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Review Article

Chemopreventive Activity Of Myristica Fragrans (Nutmeg) In The Prevention And Treatment Of Cancer – A Systematic Review

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ABSTRACT:

Background: Although nutmeg exerts its potential anti-cancer properties, its mechanism of action remain poorly understood. Conventional therapy can be supported by evidence-based suggestions to include natural compounds in the diet for cancer prevention and treatment, which can also help to lessen the burden of treatment. **Aim:** The study aims to systematically review the chemopreventive properties of nutmeg (Myristica fragrans) and its bioactive compounds in cancer prevention and treatment. **Materials and Method:** Electronic databases including PubMed, Wiley Online Library, Medline, SpringerLink and Elsevier Science Direct were employed for effective searching. Boolean operators fed by keywords such as "Chemoprotective activity," "Cancer prevention," "Nutmeg," "Cancer treatment," and "Myristica Fragrans" were extensively used. The studies on nutmeg-derived compounds, biosynthesis of copper nanoparticles using nutmeg oleoresin, and in vitro and in vivo studies such as KB cells and genetically predisposed mice were included for the systematic review. The biochemical assays considered included MTT assay, FCM, Transwell assay, caspase-3 activity detection, qRT-PCR, and western blot. Quality Assessment was carried out using OHAT tool. **Results:** The results of the study confirm that Myristica fragrans have extremely potent anticancer properties due to their antioxidant, anti-inflammatory, and antiproliferative activities. Nutmeg extracts inhibited growth in cancer cells, induced apoptosis, and lowered cell invasiveness. Tumor-suppressing effects were observed in in-vivo studies conducted on rodents, and molecular analysis was performed to confirm the downregulation of oncogenic markers and activated apoptotic pathways. **Conclusion:** Integration of phytochemicals, in vitro, in vivo, and cohort-based epidemiological strategies suggests that nutmeg and its bioactive compounds may play a role in cancer prevention and treatment.

Keywords: Nutmeg, Cancer, Myristica Fragrans, Phytochemicals, Chemoprevention.

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INTRODUCTION

The Global Cancer Observatory (GLOBOCAN) estimates that there were 19.3 million new cancer cases worldwide in 2020 [1]. Following the United States and China, India ranked third. GLOBOCAN predicts that India will see 2.08 million cancer cases by 2040, marking a 57.5% increase from 2020 [2]. Cancer is still a major source of morbidity and mortality globally, with its prevalence increasing despite advancements [3].There are several reasons that account for the increasing incidence of cancer. Some of the most important include the aging population because the risk of developing cancer increases with age [4]. Lifestyle changes, environmental factors, and genetics are also responsible for this trend.

Nutmeg, a spice from the seeds of the tree Myristicafragrans, has been used for centuries in both culinary and medical traditions. In recent years, scientific studies have started investigating its possible health advantages, including its properties that may contribute to cancer prevention. Nutmeg contains several compounds that may help prevent cancer through antioxidants, anti-

inflammatory agents, and antiproliferative effects. It is rich in phenolic compounds that neutralize free radicals and cause oxidative stress, leading to cellular damage and mutations that may promote cancer. By reducing oxidative stress, nutmeg may lower the risk of cancer [5]. Nutmeg also has anti-inflammatory properties, and chronic inflammation is a known risk factor for cancer. Compounds like Myristicin, elemicin, and eugenol in nutmeg have shown anti-inflammatory effects, which could potentially reduce cancer progression [6]. Some studies suggest that Myristicin may induce apoptosis (programmed cell death) in cancer cells, a crucial mechanism for preventing cancer cell proliferation and inhibiting tumor growth. Nutmeg extracts have been shown to have cytotoxic effects, meaning they can slow the growth and spread of cancer cells, particularly important for preventing metastasis [7]. While myristicin by itself has no cytotoxic effects, it works in concert with chemotherapy medications to reduce cell viability by 50% [8]. However, nutmeg has to be consumed in mminimum quantity, as excessive intake can cause toxicity and adverse effects due to compounds like Myristicin [9].

Myristica fragrans has been found to offer various health benefits, such as pain relief, aiding digestion, enhancing cognitive function, detoxifying the body, promoting skin health, treating oral conditions, reducing insomnia, boosting the immune system, preventing leukemia, and improving blood circulation [10]. Myristica fragrans is a native, evergreen Maluku Island Indonesia tree. It has a seed kernel that can be used globally in Indian indigenous medicine to remedy different conditions [11]. Several studies try to summarise and evaluate the pharmacology potential of the Myristica fragrans extract, both chemical and aqueous. However, the pharmacological potential of nutmeg essential oil has not been fully explored. This study aims to comprehensively review the chemical composition and therapeutic potential of Myristica fragrans essential oil (MFEO).

MATERIALS AND METHODS

Information Sources

According to PRISMA guidelines, the following electronic databases were searched PubMed, Wiley Online Library, Medline, SpringerLink and Elsevier Science Direct.

Search Category

Boolean operators were used in the search strategies for the following keyword combination "Chemoprotective activity," "Cancer prevention," "Nutmeg," "Cancer treatment," and "Myristica Fragrans"

Eligibility Criteria

The study included biosynthesis of copper nanoparticles using nutmeg oleoresin, KB cell lines, and nutmeg extract used in mice with a genetic predisposition to colorectal cancer. The study also included the articles that maintained standardized biochemical assays such as MTT, FCM, Transwell caspase-3 activity detection, qRT-PCR, and western blot. Only the original studies published in English were included. Those studies that had correct statistical treatment and standardized assessment methods were also considered. The study excluded abstract only, irrelevant studies, and duplicate publications.

Methodology

This study utilized a combination of cell lines and in vivo studies to investigate the pharmacological and anticancer properties of Myristica fragrans (nutmeg). The data extracted from all the studies included the citation (author/year), the location of the study, the number and type of samples collected, the intervention implemented, the techniques and methods utilized to measure, findings and inference. Quality Assessment was carried out using Office of Health Assessment and Translation (OHAT) Scale [12].

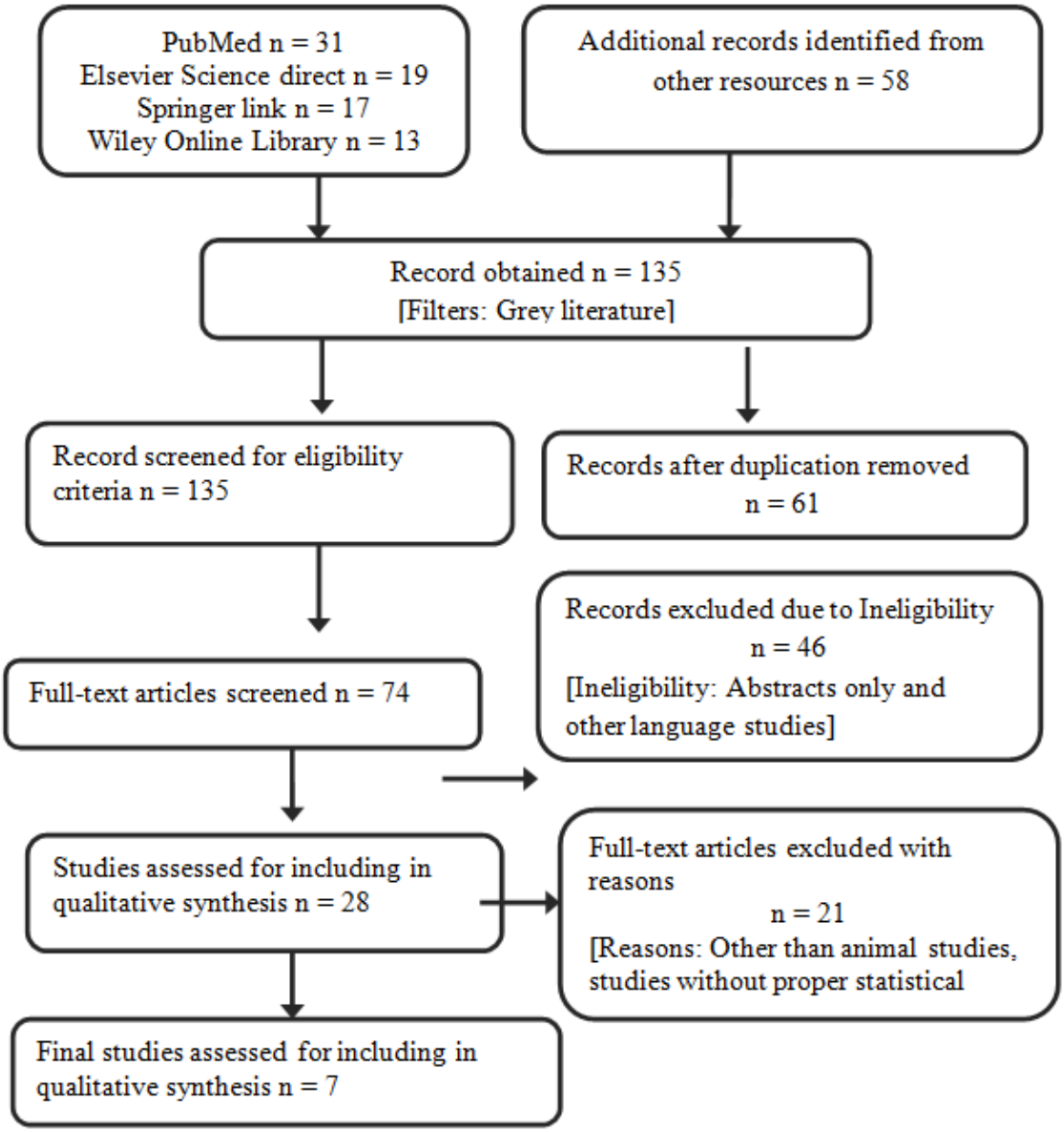

Figure 1: A flowchart depicting the steps of the systematic review in accordance to PRISMA Guidelines

RESULTS

Original articles from the beginning to the present have been compiled for this study. Out of the 138 total papers, five full-text articles underwent independent evaluation. Following the evaluation of eligibility using the inclusion and exclusion criteria, the removal of duplicate articles and those with basic abstracts, and other processes, five papers that satisfied the inclusion criteria were included to the study. The flowchart below provides a summary of the procedures followed in accordance with PRISMA standards in the included studies.

Table 1: Characteristics of all the studies included

First author	Year of Study	Place of study	Type of Study	Sample	Intervention	Methods of measurement
Trisha Sasikumar et al [13]	2021	India	Randomized Control Trial	Ten nauplii (freshly brine shrimp larvae) were transferre	5 wells were loaded with 2ml of nutmeg oleoresin copper nanoparticles in concentrations 5µL, 10 µL, 20µL, 40µL,	UV- Visible Spectroscopy The formula for calculating inhibition: % Inhibition = Absorbance of control - Absorbance of sample x 100 / Absorbance of control

				d into 6 elisa wells containing 2g of non-iodized salt dissolved in 200 mL of distilled water.	80µL to which 50% methanol along with 0.1mm of DPPH solution were also added. 1 well – Control without nanoparticles. Wells were then put for incubation for 30 minutes in a dark place at room temperature.	
Gayathri. R et al [14]	2018	India	Randomized Control Trial	42 specific and pathogen-free Wistar strain rats Divided equally into 7 groups.	Group I: Control Group II: Carcinoma control group 4-nitroquinoline-1-oxide(4NQO) at 30ppm conc. In drinking water for more than 14 weeks without any treatment Group III, IV, V: Treatment groups Single-dose mace extract was given to 3 test groups at the doses of 100, 250, and 500mg per kg body weight orally for 14 weeks Group VI: 5-flourouracil (5FU) at a conc. Of 50mg/kg body weight orally as a single dose. Group VII: Drug control 250mg/kg body weight mace extract as a single dose for 14 weeks	Tumor growth was measured using the formula by Carlsson: $V=ab^2/2$ a = longest diameter b = shortest diameter of the tumor. Histological Examination using hematoxylin and eosin stain under light electric microscope
Gayathri R et al [15]	2018	Tamil Nadu, India	In vitro studies	Human oral epidermal carcinoma KB cell lines	KB cells were treated with concentrations of 25,50, 75, 100, and 125µg/mL of dried mace powder extract. Control cells were treated with 0.1% DMSO.	Micro-culture tetrazolium assay (MTT). Cellular morphology was studied under a phase contrast light microscope after 24 and 48 hours. Annexin/ PI assay was evaluated using Becton Dickinson FACScan instrument Western blot analysis RT-PCR
Fei Li et al [16]	2015	United States	Randomized Control Trial	20 four-week-old male $Apc^{min/+}$	Experiment: 5 $Apc^{min/+}$ and 5 wild-type mice treated with AIN-	Ultraperformance Liquid Chromatography with electrospray ionization quadrupole time-of-flight mass spectrometry (UPLC-ESI-

				and wild-type mice were divided into 2 groups.	93G with 2.5% CO_2 Nutmeg extract for 4 months. Control: 5 $Apc^{min/+}$ and 5 wild-type mice treated with vehicle diet (AIN-93G) for 4 months.	QTOFMS) and ion mass signals. Serum biomarkers Culture of Primary Hepatocytes using quantitative real-time PCR (qRT-PCR) Gene Expression Analysis Serum Chemistry
Hailan Bao et al [17]	2021	China	In-vitro studies	Human hepatic carcinoma cell lines (HCC) line Huh7 and HCCLM 3	Human cell lines were treated with Myristicin at concentrations of 0.5Mm, 1mM, and 5mM for 24, 48, and 72 hours. Control cell lines were not treated.	MTT assay Annexin V-FITC and PI fluorescence were assessed by BD FACSCalibur flow cytometer qRT-PCR assay Western Blot Assay
Phuong Thien Thuong et al [18]	2013	Vietnam	In-vitro studies	Swiss mice of 5-6 weeks of age weighing 20-22g Eight Human Cancer Cell lines H1299, H358, H460 Hela, HepG2, KPL4, MCF7, RD, and MDCK cells	Group 1: Water treated Group 2: PBS treated – 0.2mL Group 3: Mercaptopurine (MP) – 0.96mg/kg/day daily for 24 days Group 4: Dihydroguaiaretic acid (DHGA)/Macelignan/Fragransin A_2/ Nectandrin suspended in PBS solution at a concentration of 10, 5 and 2mg/kg/day	Tumor volume, survival rate and body weights was used to evaluate the antitumor activity among Swiss mice. IC_{50} value was used to estimate the cytotoxic activity against human cancer cells.
Rahul Checker et al [19]	2008	Mumbai, India	Systematic review	Spleen cells were obtained from 6-8 week-old inbred Swiss male mice weighing 20-25g	Experiment group: Polyclonal T cell mitogen concanavalin A was treated with Mace Lignans (ML) at doses 100µg/ml to 500 µg/ml added Controls: No treatment	Analysis of ML components by Gas Chromatography-Mass Spectrometry (GC-MS) Cell proliferation was quantified by dye dilution in a Partec PAS III flow cytometer using Carboxy fluorescein diacetate succinimidyl ester (CFSE) Fluorescence. Measurements of cytokine secretions such as IL-2, IL-4, and IFN-γ using ELISA test. Estimation of mRNA expression by RT-PCR Radiation-induced ROS – Spectrofluorimeter Radiation-induced apoptosis using DNA ladder assay

Table 1 shows the characteristics of the each study including author name, year, place of study, type of samples, intervention and methods of measurement which were written by Trisha Sasikumar et al., Gayathri R et al., Fei Li et al., Hailan Bao et al., Phuong Thien Thuong et al., and Rahul Checker et al.

Table 2: Results and inference of the included interventional studies showing the effectiveness of nutmeg in the cancer prevention and treatment

Study	Results	Inference
Trisha Sasikumar et al., 2021 [13]	The results have shown that the percentage of live nauplii was 90% at 5µL and was only 50% at the highest concentration of 80µL. This proves that the cytotoxicity increased with the concentration of the nutmeg oleoresin-mediated copper nanoparticles. The free radical scavenging activity was 18% at 10µL concentration, and the highest value was 84% at 50µL. The percentage of inhibition at 10µL was 64%, at 20µL was 68%, at 30µL was 84%, at 40µL was 86% and 50µLwas 96%.	Nutmeg oleoresin-mediated copper nanoparticle extract has shown high cytotoxicity and good free radical scavenging with increased concentration. It also showed good antioxidant activity with the DPPH assay.
Gayathri. R et al., 2018 [14]	Group II 4NQO alone caused group exhibits the maximum rate of tumor occurrence and tumor number. All other different doses of mace-treated groups showed a decreased level of tumor incidence and tumor multiplicity ($p<0.05$).	These experimental results unveil that MAE is effective in curing oral cancer.
Gayathri R et al., 2018 [15]	Cell viability of mace extract for 25, 50, 75, 100, and 125 µg/mL concentrations were found to be 41.40, 46.99, 51.52, 55.61, and 58.51%, respectively, after 24 hours of treatment. Half maximal inhibitory concentration of mace extract was at the concentration of 75 µg/mL.	Mace extract acts as a broad-spectrum anticancer agent in human cancer cells by inhibiting the cell cycle and subsequently inducing apoptosis through the intrinsic pathway. Moreover, the mace extract induces less cytotoxicity in normal cells and is selective in inducing apoptosis between cancer and normal cells.
Fei Li et al., 2015 [16]	Colon tumorigenesis decreased by 65% in nutmeg-treated $Apc^{min/+}$ mice compared to vehicle-treated $Apc^{min/+}$ mice, whose tumor initiation was reduced only by 37% ($p<0.05$). Compared to $Apc^{min/+}$ mice, wild-type mice show significantly lower levels of BUN and elevated levels of albumin and total protein. Cytochrome P450 4A10 was significantly reduced by 69% in $Apc^{min/+}$ mice compared to a 55% reduction in wild-type mice ($p<0.05$).	The study demonstrated that nutmeg extract prevents the mice from undergoing colon tumorigenesis via modulating gut microbial metabolism and improving dysregulated lipid metabolism.
Hailan Bao et al., 2021 [17]	Western blot assay indicated that compared to the control group. Myristicin increased E-cadherin expression and decreased N-cadherin expression in HCC cells. qRT-PCR E-cadherin was significantly up-regulated, and N-cadherin was down-regulated in HCC cells compared to the control group. An increase in myristicin concentration inhibited the ability of Huh-7 cells compared to the control group.	Myristicin suppressed cell proliferation and triggered apoptosis in Huh-7 and HCCLM3 cells. Myristicin produces an effective therapeutic action for hepatic carcinoma by repressing the PI3K/Akt/mTOR pathway.
Phuong Thien Thuong et al., 2014 [18]	Macelignan exhibited cytotoxicity activity with IC_{50} values of 10.2 and 25.1µM against H358 and Hela cancer cells, respectively. Fragrance A_2 showed weak inhibitory activity, and nectarine B showed weak inhibitory activity. The tumor volume was reduced by 7.4% (2mg/kg), 49.5% (5mg/kg), and 71.9% (10mg/kg) compared to water treated 7.7 % (2 mg/kg), 51.3 % (5 m/kg), and 74.6 % (10 mg/kg). DHGA exhibited the most potent cytotoxicity and antitumor effect on Sarcoma 180 tumor-bearing mice ($p < 0.05$).	DHGA demonstrated greater antitumor activity when administered orally to the allogeneic tumor-bearing mice, tumor size was significantly reduced, and the life spans of the tumor-bearing mice were elongated.
Rahul Checker et al., 2008	ML-treated cells failed to enter the first cell division cycle, showing inhibition of T-cell proliferation and increased apoptosis compared to control cells. Inhibition	ML exhibited antioxidant, radioprotective, and immunomodulatory properties by significantly acting against radiation-

[19]	of Con A and down-regulation of IL-2, IL-4, IFN-γ in a dose-dependent manner was found significantly in the presence of ML.	induced intracellular ROS production, radiation-induced DNA damage, and downregulation of IL-2, IL-4, and IFN-γ

Table: 2 shows the results and inference of all the included studies

Table 3: Quality Assessment of all the in-vivo studies

Author name	Randomization	Allocation Concealment	Comparison group	Confounding	Experimental conditions	Blinding	Complete outcome data	Exposure Characterization	Outcome Assessment	Outcome Reporting	No other threats
Trisha Sasikumar et al., 2021[13]											
Gayathri R et al., 2018 [14]											
Fei Li et al., 2015 [16]											
Phuong Thien Thuong et al., 2013[18]											

Definitely low risk of bias

Probably low risk of bias

Probably a high risk of bias

Definitely High risk of bias

Table 4: Quality Assessment of all the cell lines studies

Author name	Sample Selection & Experimental Setup	Reagents & Cells	Sample size	Allocation to groups	Allocation concealment	Blinded Assessment of Outcome	Attrition
Gayathri. R et al., 2018 [15]	Yes	Yes	No	Yes	No	No	Unclear
Hailan Bao et al., 2021 [17]	Yes	Yes	No	Yes	Unclear	Unclear	No
Phuong Thien Thuong et al., 2013 [18]	Yes	Yes	Yes	Unclear	No	Unclear	No
Rahul Checker et al., 2008 [19]	Yes	Yes	Yes	Yes	Yes	No	No

Table 3 and 4 shows the risk of bias assessment of all the included studies according to the OHAT [Office of Health Assessment and Translation] tools [12]

DISCUSSION

This systematic review aims to understand the chemical composition, pharmacological properties and therapeutic potential of Myristica fragrans essential oil (MFEO). Natural products continue to remain an essential source of new anticancer drugs. Several studies have proven the anti-oxidant, anti-inflammatory and anti-cancenrous properties of many natural compounds including gingerol, fermented rice, olive oil, coconut oil and citrus peel extract. Evidence-based recommendations to incorporate natural compounds in the diet for cancer prevention and treatment can assist conventional therapy and reduce treatment burden. Anjum et al., (2024) study proved that by altering the gut microbial habitat, consumption of Aspergillus oryzae-fermented brown rice and fermented brown rice drinks was discovered to have a protective impact on the digestive system and accessory digestive organs. Such an environment has a preventive effect against carcinogenic variations

that might affect the digestive system and its accessory organs [20]. Noor JJ et al., (2024) study showed the modulatory effects of gingerol on cancer cell proliferation. The study also highlights that gingerol can both activate and decrease several signal pathways that are involved in the initation of cancer [21].

Myristica fragrans has been seen to possess several health benefits that range from acting against pain to sedating indigestion, improving cognitive capability, detoxifying the body, improving skin well-being, remedying oral affections, dispelling insomnia, enhancing immune capacity, and restraining leukemia, in addition to normalizing blood flow [22] Nutmeg is also rich in anti-inflammatory compounds called monoterpenes. As a significant class of plant constituents, Lignans exhibit diverse biological activities, including antitumor, anti-mitotic, antiviral, and anti-atherosclerotic activities. Lignan antitumor activity can also be responsible for cytotoxic activity in M. fragrans Houtt [13].

This is the first attempt to compile data on the oil yield, composition, and biological activities of MFEO. The essential oils of its leaf, mace, kernel, and seed are used globally in Ayurvedic medicine and as fragrances [23]. The primary chemical constituents of MFEO include sabinene, eugenol, Myristicin, caryophyllene, β-myrcene, and α-pinene. Clinical and experimental studies confirm the antioxidant, antimicrobial, anti-inflammatory, anticancer, antimalarial, anticonvulsant, hepatoprotective, antiparasitic, insecticidal, and nematocidal activities of MFEO [24].

Several studies have shown that some naturally occurring medicinal plants suppress the growth of many cancers, methanol extract of M. fragrans Houtt bark suppressed T Leukemia cell line growth through induction of apoptosis and induced SIRT1m RNA [14, 16] The present study showed Myristicin suppressed cell proliferation and induced apoptosis in Huh-7 and HCCLM3 cells in hepatic carcinoma [17]. The development of hepatic carcinoma has seriously affected people's living standards. In recent years, although the medical level has been continuously improved, hepatic carcinoma has a high mortality rate due to the difficulty of early diagnosis of hepatic carcinoma patients, fewer therapeutic targets, and poor postoperative recovery [18].

Nutmeg is a rich source of antioxidants, including terpene α/β-pinene and neolignandehydrodiisoeugenol. Antioxidant supplements help lower the incidence of different carcinomas, especially colon cancer. The study demonstrated that colorectal cancer is closely linked to oxidative stress so that antioxidants could be beneficial for both the prevention and treatment of this cancer [25]. In India, nutmeg mace is used traditionally as a medicine and a food additive. Water-soluble lignans from Nutmeg mace showed a selective immune inhibitory activity [26]. According to Phuong Thien Thuong et al., a study in 2013 showed that DHGA, a major component of Vietnamese M. fragrans, together with the other three lignans—malignant, fragrans A2, and nectarine B—had cytotoxic effects on several cancer cell lines. To assess the anticancer potential of Vietnamese nutmeg, the isolates were tested in vitro cytotoxicity against various cancer cell lines, H1299, H358, H460, Hela, HepG2, KPl4, MCF7, and RD [15,19]. Sedative and toxic properties, nutmeg consumption in the range of 20-80g powder was not fatal or life-threatening. Chemical characterization of nutmeg extracts identified more than 50 compounds, such as flavonoids, alkaloids, and polyphenols, that are antioxidant in nature and have potential as phytochemicals [21]. Future research is needed to understand further the mechanisms of action of MFEO and its bioactive constituents.

CONCLUSION

This systematic review assesses the long-term health implications of nutmeg consumption and, its anticancer potential. By integrating biological assays, oxidative stress analysis, and cancer incidence tracking, this research enhances the understanding of nutmeg as a preventive and therapeutic agent in oncology. Further clinical trials in humans should be conducted to substantiate nutmeg's efficacy and therapeutic potential in oncology.

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