Anti-Parkinson's Activity of Eugenol: A Review on Natural Compound with Therapeutic Potential

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***Abstract*—Parkinson's disease (PD), the second most common neurodegenerative disorder, is marked by dopaminergic neuronal loss in the substantia nigra and α-synuclein aggregation in Lewy bodies. While genetic mutations contribute to some cases, most are idiopathic. Current therapies, such as immunotherapies, drug repurposing, and monoamine oxidase inhibitors, provide symptomatic relief but limited neuroprotection. Natural compounds have emerged as potential alternatives. Eugenol, the major component of clove oil, shows antioxidant and neuroprotective effects. Preclinical studies in 6-hydroxydopamine (6-OHDA) and MPTP-induced models demonstrated that eugenol reduces oxidative stress, restores glutathione levels, and improves behavioural deficits, with synergistic benefits when combined with levodopa. *In-vitro*, eugenol derivatives exhibited selective inhibition of MAO-A and MAO-B. Clove an essential oil also enhanced neuronal survival and locomotor performance in PD rat models. Collectively, evidence suggests that eugenol is a promising neuroprotective adjunct for PD management, though clinical validation is required.**

***Index Terms*—Parkinson's Disease, Eugenol, MPTP, MAO-A and MOA-B**

I. INTRODUCTION

The neurodegenerative condition known as Parkinson's disease typically manifests in later life as bradykinesia, or a generalised slowing of movements, along with at least one additional symptom of stiffness or resting tremor. Additional symptoms include constipation, excessive salivation, mood abnormalities, sleep disturbances, loss of smell, and excessive periodic limb movements during sleep (REM behaviour disorder).[1] Parkinson's disease (PD), which is the second most prevalent neurodegenerative illness worldwide after Alzheimer's disease (AD), is characterised by Lewy bodies(LBs) in the substantia nigra pars compacta and the death of dopaminergic neurons. As a multi-centre illness, Parkinson's disease (PD) also involves the degeneration of non-dopaminergic systems, including the noradrenergic, serotonergic, and cholinergic systems.[2]

According to estimates, at least 1% of those over 60 have Parkinson's disease. Lewy bodies and the death of dopaminergic neurons in the substantia nigra are linked to the illness.

II. EPIDEMIOLOGY

The incidence of Parkinson's disease (PD) varies from 5/100,000 to over 35/100,000 new cases per year, according to estimates based on health care consumption. Between the sixth and ninth decades of life, the incidence rises five to ten times. As people age, the prevalence of PD also rises. The prevalence rose from less than 1 per cent of men and women aged 45–54 to 4 per cent of males and 2 per cent of women aged 85 or older in a meta-analysis of four North American groups. After a PD diagnosis, mortality rises after the first ten years but does not increase in comparison to those who are not afflicted.[3]

III. PATHOPHYSIOLOGY

The formation of LBs, which are mostly made up of fibrillar α-Syn, and the loss of dopaminergic neurons in the substantia nigra are pathological features of Parkinson's disease. Single gene mutations in monogenic PD have been found via genetic research on familial PD. The α-Syn-encoded genes, dardarin, vacuolar protein sorting-associated protein, parkin ligase, deglycase DJ1, and acid β-glucosidase are specifically where mutations that cause Parkinson's

disease (PD) are found. The gene (SNCA), which is connected to PD both genetically and neuropathologically, can help to explain this. Furthermore, LBs and α-Syn are identified in both idiopathic and familial Parkinson's disease. Common SNCA mutations are associated with a higher risk of idiopathic PD, in addition to the SNCA mutations and copy number variations found in monogenic PD. Since 90% of PD patients do not exhibit a monogenic inheritance pattern, the illness is regarded as idiopathic.[4]

Treatments

1. Antibodies can target and destroy extracellular α-synuclein, preventing it from "infecting" neighbouring cells and limiting its spread. In animal models, both passive and active immunisation methods against α-synuclein have been demonstrated to have neuroprotective benefits, and the findings of preliminary clinical studies in people are beginning to surface.
2. Drug Therapy: Table 1 highlights the advanced therapy and repurposed drugs

Table 1: Drugs for the treatment of PD

Drug/class	Proposed mechanism	Progress in trials
α-synuclein reduction		
β-agonists	Reduced α-synuclein transcription through acetylation of promoters and enhancers of the SNCA gene	Not started
Nilotinib	Inhibition of ABL tyrosine kinase activity and enhanced autophagy	Safe and tolerable but no clinical benefit in phaseII trial
Terazosin	Activation of PGK1 and HSP90, increased ATP levels, and reduced α-synuclein levels	Single-centre randomised placebo-controlled trial currently enrolling patients

3. Targeting non-dopaminergic neurotransmitter systems: Safinamide, a new medication with multi-modal activities, was recently approved for treatment in Parkinson's disease. Being a strong reversible monoamine oxidase B inhibitor, it has potential benefits for treating the dopaminergic components of Parkinson's disease. Additionally, it alters glutamate transmission, which might be connected to some of Parkinson's disease's non-motor symptoms.[5]

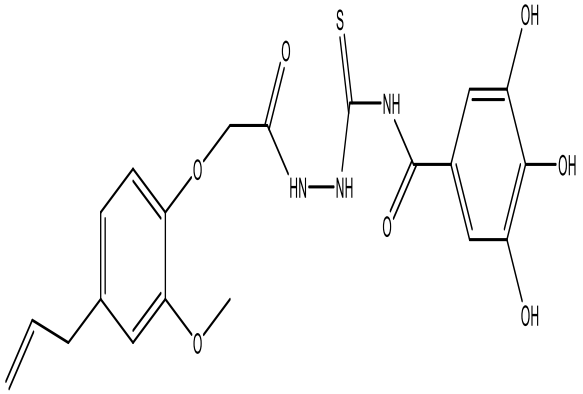
Research on natural products from plants, animals, and fungi has shown potential as therapeutics for various illnesses, including cancer, diabetes, heart disease, hypertension, reproductive disorders, and neurodegenerative diseases. Targeting multiple mechanisms and neuroprotection approaches could be promising strategies for preventing and treating neurodegenerative diseases.[6]

Eugenol acts on the central nervous system in addition to its peripheral effects. In order to enter the brain and carry out its function *in-vivo*, Eugenol's hydrophobic characteristic enables it to effectively cross the blood-brain barrier. The oxidative and excitotoxic damage caused by N-methyl-D-aspartate (NDMA) is prevented by eugenol. Because it can lower brain-derived neurotrophic factor (BDNF) and delay amyloid-β peptide (A-β)-induced cell death by abnormally blocking Ca^{2+} (caused by A-β), Eugenol has the potential to be neuroprotective in hippocampus tissues. It also aids in neuroprotection by limiting the effects of excitotoxicity and antioxidants. The functions of several glutathione-related proteins are enhanced in cell models by eugenol, which also protects vital brain cells against excitotoxic and oxidative damage.[7] A thorough literature survey revealed the following documents supporting eugenol's activity on Parkinson's disease.

1. Carlos *et al*. investigated the effects of eugenol and its combined action with levodopa on Parkinson's disease in a 6-hydroxydopamine-induced model. Wistar rats received an intrastriatal injection of 21 μg of 6-hydroxydopamine, followed by oral treatment for 14 days with either 0.1, 1, or 10 mg/kg of eugenol, 25 mg/kg of levodopa, or their combination (10 mg/kg of eugenol and 12.5 mg/kg of levodopa). Following euthanasia and the dissection of the

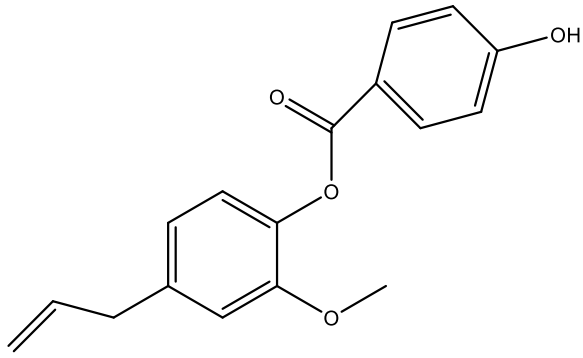
brain regions, behavioural tests and neurochemical investigations were conducted. Results showed that eugenol reduced oxidative stress and behavioural disturbances induced by 6-hydroxydopamine. In comparison to levodopa alone, the combination of eugenol and levodopa caused an increase in reduced glutathione levels and was more successful in certain behavioural metrics and body weight gain. Eugenol's neuroprotective properties against neurochemical and motor abnormalities were noted, and the combination showed promise when compared to traditional treatment.[8]

2. Urmi *et al*. investigated the effect of eugenol on Parkinson's disease (PD) in a mouse model induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The study found that eugenol had potent antioxidant properties. Three oral eugenol dosages (25, 50, and 100 mg/kg/day) were administered before and after treatment. The effects were evaluated in terms of behavioral and biochemical parameters as well as the binding mode in the human myeloid differentiation factor-2 (hMD-2). The results of several behavioral tests demonstrated that giving mice MPTP caused motor impairment resembling Parkinson's disease. While a high dose of eugenol after therapy exacerbated akinesia symptoms, pretreatment eugenol restored motor dysfunction. Eugenol decreased reduced glutathione levels and mitigated the elevated lipid peroxidation brought on by MPTP. Eugenol's binding affinity for the toll-like receptor-4 (TLR4) MD2 coreceptor was -6.897 kcal/mol. Studies using biochemical and neurobehavioral methods demonstrated that while eugenol has a preventive effect, it is not a cure for Parkinson's disease.[9]
3. Dhiman et.al studied *In-vitro* human MAO-A and human MAO-B inhibition experiments revealed that eugenol-based derivative compounds 5b (Structure 1**)** and 16 (Structure 2) were the most active hMAO-A inhibitors, with IC50 values of 5.989 ± 0.007 µM and 7.348 ± 0.027 µM, respectively. The presence of a carboxylic moiety in the 2-(4-allylphenoxy) acetyl nucleus and the presence of 4-hydroxy-3-methoxyphenyl-acrylate on the 4-allyl 2-methoxyphenyl moiety demonstrated the importance of esteric linkage for h-MAOA active site. Compound 17, with the absence of 2-methoxyphenyl groups at 3-phenylacrylate, was a significant hMAO-A inhibitor, while compound 7 showed significant hMAOA inhibition with IC50 values of 10.46±0.072 µM and a selectivity index of 0.24. The active site of MAO-A is highly hydrophobic, making it rational to design inhibitors with large aromatic structures. In contrast, compounds 13a (Structure 3) and 13b (Structure 4) were the most active hMAO-B inhibitors, with IC50 values of 7.494±0.014 µM and 9.183±0.034 µM, respectively. The methoxy group slightly reduced hMAO-B inhibitory efficacy compared to 13a. The amino acid residue Ile199 acts as a "gate keeper" for the substrate/inhibitor, and compounds 13a and 13b are smaller than other structures, making them easier to assess for inhibition.[10]



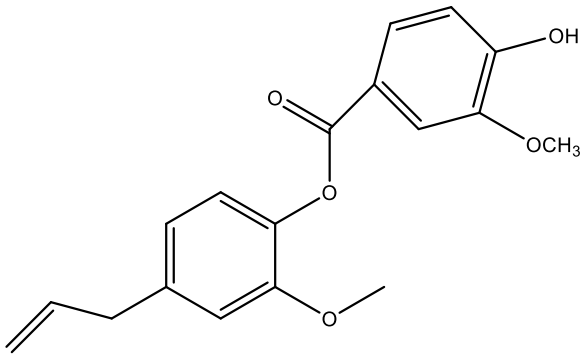
N-(2-(2-(4-allyl-2methoxyphenoxy) acetyl)hydrazine-1-carbo-nothioyl)-3,4,5-trihydroxybenzamide

Structure 1:5b



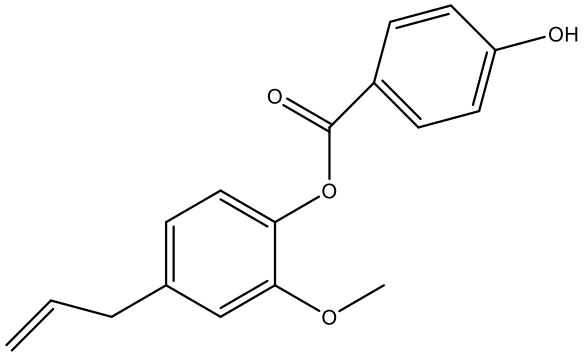
4-allyl-2-methoxyphenyl 4-hydroxybenzoate

Structure 2: 16



4-allyl-2-methoxyphenyl 4-hydroxy-3-methoxybenzoate

Structure 3: 13a



4-allyl-2-methoxyphenyl 4-hydroxybenzoate

Structure 4: 13b

4. Hamdi *et.al* studied the potential of natural therapies becoming more popular for preventing Parkinsons disease. Clove Essential Oil (CEO), a strong antioxidant extracted from *Syzygium aromaticum* buds, was evaluated for its capacity to prevent 6-OHDA-induced cell death both *in-vitro* (SH-SY5Y) and *in-vivo* (PD rat model). Twenty-four hours of SH-SY5Y cells' exposure to 6-OHDA (100µM) drastically decreased cell viability. At doses lesser than 20µg/ml, CEO and its main component, Eugenol (EG) had no cytotoxic effect on SH-SY5Y. CEO and EG significantly protected neurons from 6-OHDA-induced cell death at dosages of 2.5–20 µg/ml. By injecting 6-OHDA (21µg/animal) unilaterally into the striatum, a PD rat model was created. It is possible to forecast the loss of neurons in the *Substancia Nigra Compacta* (SNc) by evaluating motor performance. One and two weeks following 6-OHDA-lesion, the locomotor performance (actimetry and cylinder tests) of rats treated with CEO (10 mg/Kg) was considerably better than that of animals treated with 6-OHDA-lesion. Tyrosine Hydroxylase (TH) cell count showed a significant decrease in cell death in ipsilateral SNc in both CEO treated and 6-OHDA-lesioned rats when compared to contralateral. The ipsilateral SNc of the CEO-treated group displayed a noticeably higher number of TH cells than the 6-OHDA-lesioned group. The current study showed that CEO had a neuroprotective impact against 6-OHDA cytotoxicity both *in-vitro* and *in-vivo*. Therefore, CEO could be used as a food supplement for PD prevention.[11]

IV. CONCLUSION

Parkinson's disease is a progressive neurodegenerative disorder with limited treatments. Current therapies, including pharmacological and immunotherapeutic approaches, do not stop or reverse dopaminergic neuronal degeneration. Eugenol, a constituent of clove oil, has potential as an adjunctive due to its antioxidant, anti-inflammatory, and neuroprotective properties. Studies show that eugenol alleviates oxidative stress, restores glutathione balance, reduces lipid peroxidation, and improves behavioural outcomes. Combining eugenol with levodopa can enhance conventional therapy and minimise motor complications. In future, eugenol-based formulations could complement the existing therapies and offer a natural, accessible, and effective strategy for mitigating Parkinson's disease progression.

REFERENCES

[1] Zafar S, Yaddanapudi SS. Parkinson disease. InStatPearls [Internet] 2023 Aug 7. StatPearls Publishing.

[2] Moreira Vasconcelos CF, da Cunha Ferreira NM, Hardy Lima Pontes N, de Sousa dos Reis TD, Basto Souza R, Aragão Catunda Junior FE, Vasconcelos Aguiar LM, Maranguape Silva da Cunha R. Eugenol and its association with levodopa in 6-hydroxydopamine-induced hemiparkinsonian rats: Behavioural and neurochemical alterations. Basic & Clinical Pharmacology & Toxicology. 2020 Oct;127(4):287-302.

[3] Simon DK, Tanner CM, Brundin P. Parkinson disease epidemiology, pathology, genetics, and pathophysiology. Clinics in geriatric medicine. 2020 Feb 1;36(1):1-2.
[4] Mohamad KA, Wahdan SA, Elnaga RN. Overview on Parkinson's disease: pathophysiology, and experimental models. Archives of Pharmaceutical Sciences Ain Shams University. 2021 Dec 1;5(2):212-24.
[5] Stoker TB, Barker RA. Recent developments in the treatment of Parkinson's Disease. F1000Research. 2020 Jul 31;9:F1000-aculty.
[6] Hamdi D, Ouachikh O, Omara-Reda H, Messaoud C, Hafidi A. The neuroprotective effect of Clove essential oil against 6-OHDA-induced cell death in SH-SY5Y and a rat model of Parkinson's disease. Austin Alzheimer's and Parkinson's Disease. 2023;6(2):1039.
[7] Nisar MF, Khadim M, Rafiq M, Chen J, Yang Y, Wan CC. Pharmacological properties and health benefits of eugenol: A comprehensive review. Oxidative medicine and cellular longevity. 2021;2021(1):2497354.
[8] Moreira Vasconcelos CF, da Cunha Ferreira NM, Hardy Lima Pontes N, de Sousa dos Reis TD, Basto Souza R, Aragão Catunda Junior FE, Vasconcelos Aguiar LM, Maranguape Silva da Cunha R. Eugenol and its association with levodopa in 6-hydroxydopamine-induced hemi-parkinsonian rats: Behavioural and neurochemical alterations. Basic & Clinical Pharmacology & Toxicology. 2020 Oct;127(4):287-302.
[9] Vora U, Vyas VK, Wal P, Saxena B. Effects of eugenol on the behavioural and pathological progression in the MPTP-induced Parkinson's disease mouse model. Drug Discoveries & Therapeutics. 2022 Aug 31;16(4):154-63.
[10] Dhiman P, Malik N, Khatkar A. Lead optimisation for promising monoamine oxidase inhibitor from eugenol for the treatment of neurological disorder: Synthesis and in silico-based study. BMC Chemistry. 2019 Mar 26;13(1):38.
[11] Mohd Sairazi NS, Sirajudeen KN. Natural products and their bioactive compounds: neuroprotective potentials against neurodegenerative diseases. Evidence-Based Complementary and Alternative Medicine. 2020;2020(1):6565396.