucinations, vomiting, and tachycardia (Abernethy & Becker, 1992; Panayotopoulos & Chisholm, 1970).

Poisonous effects have been experienced by persons taking *M. fragrans* in quantities surpassing 5 g (Green, 1918; Mack, 1982).

Those toxicities have taken place unintentionally or intentionally, frequently in turn to attain a mind-changing experience, as myristicin, and possibly also other constituents of *M. fragrans*, nutmeg have caused hallucinogen effects. From the Middle Ages, *M. fragrans* has been utilized as a stimulant, abortifacient, agent for relieving flatulence, narcotic, and emmenagogue (Hall, 1973).

The research was executed with 25 white male rodents. Myristicin was prescribed at quantity levels from 200 to 1000 mg/kg body weight. Huge doses evoked hyperexcitability accompanied by central nervous system depression. It was concluded that intraperitoneal LD₅₀ > 1 mg/kg in mice (Truitt et al., 1961).

Furthermore, myristicin is a noxious phenylpropene/allylbenzene complex and has hallucination-creating properties, performing as a psychoactive agent at excessive levels of intake (Hallström & Thuvander, 1997). At a dose of 400 mg (equivalent to 6–7 mg/kg of body weight), myristicin caused “mild cerebral provocation” in 4 out of 10 human beings. A number of intoxications have, conversely, been accounted for after the consumption of around 5 g of *M. fragrans* subsequent to approximately 1–2 mg myristicin/kg of body weight. In accordance with a study performed on mutagenicity of the *M. fragrans*, the myristicin in this plant maybe have inadequately mutagenic. Alternatively, myristicin was not established to be genotoxic in an unscheduled DNA synthesis assay. Sequentially to observe the mutagenic prospective of myristicin, more researches would be needed (Hallström & Thuvander, 1997).

3 | MECHANISMS OF ACTION OF MYRISTICIN

As a pure compound, myristicin showed antioxidant, anti-inflammatory, and antiproliferative effects (Figure 3). In a colitis model induced by acetic acid in mice, myristicin (200 mg/kg) increased the concentration and activity of antioxidant enzymes, such as catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase, and prevented lipid peroxidation (Badr et al., 2020). In the same study, myristicin showed anti-inflammatory effects such as lowering inflammatory markers (myeloperoxidase activity, TNF- α , interleukin (IL)-1, and IL-17) and inhibited nuclear factor-kappa B (NF- κ B) levels in the colitis model. In another study, performed in a rat ulcerative colitis model, the authors showed that myristicin (150 mg/kg/day) acts against colonic oxidative, inflammatory, and apoptotic processes induced in the model (Ismail Abo El-Fadl & Mohamed, 2022). The authors

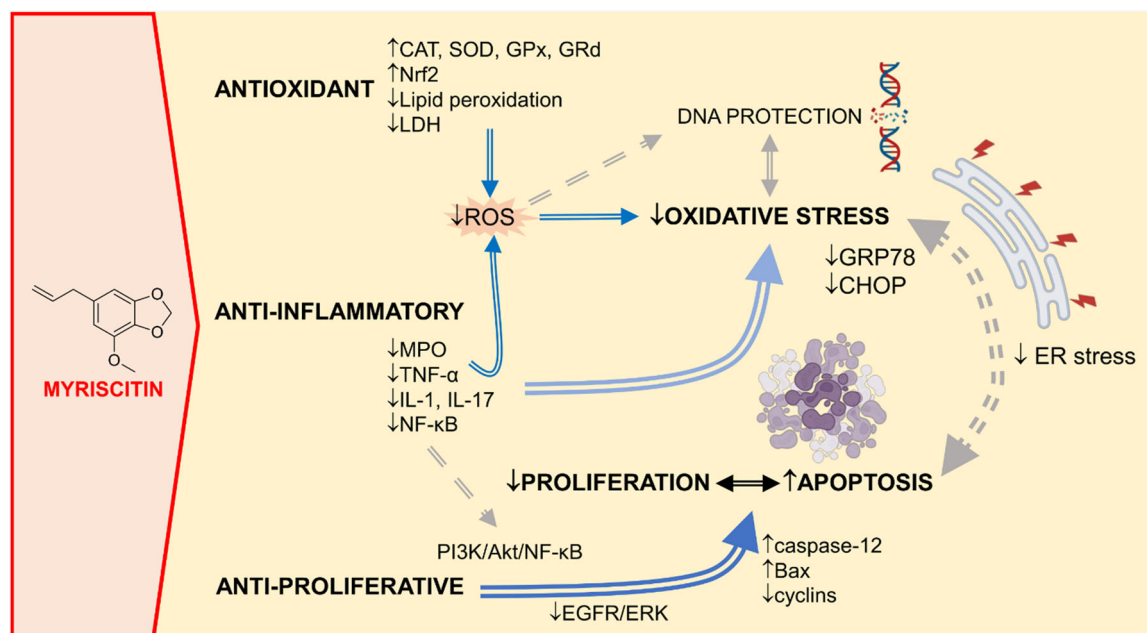


FIGURE 3 Mechanisms of action of myristicin. CAT, catalase; CHOP, CCAAT/enhancer-binding protein homologous protein; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; ERK, extracellular-signal regulated kinase; GPx, glutathione peroxidase; GRd, glutathione reductase; GRP78, glucose-related protein 78; IL, interleukin; LDH, lactate dehydrogenase; MPO, myeloperoxidase; NF-κB, nuclear factor-kappa B; Nrf2, nuclear factor-erythroid-2; PI3K, phosphatidylinositol-3-kinase; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α.

suggest that myristicin mediates the downregulation of endoplasmic reticulum stress, glucose-related protein 78 (GRP78), and CCAAT/enhancer-binding protein homologous protein (CHOP) genes expression and apoptosis, increase the expression of nuclear factor-erythroid-2 and decrease the antioxidant signaling pathway, and downregulates NF-κB resulting in a mucosal DNA protection. In rat dorsal root ganglion neurons, myristicin has been tested against hypoxia-induced apoptosis and endoplasmic reticulum stress (Zhao et al., 2017). Myristicin (50 μM) showed cytoprotective effects and also decrease malondialdehyde and lactate dehydrogenase production, upregulate superoxide dismutase and glutathione peroxidase, and reduced GRP78, CHOP, and cleaved caspase-12.

In oxidized low-density lipoprotein-treated human vascular smooth muscle cell and human umbilical vein endothelial cells myristicin regulated proliferation and apoptosis via the phosphatidylinositol-3-kinase/Akt/NF-κB signaling pathway (Luo et al., 2022). In human gastric cancer cells, myristicin (7.9, 15.6, and 31.3 μM; for 48 h) retarded proliferation and induced ER stress and apoptosis (Song et al., 2023). The authors observed a decreased expression of cyclins, increased Bax expression, activated caspases, and enhanced cytochrome C release and mitochondrial reactive oxygen species. In addition, the epidermal growth factor receptor (EGFR) activated extracellular-signal regulated kinase signaling pathway was restrained by myristicin.

Recently, pharmacological and therapeutical potential of myristicin and EOs of plants rich in myristicin has been revised by Seneme et al. (2021).

4 | BIOAVAILABILITY OF MYRISTICIN

Bioavailability is influenced by the absorption as well as the route of administration, metabolism during its movement to the systemic circulation, and food matrix. Human exposure to myristicin through foods, beverages, food supplements, and traditional medicines is elevated. EU imports data for nutmeg and may suggest a daily maximum dietary intake level for myristicin 684 μg/person (WHO, 2009).

Myristicin is highly bioavailable following the consumption of spices containing it. Additionally, myristicin readily crosses the placental barrier (Beyer et al., 2006; Vesselinovitch et al., 1979). The poisoning symptoms of myristicin or foodstuffs containing it, usually occur 3–6 h after the ingestion and persist up to 72 h (Sangalli et al., 2000).

4.1 | Absorption, distribution, and excretion

Muchtaridi et al. (2010) mentioned that larger doses and longer administrations of *M. fragrans* seed EOs by inhalation in mice, exhibited greater locomotor

inhibition. Half an hour after the addition of 1 mL/cage of *M. fragrans* seed EOs, the plasma concentration of myristicin was 3.7 µg/mL; 1 and 2 h after the addition, the levels were 5.2 and 7.1 µg/mL, respectively (Muchtaridi et al., 2010). In one girl hospitalized with atropine like symptom 6 h after ingestion of 14–21 g or 280–420 mg/kg, a myristicin blood level of 2 µg/mL was measured 8 h after ingestion, typical symptoms were seen up to 20 h after ingestion, and recover without any sequelae (Stein et al., 2001).

A dose of 400 mg of myristicin taken orally by a human, appears to have no psychotropic effect and it is not sufficiently potent to explain the psychotropic effects of nutmeg (Truitt, 1967; Truitt et al., 1961).

Orally administered myristicin [¹⁴C-methylene] has been studied in rats and mice (~0.60 mg/kg body weight). After 48 h, 73% of the radioactivities were recovered from administered myristicin, as expired carbon dioxide, presumably arising from *O*-demethylenation metabolism.

In addition, 15% and 3% of the radio-labeled myristicin were recovered from the urine and feces, and less than 2.5% of the radioactivity was detected in the liver (Casida et al., 1966; Kamienski & Casida, 1970; Peele, 1976). In both species the excretion was rapid and in rat's excretion occurred largely via the urinary route (Kamienski & Casida, 1970), whereas in mice via the respiratory air (Braun & Kalbhen, 1972; Casida et al., 1966). It can be concluded that myristicin is rapidly absorbed by the oral route (WHO, 2009).

4.2 | Metabolism

Phase I metabolic reactions of myristicin included dehydration, hydroxylation, ring-opening of dioxolane, while the phase II metabolic reaction of myristicin contained *N*-acetylcysteine and glucuronic acid conjugation (Zhu et al., 2019). Myristicin, 1'-hydroxymyristicin, and most of their metabolites were primarily excreted in urine. Allyl and methylenedioxy were the major metabolic sites of myristicin and 1'-hydroxymyristicin (Zhu et al., 2019).

Myristicin metabolism has only been observed for liver microsomes, detected with the presence 2',3'-dihydroxymyristicin, 3'-hydroxymyristicin, 1'-hydroxymyristicin, and 5-allyl-2,3-dihydroxyanisole metabolites (Guenthner & Luo, 2001; Luo & Guenthner, 1996; Luo et al., 1992). For both rats and humans exposed to nutmeg, the corresponding *O*-demethylenation metabolite of myristicin was predominant metabolite (Beyer et al., 2006).

After administration of high doses of myristicin (100 mg/kg body weight) or a high dose of nutmeg (500 mg/kg body weight) in rats, urine showed the presence of hydrolysis product of the 2',3'-dihydroxy metabolite (Al-Malahmeh et al., 2017). From in vitro and in vivo studies in rats, two metabolites were identified, 1'-hydroxymyristicin and 5-allyl-1-methoxy-2,3-dihydro-

xybenzene (Lee et al., 1998). Cytochromes P450 (CYP)-catalyzed (CYP3A4 and CYP1A2) were the enzymes primarily responsible for the oxidation of myristicin (Yun et al., 2003).

5 | MYRISTICIN-BASED CLINICAL TRIALS

Despite the potential therapeutic value of myristicin, there is no evidence to support this fact by well-designed randomized clinical trials on humans. A case report in 1975 noted that a 41-year-old woman with medullary thyroid carcinoma responded favorably to nutmeg treatment for her diarrhea (Barrowman et al., 1975). A possible explanation for this was that the patient's diarrhea was caused by high levels of prostaglandin-like materials, and that nutmeg inhibits prostaglandin synthesis in human isolated colonic mucosa (Bennett et al., 1974). There are no clinical trials on examining the effects of myristicin in isolation. The only two relevant studies on the effects of nutmeg that we could identify (Beattie, 1968; Motilal & Maharaj, 2013) are presented below and the reported findings were found statistically insignificant.

A trial conducted by Beattie on 45 first-year psychology university students treated one group with 6 g of ground nutmeg while the other group ingested gravy browning as a placebo control (Beattie, 1968). Each group was further divided into two subgroups: a low-suggestion group and a high-suggestion group. In the low-suggestion groups, participants were informed that the treatment they were receiving could not have any effects, while those in high-suggestion groups were informed that the treatment produced varied but marked effects, and that they should report any difficulty they experienced. The trial studied the effects of nutmeg on problem solving and any associated subjective feelings. It was also hypothesized that heightened suggestion would increase reported effects. Outcome was assessed by three measures: (1) speed and accuracy of answering several difficult letter series questions; (2) questionnaire on the perceived difficulty of the letter series questions; and (3) questionnaire on subjective feelings of the participants (visual clarity, stiffness, and pain). The study concluded that nutmeg does not affect problem solving nor does it induce subjective feelings. However, this study has an unclear risk of selection bias as randomization was not reported. It was also not reported whether the investigators were blinded. Moreover, the trial had a small sample size ($n = 45$).

A double-blind, randomized controlled trial that studied the effect of topical nutmeg administration (spray) on painful diabetic neuropathy was published in 2013 (Motilal & Maharaj, 2013). Diabetic patients ($n = 74$) who met the criteria for painful diabetic neuropathy were randomized into two groups. The treatment group received topical nutmeg extract (comprising 2% mace

EOs and 14% nutmeg EOs), while the control group received placebo. The study lasted 4 weeks. Outcomes (pain and quality of life) were assessed by the Brief Pain Inventory for Diabetic Painful Neuropathy and Neuropathic Pain Symptom Inventory. There were similar reductions in reported pain scores in both groups (treatment and control). A possible explanation for this was that both the nutmeg extract and placebo contained menthol (6%) and methyl salicylate (6%), which may have contributed to the pain reduction in both groups. There was a low risk of bias in this study, as randomization, allocation concealment, and blinding were described, and an intention-to-treat analysis was performed. However, the study had a small sample size ($n = 74$).

Myristicin is a prevailing natural biometabolite to put a stop to postprandial hyperglycemia and type 2 diabetes mellitus by spreading glucose uptake in muscle; repressing postprandial hyperglycemia.

Another clinical trial performed in 64 dysmenorrheic patients studied the efficacy of herbal decoction (pods of *Cassia fistula* Linn. and Arils of *M. fragrans*) with mefenamic acid in spasmodic dysmenorrhea (Anjum & Sultana, 2018). The authors concluded that the herbal decoction was effective to relieve pain and to improve health-related quality of life in spasmodic dysmenorrhea, however the beneficial effect cannot be attributed to *M. fragrans* or myristicin.

6 | MYRISTICIN—ECOLOGICAL REMEDY IN PLANTS PROTECTION

Plants, algae, and other organisms produce a wide variety of natural metabolites that can inhibit crop pests and diseases, such as the compound myristicin. Worldwide, one of the most used “botanical substances” is the EOs containing myristicin, an insecticide extracted from plants mentioned in this review. Myristicin EOs and other plants are used as biopesticides for both pests and diseases, while an extract has been developed as a biofungicide for Powdery Mildew. Plants containing myristicin, that is, Apiaceae family, have properties to protect themselves against certain pests, and growing plants containing this substance is a good method of pest control (Heshmati Afshar et al., 2017). Organic agriculture is increasingly popular, and if we look at the evolutionary trend, we can say that this will become an increasingly used option because it offers healthy, safe, and high-quality products (Tunali et al., 1999). Isolated myristicin has been shown to be an effective insecticide against many agricultural pests, including *Aedes aegypti* mosquito larvae, *Spilosoma obliqua* (hairy caterpillars), *Epilachna varivestis* (Mexican bean beetles), *Acyrtosiphon pisum* (pea aphids), mites and *Drosophila melanogaster* (fruit flies). Myristicin has been shown to be an effective repellent and causes mortality by direct and

systemic exposure. It also displayed a synergistic effect when administered to insects in combination with existing insecticides (Tunali et al., 1999).

Myristicin is a biodynamic compound with multiple roles: insecticide (fights over 400 different types of insects); fungicide (combats the most important diseases in vegetable crops: fusarium, septorios, sclerotinia, vascular drying, brown spot, bacterial fire, fruit drop, flower drop, etc.) and, last but not least, acaricide (destroys over 30 types of mites, still from contact) (Tunali et al., 1999). It is an insecticide and has been shown to enhance the effectiveness of other insecticides, alone and in combination.

The mechanism of action to destroy weeds sensitive to myristicin occurs through: interposition of cell growth and elongation, impairment of respiration, lessening of photosynthesis, lessening of primary cell division, lessening of ribosomal RNA synthesis, metabolism into inactive compounds, lessening of root growth, of protein and lipid synthesis, of mitotic division, lessening of the Hill reaction, lessening of water photolysis in the photosynthesis process, lessening of seed germination, accumulation of the product in the meristematic tissues of underground nodes and buds that they necrotize and dry (Targa) and even incompletely known mechanisms. The cytoplasmic membrane is a frequent target of myristicin, but also can interfere with DNA and protein synthesis, protein folding, and cell wall synthesis (Tunali et al., 1999). Myristicin has also been shown to inhibit cytochrome P450 enzymes, which are responsible for metabolizing a variety of substrates, including hormones and toxins, allowing the accumulation of these substrates. This can compound its own toxicity and/or lead to increased bioavailability of other substances (Tunali et al., 1999). In addition, myristicin can undoubtedly contribute, through the aromatic smell, to the attraction of insects, indirectly favouring pollination. Myristicin is also a plant defense product against some animals (Tunali et al., 1999).

7 | CONCLUSIONS

Myristicin is a complex chemical compound found in a number of plants, for instance, *M. fragrans*, *F. vulgare*, *A. graveolens*, *P. crispum*, *A. nodiflorum*, and *E. spinosa*, and has exhibited strong biological effects, like, immune modulator, antibacterial, antifungal, insecticide, antioxidant, anticancer, antidiabetic, hepatoprotective, and other traditional uses in the treatment of complications related to gastrointestinal tract, respiratory, gynecological disorders and as an antimicrobial as well. However, there are no existing clinical studies that support these pharmacological studies. There is no clinical trial that has tested the effect of isolated myristicin and the only two relevant studies on the effects of *M. fragrans* and these were not statistically significant. The reported cases of toxicity have been due to unusual high intakes of

spices, plants, or seeds, so the most worrying thing is the possibility of obtaining a hallucinogenic drug at a low cost. As a cheap hallucinogenic intoxicant, *M. fragrans* seeds are consumed by college students, adolescents, and prisoners, usually when ethanol or other drugs are not readily available. Further studies are needed to evaluate the mutagenic, genotoxic, or carcinogenic potential of myristicin, and other biological activities previously reported. The plant with most pharmacological effects reported is *M. fragrans* but also, it is the plant with most contraindication and toxically reports. Myristicin acts strongly, directly on the target being a vegetable essence, increasing resistance to harmful environmental factors and epidemics. They retain their antimicrobial action even if they are administered repeatedly to the same person (we do not become resistant to their therapeutic action). If administered correctly following the specialist's recommendation, myristicin is free of side effects. As a limitation, new preclinical studies are needed to support the traditional activities of myristicin-rich plants. Moreover, the pharmacological doses of myristicin and plant extract composition of these studies are need to be clearer. The clinical efficacy of myristicin in diverse diseases is still to be investigated. However, the use of myristicin, myristicin-rich plants, and EOs rich in myristicin are a promissory agent to develop in green industry as ecological remedy in plants protection.

AUTHOR CONTRIBUTIONS

Karina Ramírez-Alarcón: Data curation; investigation; methodology; writing—original draft; writing—review and editing. **Miquel Martorell:** Conceptualization; data curation; investigation; project administration; supervision; validation; visualization; writing—original draft; writing—review and editing. **Eda Sönmez Gürer:** Data curation; investigation; writing—original draft; writing—review and editing. **Ismail Laher:** Data curation; investigation; writing—original draft; writing—review and editing. **Hei-Long Lam:** Data curation; investigation; writing—original draft; writing—review and editing. **Ebtihal Abdalla M. Mohieldin:** Data curation; investigation; writing—original draft; writing—review and editing. **Ali Mahoumd Muddathir:** Conceptualization; investigation; writing—original draft; writing—review and editing. **Muhammad Akram:** Investigation; writing—original draft; writing—review and editing. **Mehwish Iqbal:** Data curation; investigation; writing—original draft; writing—review and editing. **Hamda Shafique:** Conceptualization; investigation; writing—original draft; writing—review and editing. **Gerardo Leyva-Gómez:** Data curation; investigation; writing—original draft; writing—review and editing. **Shabnum Shaheen:** Data curation; investigation; writing—original draft; writing—review and editing. **Manoj Kumar:** Data curation; investigation; methodology; validation; writing—original draft; writing—review and editing. **Javad Sharifi-Rad:** Conceptualization; investigation; project

administration; supervision; validation; visualization; writing—original draft; writing—review and editing. **Ryszard Amarowicz:** Data curation; investigation; writing—original draft; writing—review and editing. **Monica Butnariu:** Investigation; methodology; supervision; validation; writing—original draft; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data supporting this review are from previously reported studies and data sets, which have been cited. The processed data are available from the corresponding author upon request.

ETHICS STATEMENT

None.

ORCID

Karina Ramírez-Alarcón  <https://orcid.org/0000-0003-0560-7154>

Miquel Martorell  <https://orcid.org/0000-0003-3183-7623>

Javad Sharifi-Rad  <http://orcid.org/0000-0002-7301-8151>

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