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Antiparkinsonian effect of Nutmeg ethanolic extract (*Myristica fragrans* Houtt.) in haloperidol-induced Mice

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ABSTRACT

Parkinson's disease is a persistent neurological disorder that could potentially arise from the neuronal degeneration responsible for dopaminergic signals in the brain. Extrapyramidal syndrome, which is distinguished by motor dysfunctions including tremors, rigidity, and postural instability, is the defining feature of this disease. One of the contributing factors to the development of Parkinson's disease is drug-induced parkinsonism, which is precipitated by the administration of antipsychotic medications. The bioactive compounds myristicin, eugenol, and flavonoids found in nutmeg (*Myristica fragrans* Houtt.) have the potential to be utilized in the treatment of Parkinson's disease. The objective of this research endeavor was to ascertain the antiparkinsonian effect of ethanol extract of nutmeg on rodents with Parkinson's disease induced by haloperidol. A seven-day course of induction with haloperidol 1 mg/kg was administered intraperitoneally. Behavioral evaluations were conducted utilizing the cylinder and rotarod tests. Cylinder score and latency time were utilized to evaluate extrapyramidal symptoms. The therapeutic approach involved the oral administration of ethanol extract of nutmeg in varying concentrations (5, 10, and 20 mg/kg) over a period of seven days. The findings indicated that the administration of nutmeg at a rate of 20 mg/kg resulted in noteworthy enhancements ($P < 0.05$) in the motor function of animal models induced by haloperidol. Furthermore, this effect was comparable to that of the standard drug Pramipexole.

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Keywords: *Myristica fragrans*, antiparkinsonian, cylinder test, rotarod test

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INTRODUCTION

Parkinson's is a progressive neurodegenerative disease that manifests through both motor and non-motor symptoms (Hayes, 2019; Malaiwong et al., 2019). The prevalence of Parkinson's disease increases with age, affecting around 1–3% of sufferers over 60 globally (Ball et al., 2019). One of the causes of Parkinson's is the use of antipsychotic drugs (Drug-Induced Parkinsonism), which arise due to extrapyramidal side effects through dopamine receptor blockade (Grubor et al., 2020). Clinically, this condition is characterized by akinesia, tremors, bradykinesia, muscle rigidity, and postural instability that appear within days or weeks after the use of antipsychotic drugs (Erjavec et al., 2022).

Drug-induced Parkinson's (DIP) is the second-most basic etiology of parkinsonism in the elderly (Kabra et al., 2020) and is the most common type of Parkinsonism in the productive age group, with the youngest being 39 years old. DIP occurs in 11 of 15 cases of Parkinsonism (Jeong et al., 2021). Haloperidol is a typical antipsychotic that has stronger extrapyramidal effects than atypical antipsychotics. The increase in Parkinsonism due to extrapyramidal effects can trigger an increase in the prevalence of Parkinson's disease in the productive age group in Indonesia.

In psychiatric treatment, antimuscarinic antiparkinsonian medicines are commonly used to alleviate extrapyramidal motor symptoms caused by neuroleptic antipsychotic medications. However, when used in conjunction with antipsychotics, antimuscarinic antiparkinsonian agents have been reported to antagonize the therapeutic effects of neuroleptics; there have also been several reports of antimuscarinic antiparkinsonian agents actually causing various psychotic syndromes, elevated mood and stimulant effects, stereotypy, dyskinesia, and behavioral agitation. Extensive data has demonstrated that antimuscarinic antiparkinsonian medicines have the additional effect of acting as strong, indirect dopamine-agonists Vaiman et al., 2022. Antiparkinsonian alternatives are needed for safe antipsychotic adjunct therapy for patients with psychotic disorders. Many naturally derived medicines are now being researched for parkinsonism.

Indonesia has a biodiversity of plants that have the potential to be used as medicinal plants, one of which is nutmeg. Nutmeg (*Myristica fragrans* Houtt.) contains secondary metabolites of alkaloids, saponins, tannins, flavonoids, terpenoids, and essential oils (Noviyandri et al., 2021). Tannic acid (tannin) and myristicin (essential oil) are secondary metabolites that possess the potential to exhibit antiparkinsonian actions. Kawano et al. (2020) demonstrated the mechanism by which tannic acid functions as a dopamine agonist in mice with experimentally induced colitis. Prior experiments conducted on animals utilizing the Forced Swim Test (FST) demonstrated that the ethanol extract derived from nutmeg seeds effectively diminished anxiety levels. The observed impact is linked to the mechanism of inhibiting the Mono Amine Oxidase (MAO) enzyme, with the chemical believed to be responsible being Myristisin (Hasanusi et al., 2020). The ethanol extract of nutmeg seeds has been found to contain 11.17% of the myristicin chemical, as reported by Ghorbanian et al. in (2019). In addition, nutmeg has been scientifically demonstrated to elevate serotonin (5-HT), norepinephrine, and dopamine levels in the hippocampus (Plaingam et al., 2017) and myristicin (essential oil) through inhibition of the monoamine oxidase enzyme (Hasanusi et al., 2020). This research was to determine the antiparkinsonian effect of an ethanol extract of Myristica fragrans on haloperidol-induced mice using the rotarod and cylinder tests.

MATERIALS AND METHOD

Materials

Drugs and chemical

Haloperidol injection (Haldol®), pramipexol tablets (Sifrol®), and other chemicals used in this study were procured from Sigma-Aldrich.

Methods

Extract preparation

Nutmeg (*Myristica fragrans* Houtt.) was purchased from Ungaran, Semarang Regency, Central Java. A fine powder is obtained by grinding dried nutmeg. The powder was extracted using the maceration method, and the sample was soaked in 96% ethanol solvent for 3 x 24 hours at room temperature. The ethanol extract of nutmeg (EEN) is filtered using Whatman filter paper and then concentrated using a rotary evaporator at a temperature of 40°C.

Phytochemical screening

The prepared nutmeg ethanol extract was put to different qualitative tests according to the color assay procedure to evaluate the presence of phytochemical components such as saponins, flavonoids, alkaloids, tannins, and saponines.

Animals

The animals used were mice of the Balb/C strain obtained from the animal experimental laboratory of the Semarang Yayasan Pharmacy College of Pharmaceutical Sciences, which weighed 20–40 g. All animals were kept in a room heated to 25–30 degrees Celsius and kept on a 12/12 hour light-dark cycle. The animals were acclimatized for 7 days, had free access to water, and were not overfed in any way besides the regular fare. The procedures and methods in this research have been approved by the ethics committee of the Semarang Yayasan Pharmacy College of Pharmacy with number 375/YP-NA/KEPK/STIFAR/EC/ V/2022.

Experimental design

We picked six groups of mice at random. Group 1 was a normal group that got CMC-Na solution instead; Group 2 was a negative control group that got haloperidol intraperitoneally and CMC-Na solution (as a vehicle) orally; Group 3 was given intraperitoneal haloperidol and 0.5 mg/kg pramipexole solution orally as a positive control group; and finally, Groups 4, 5, and 6 were given haloperidol and ethanol extract of nutmeg, respectively 5, 10, and 20 mg/kg orally. Mice were induced by administering 1 mg/kg haloperidol intraperitoneally every day from day 1 to day 7. The induction dose and duration are determined according to the methodology described by Saeed (2017). During induction, extrapyramidal effects were observed 45 minutes after the injection of haloperidol. Nutmeg ethanol extract and pramipexole were intentionally given every day for a week from day 8 to day 15. The changes in motor condition were determined on day 15 with rotarod and cylinder scores.

Motor coordination test

The test animal is placed on a rotarod device with a maximum observation time of 300 seconds and a speed of 10 rpm for the rotarod test. Before beginning therapy, each mouse was trained to adjust to the rotarod equipment. For the three experiments, the average time (fall latency) was obtained.

Locomotor activity test

The cylinder test is carried out in an acrylic tube of a certain size. Observations were carried out for 3 minutes in a dark and quiet environment. The score in the cylinder test analysis is obtained from the ability of the test animal to lift its two front arms, touch the cylinder wall, and land, which is observed via video recording at a speed of 0.5x slower.

Data Analysis

Standardized mean values were reported with a margin of error. The data was analyzed using one-way ANOVA and LSD post hoc test.

RESULT AND DISCUSSION

Bioactive compounds from nutmeg were extracted by maceration in 96% v/v ethanol solvent and produced a yield of 29.98%. The results of phytochemical screening and TLC from ethanol extract of nutmeg (EEN) showed the presence of several bioactive contents such as flavonoids, triterpenoids and essential oils (Table 1).

Table 1. Phytochemical screening of ethanol extract of Nutmeg (*Myristica fragrans* Houtt.)

Phytochemical	Observation
Flavonoids	+
Tannin	-
Saponin	-
Triterpenoid	+
Steroid	-
Essential oil	+

(+) present; (-) absent

Phytochemical tests reveal that nutmeg extract includes flavonoid chemicals, as evidenced by the production of a red colour in the amyl alcohol layer. According to Harborne (1984), the Liebermann-Bucchard method is used to determine the terpenoid or steroid content of plants, with terpenoids appearing orange and steroids appearing blue or purple. The reaction of nutmeg extract with the Liebermann-Bucchard reaction yielded a purple colour, indicating the presence of triterpenoid chemicals. Thin-layer chromatography tests of nutmeg extract to detect essential oils revealed the presence of red stains on silica plates. These findings support the presence of essential oils in nutmeg extract. The result of phythochemichal screening of EEN allign with previous study by Sultan et al. (2023) which also verified the existence of essential oil, flavonoids, and triterpenoids in nutmeg. Geographic region and environmental factors play an imperative role in forming the phytochemical composition (Vignesh et al., 2024).

The rotarod and cylinder tests were used to measure the antiparkinsonian effect by watching how the test animal's motor skills changed. Impaired motor function is the main symptom of Parkinson's disease. The rotarod test is used to measure motor performance, including motor coordination, in animal models of Parkinson's disease (Leem et al., 2022). The assessment of latency time obtained from the lenght of time the animal model persist on the rotarod device in rotating condition until it falls down.

The results of observing the latency time (Figure 1) show that haloperidol induction causes a decrease ($p < 0.05$) in the motor coordination of mice. Muscle stiffness in the limbs is the most common sign in Parkinson-like syndrome, which makes it hard for the animal to move its body. Muscle weakness in the legs, tremors, and muscle stiffness are associated with neurodegeneration and basal ganglia dysfunction (Skinner et al., 2019; Saleem et al., 2021). The selective loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) as well as oxidative stress due to α-synuclein (Lewy body) aggregation and mitochondrial dysfunction (Harris et al., 2020; Saleem et al., 2021) cause neurodegeneration in Parkinson's disease. Mice with healthy motor conditions were able to survive for a long time beyond the testing time. On the other hand, mice with decreased motor conditions will fall faster than the specified time (Yulianita, 2019).

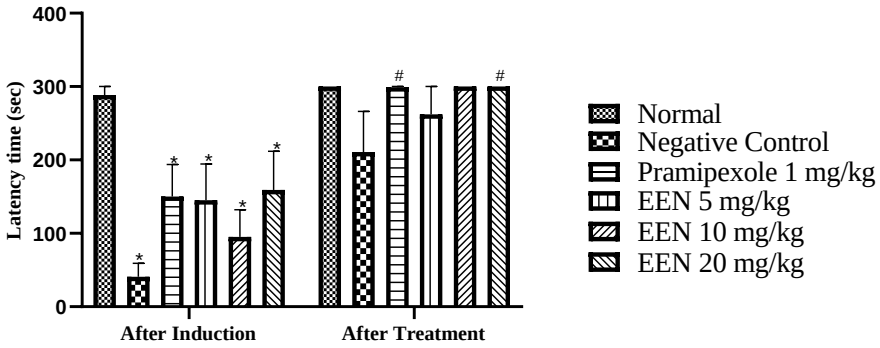

Figure 1. Latency time of haloperidol-induced parkinson's mice after administering ethanol extract of Nutmeg (*Myristica fragrans Houtt.*). *The values are mean ± SEM; n = 5; *p < 0.05 when compared with the normal group; # p < 0.05 when compared with the negative control group*

Haloperidol causes dopamine to be metabolized to 3,4-dihydrophenylacetic acid by the oxidation of the enzyme monoamine oxidase (MAO) and hydrogen peroxide. Increasing the amount of hydrogen peroxide causes oxidative stress and triggers extrapyramidal side effects (Saleem et al., 2021). Extrapyramidal symptoms include decreased motor conditions such as stationary tremor, bradykinesia, and postural instability (Hayes, 2019). Twenty to forty percent of people who take antipsychotics also have Parkinson's signs. These symptoms often start slowly, and most of the time, they start within a few days of starting antipsychotics. The intensity of symptoms can vary. They may get better on their own or get worse over time (D'Souza & Hooten, 2023).

In Figure 1, a slight increase in the latency time on negative control indicates the possibility of improvement, even if the statistics do not support it. After 7 days of therapy, it was revealed that only EEN 20 mg/kg resulted in a substantial increase ($p<0.05$) in latency time when compared to the negative control group.

Although Parkinson's disease is frequently associated with motor symptoms such as stiffness and poor balance, the early signs are often sensory, such as a loss of touch and scent. Sensory impairment can eventually lead to motor abnormalities via the sensorimotor integration process (Ketzef, 2017). The cylinder test is used to assess the antiparkinsonian effect through behavioral changes, specifically the tendency of the rodent's forelimbs to be used (Magno et al., 2019; Jiang et al., 2019) by placing the test animal in a glass cylinder and counting the number of times it uses both forelimbs and touches the cylinder walls. Sensorimotor disorders are linked to these behavioral abnormalities.

Pramipexole is a class of first-line drugs for Parkinson's disease therapy. This drug has mechanism as partial dopamine receptor agonist that acts on D2 receptors with preferential affinity for D3 receptors. As a partial agonist, pramipexole can unblock D2 receptors in the substantia nigra and striatum that have been blocked too much. This is why this drug is also used to treat extrapyramidal side effects (Weng et al., 2019).

The presence of spesific bioactive compound in nutmeg can offer assistance in managing Parkinson’s disease. Flavonoid, triterpenes and essential oil as neuprotective agents, protect the dopaminergic neurons by reducing oxidative stress and neuroinflammation generated by the disease (Devi et al., 2021), against dopaminergic cell death and ameliorating the behavioural impairement in Parkinson’s disease animal model (Spisni et al., 2023). This activity is attributed to the inhibition of monoamine oxidase (MAO) and the regulation of neurotransmitters, including dopamine, norepinephrine (NE), and serotonin (5-HT), inside the substantia nigra (Khazdair et al., 2020).

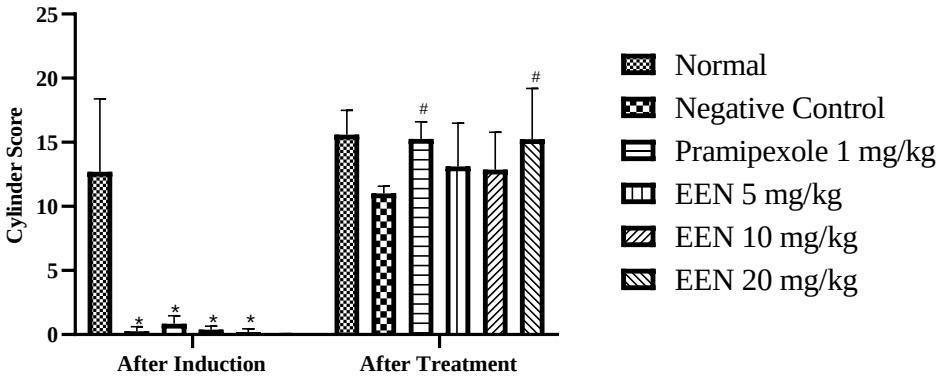

Figure 2. Cylinder score of haloperidol-induced parkinson's mice after administering ethanol extract of Nutmeg *(Myristica fragrans Houtt.)*. *The values are mean ± SEM; n = 5; *p < 0.05 when compared with the normal group; # p < 0.05 when compared with the negative control group*

In this current study, the antiparkinsonian effect of nutmeg was proven, and it is suspected that several of its bioactive compounds play a role in providing the effect through various mechanisms. Further research is needed to determine more specific bioactive compounds that provide antiparkinsonian effects in isolated form, accompanied by brain histopathology and measurements of dopamine neurotransmitter levels in brain samples from test animals.

CONCLUSION

The administration of a 20 mg/kg dose of ethanol extract derived from nutmeg (*Myristica fragrans* Houtt.) has been found to ameliorate the motor condition of mice with Parkinson's disease induced by haloperidol. This improvement is evidenced by an increase in both latency time and cylinder score.

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REFERENCES

Ay, M., Luo, J., Langley, M., Jin, H., Anantharam, V., Kanthasamy, A., & Kanthasamy, A. G. (2017). Molecular mechanisms underlying protective effects of quercetin against mitochondrial dysfunction and progressive dopaminergic neurodegeneration in cell culture and MitoPark transgenic mouse models of Parkinson's Disease. *Journal of neurochemistry*, *141*(5), 766–782. https://doi.org/10.1111/jnc.14033

Ball, N., Teo, W. P., Chandra, S., & Chapman, J. (2019). Parkinson's disease and the environment. *Frontiers in neurology*, *10*, 218. https://doi.org/10.3389/fneur.2019.00218

Erjavec, G. N., Grubor, M., Zivkovic,M., Bozina, M., Sagud, M., Perkovic, M.N., et al. (2022). SLC6A3, HTR2C and HTR6 gene polymorphisms and the risk of haloperidol-induced parkinsonism, *Biomedicines*, 10(3237), 1-16 https://doi.org/10.3390/biomedicines10123237

Devi, S., Kumar, V., Singh, S. K., Dubey, A. K., & Kim, J. J. (2021). Flavonoids: potential candidates for the treatment of neurodegenerative disorders. *Biomedicines*, 9(2), 99. https://doi.org/10.3390/biomedicines9020099

D'Souza R.S, Hooten W.M. Extrapyramidal Symptoms. [Updated 2023 Jul 31]. In: StatPearls

[Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534115/

Essam, R. M., & Kandil, E. A. (2023). p-CREB and p-DARPP-32 orchestrating the modulatory role of cAMP/PKA signaling pathway enhanced by Roflumilast in rotenone-induced Parkinson's disease in rats. *Chemico-biological interactions*, *372*, 110366. https://doi.org/10.1016/j.cbi.2023.110366

Ghorbanian, D., Ghasemi-Kasman, M., Hashemian, M., Gorji, E., Gol, M., Feizi, F., Kazemi, S., Ashrafpour, M., & Moghadamnia, A. A. (2019). *Myristica Fragrans* Houtt Extract Attenuates Neuronal Loss and Glial Activation in Pentylenetetrazol-Induced Kindling Model. *Iranian journal of pharmaceutical research : IJPR*, *18*(2), 812–825. https://doi.org/10.22037/ijpr.2019.1100670

Grubor, M., Zivkovic, M., Sagud, M., Nikolac Perkovic, M., Mihaljevic-Peles, A., Pivac, N., Muck-Seler, D., & Svob Strac, D. (2020). *HTR1A, HTR1B, HTR2A, HTR2C* and *HTR6* gene polymorphisms and extrapyramidal side effects in haloperidol-treated patients with Schizophrenia. *International journal of molecular sciences*, *21*(7), 2345. https://doi.org/10.3390/ijms21072345

Hanifah, A. & Tristantini, D. (2019). Total phenolic, UPLC-QTOF-MS analysis and antidepressant-like effect in the mice forced swim test of Jamu Neuropathic Pain Reducer. *AIP Conference Proceedings*: *Biomedical Engineering's Recent Progress in Biomaterials, Drugs Development, Health, and Medical Devices*, 2193 (1). https://doi.org/10.1063/1.5139347

Harris, J. P., Burrell, J. C., Struzyna, L. A., Chen, H. I., Serruya, M. D., Wolf, J. A., Duda, J. E., & Cullen, D. K. (2020). Emerging regenerative medicine and tissue engineering strategies for Parkinson's disease. *NPJ Parkinson's disease*, *6*, 4. https://doi.org/10.1038/s41531-019-0105-5

Harbone, J. B. (1984). *Phytochemical Methods: A Guide to Modern Techniques of Plant Analysis.* Second ed. London New York Chapman and Hall.

Hasanusi I. N., Silalahi P. Y., Bension J. B., Huwae L. B., Angkejaya O. W., & Taihuttu Y. M. J. (2020). Effects of ethanol extract of Nutmeg seeds (Myristica fragrans Houtt) on Mice anxiety. *Pattimura Medical Review*, *2*(1), 36–46. https://doi.org/10.30598/ pamerivol2issue1page36-46

Hayes M. T. (2019). Parkinson's Disease and Parkinsonism. *The American journal of medicine*, *132*(7), 802–807. https://doi.org/10.1016/j.amjmed.2019.03.001

Jeong, S., Cho, H., Kim, Y. J., Ma, H. I., & Jang, S. (2021). Drug-induced Parkinsonism: A strong predictor of idiopathic Parkinson's disease. *PloS one*, *16*(3), e0247354. https://doi.org/10.1371/journal.pone.0247354

Jiang, P. E., Lang, Q. H., Yu, Q. Y., Tang, X. Y., Liu, Q. Q., Li, X. Y., & Feng, X. Z. (2019). Behavioral Assessments of Spontaneous Locomotion in a Murine MPTP-induced Parkinson's Disease Model. *Journal of visualized experiments : JoVE*, (143), 10.3791/58653. https://doi.org/10.3791/58653

Jung, U. J., & Kim, S. R. (2018). Beneficial effects of flavonoids against parkinson's disease. *Journal of medicinal food*, *21*(5), 421–432. https://doi.org/10.1089/jmf.2017.4078

Kabra, A., Baghel, U. S., Hano, C., Martins, N., Khalid, M., & Sharma, R. (2020). Neuroprotective potential of Myrica esulenta in Haloperidol induced Parkinson's disease. *Journal of Ayurveda and integrative medicine*, *11*(4), 448–454. https://doi.org/10.1016/j.jaim.2020.06.007

Kawano, M., Saika, K., Takagi, R., Matsui, M., & Matsushita, S. (2020). Tannic acid acts as an agonist of the dopamine D2L receptor, regulates immune responses, and ameliorates experimentally induced colitis in mice. *Brain, behavior, & immunity - health*, *5*, 100071. https://doi.org/10.1016/j.bbih.2020.100071

Ketzef, M., Spigolon, G., Johansson, Y., Bonito-Oliva, A., Fisone, G., & Silberberg, G. (2017). Dopamine depletion impairs bilateral sensory processing in the striatum in a pathway-dependent manner. *Neuron*, *94*(4),855–865.e5. https://doi.org/10.1016/j.neuron.2017.05.004

Khazdair, M. R., Kianmehr, M., & Anaeigoudari, A. (2021). Effects of medicinal plants and flavonoids on parkinson's disease: a review on basic and clinical evidences. *Advanced pharmaceutical bulletin*, *11*(2), 224–232. https://doi.org/10.34172/apb.2021.026

Kumari, N., Anand, S., Shah, K., Chauhan, N. S., Sethiya, N. K., & Singhal, M. (2023). Emerging role of plant-based bioactive compounds as therapeutics in parkinson's disease. *Molecules*, 28(22), 7588. https://doi.org/10.3390/molecules28227588

Leem, Y. H., Park, J. S., Park, J. E., Kim, D. Y., & Kim, H. S. (2022). Neurogenic effects of rotarod walking exercise in subventricular zone, subgranular zone, and substantia nigra in MPTP-induced Parkinson's disease mice. *Scientific reports*, *12*(1), 10544. https://doi.org/10.1038/s41598-022-14823-5

Magno, L. A. V., Collodetti, M., Tenza-Ferrer, H., & Romano-Silva, M. A. (2019). Cylinder Test to Assess Sensory-motor function in a Mouse model of Parkinson's disease. *Bio-protocol*, *9*(16), e3337. https://doi.org/10.21769/BioProtoc.3337

Maher P. (2019). The potential of flavonoids for the treatment of neurodegenerative diseases. *International journal of molecular sciences*, *20* (12),3056. https://doi.org/10.3390/ijms 20123056

Malaiwong, N., Chalorak, P., Jattujan, P., Manohong, P., Niamnont, N., Suphamungmee, W., Sobhon, P., & Meemon, K. (2019). Anti-parkinson activity of bioactive substances extracted from Holothuria leucospilota. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, *109*, 1967–1977. https://doi.org/10.1016/j.biopha.2018.11.063

Modell, J. G., Tandon, R., & Beresford, T. P. (1989). Dopaminergic activity of the antimuscarinic antiparkinsonian agents. *Journal of clinical psychopharmacology*, *9*(5), 347–351.

Nedic E., G., Grubor, M., Zivkovic, M., Bozina, N., Sagud, M., Nikolac Perkovic, M., Mihaljevic-Peles, A., Pivac, N., & Svob Strac, D. (2022). *SLC6A3*, *HTR2C* and *HTR6* Gene Polymorphisms and the Risk of Haloperidol-Induced Parkinsonism. *Biomedicines*, *10*(12), 3237. https://doi.org/10.3390/biomedicines10123237

Noviyandri, P. R., Nurhadisah & Chismirina, S. (2021). Effect of Nutmeg flesh (Myristica fragrans Houtt) against Streptococcus mutans growth. *Journal of Syiah Kuala Dentistry Society*, 5(1), 42–46. https://doi: 10.24815/jds.v5i1.19682.

Plaingam, W., Sangsuthum, S., Angkhasirisap, W., & Tencomnao, T. (2017). *Kaempferia parviflora* rhizome extract and *Myristica fragrans* volatile oil increase the levels of monoamine neurotransmitters and impact the proteomic profiles in the rat hippocampus: Mechanistic insights into their neuroprotective effects. *Journal of traditional and complementary medicine*, *7*(4), 538–552. https://doi.org/10.1016/j.jtcme.2017.01.002

Saeed, A., Shakir, L., Khan, M.A., Ali, A.A., Yousaf, M.S., & Zaidi, A.A. (2017). Haloperidol induced Parkinson's disease mice model and motor-function modulation with Pyridine-3-carboxylic acid. *Biomedical Research and Therapy*, *4*, 1305-1317. https://doi.org/ 10.15419/bmrat.v4i05.169

Saleem, U., Gull, Z., Saleem, A., Shah, M. A., Akhtar, M. F., Anwar, F., Ahmad, B., & Panichayupakaranant, P. (2021). Appraisal of anti-Parkinson activity of rhinacanthin-C in haloperidol-induced parkinsonism in mice: A mechanistic approach. *Journal of food biochemistry*, *45*(4), e13677. https://doi.org/10.1111/jfbc.13677

Seneme, E. F., Dos Santos, D. C., Silva, E. M. R., Franco, Y. E. M., & Longato, G. B. (2021). Pharmacological and therapeutic potential of myristicin: a literature review. *Molecules (Basel, Switzerland)*, *26*(19), 5914. https://doi.org/10.3390/molecules26195914

Shin, S. W., Lee, J. S., Abdi, S., Lee, S. J., & Kim, K. H. (2019). Antipsychotics for patients with pain. *The Korean journal of pain*, *32*(1), 3–11. https://doi.org/10.3344/kjp.2019.32.1.3

Skinner, J. W., Christou, E. A., & Hass, C. J. (2019). Lower extremity Muscle strength and force variability in persons with parkinson disease. *Journal of neurologic physical therapy : JNPT*, *43*(1), 56–62. https://doi.org/10.1097/NPT.0000000000000244

Spisni, E., Valerii, M. C., & Massimino, M. L. (2023). Essential oil molecules can break the loop of oxidative stress in Neurodegenerative diseases. *Biology*, 12(12), 1504. https://doi.org/10.3390/biology12121504

Sultan, M.T., Saeed, F., Raza, H., Ilyas, A., Sadiq, F., Musarrat, A., Afzaal, M., Hussain, M., Ahtisham, M.R., & Al Jbawi, E. (2023). Nutritional and therapeutic potential of nutmeg (Myristica

fragrans): A concurrent review. *Cogent Food & Agriculture*, 9(2). https://doi: 10.1080/23311932.2023.2279701

Vaiman, E. E., Shnayder, N. A., Khasanova, A. K., Strelnik, A. I., Gayduk, A. J., Al-Zamil, M., Sapronova, M. R., Zhukova, N. G., Smirnova, D. A., & Nasyrova, R. F. (2022). Pathophysiological Mechanisms of Antipsychotic-Induced Parkinsonism. *Biomedicines*, *10*(8), 2010. https://doi.org/10.3390/biomedicines10082010

Vignesh, A., Amal, T.C., Sivalingam, R., Subramaniam, S., Krishnan, V. (2024). Influence of ecological factors on the phytochemical composition and bioactivity of Berberis tinctoria Lesch. wild edible fruits. *Biochemical Systematics and Ecology*, 112. 104771.

Weng, J. J., Wang, L. H., Zhu, H., Xu, W. R., Wei, Y. M., Wang, Z. Y., Yu, W. J., & Li, H. F. (2019). Efficacy of low-dose D_2/D_3 partial agonist pramipexole on neuroleptic-induced extrapyramidal symptoms and symptoms of schizophrenia: a stage-1 open-label pilot study. *Neuropsychiatric disease and treatment*, *15*, 2195–2203. https://doi.org/10.2147/ NDT. S205933

Yulianita, Y., Effendi, E. M. and Firdayani, E. M. (2019). Sedative effect of Citronella (Cymbopogon nardus (L.) Rendle) towards Male Mice (Mus musculus). *Indonesian Journal of Pharmaceutical Science and Technology Journal Homepage*, 1(1), 16–23. https://doi.org/10.24198/ijpst.v1i1.19148