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Original Article

In Silico Protein-Ligand Interaction Study of Selected Phytochemicals Against Monoamine Oxidase-B

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disease associated with the death of dopaminergic neurons in the substantia nigra pars compacta. Monoamine oxidase B (MAO-B) inhibitors lessen the degree of PD but still present various side effects. Natural products such as morin, piceatannol, resveratrol, and gallic acid are vital phytochemicals from plants with numerous health benefits. This *in silico* study aimed to identify potent natural MAO-B inhibitors that could serve as better alternatives to the known MAO-B inhibitors (rasagiline and selegiline). The crystal structure of MAO-B (PDB ID: 2C65) was retrieved from the Protein Data Bank (RSCB) and prepared for molecular docking via Discovery Studio 2020 software. Molecular docking between MAO-B and morin, piceatannol, resveratrol, gallic acid, rasagiline, and selegiline utilised the PyRx software. The Discovery Studio 2020 software was used for visualization. The SwissADME server was used to study the physiochemical properties (Lipinski rule of five), pharmacokinetic parameters, and absorption, distribution, metabolism, elimination, and toxicity (ADMET) profiles of morin. Comparing results with binding affinity indicated that morin (-10.0 kcal/mol) has a superior potency against 2C65 than piceatannol (-9.0 kcal/mol), resveratrol (-807 kcal/mol), dopamine (-6.4 kcal/mol), gallic acid (-6.3 kcal/mol), rasagiline (-8.0 kcal/mol), and selegiline (-7.4 kcal/mol). Drug candidates comply with all five of Lipinski's drug-likeness rules with appropriate ADMET properties. Overall, the molecular docking results suggest that morin may be considered a suitable therapeutic candidate for PD treatment.

Keywords
Parkinson's disease, Morin, Rasagiline, Selegiline, Lipinski's rule, drug-likeness

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INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease affecting the elderly population. PD is caused by the death of dopaminergic neurons in the nigrostriatal pathway in the brain due to Lewy body formation, leading to motor dysfunction, including resting tremor, postural instability, bradykinesia, and rigidity) (Gong et al. 2018). Essentially, the loss of dopaminergic neurons in the substantia nigra par compacta is the pathological hallmark of PD, which is prevalent in 1-2% of individuals above 60 years old (Klemann et al. 2017). According to projections, there are 5-35 new cases per 100,000 individuals affected by the disease, with increasing incidence as age progresses (Pringsheim et al. 2014). Worth noting is that the number of individuals affected by PD is predicted to double by 2030 (Dorsey et al. 2007). There is currently no cure for PD. However, levodopa is the gold standard drug used in the management of PD to relieve motor dysfunction. Nevertheless, long-term use of levodopa has been associated with manifestations of dyskinesia (Calabresi et al. 2010). Carbidopa, anticholinergics, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, catechol-o-methyltransferase inhibitors, and amantadine are also used in the management of PD (Muller et al. 2004; Diaz and Waters 2009). MAO-B inhibitors act centrally by inhibiting the oxidation of dopamine in the dopaminergic synapse (Fig. 1).

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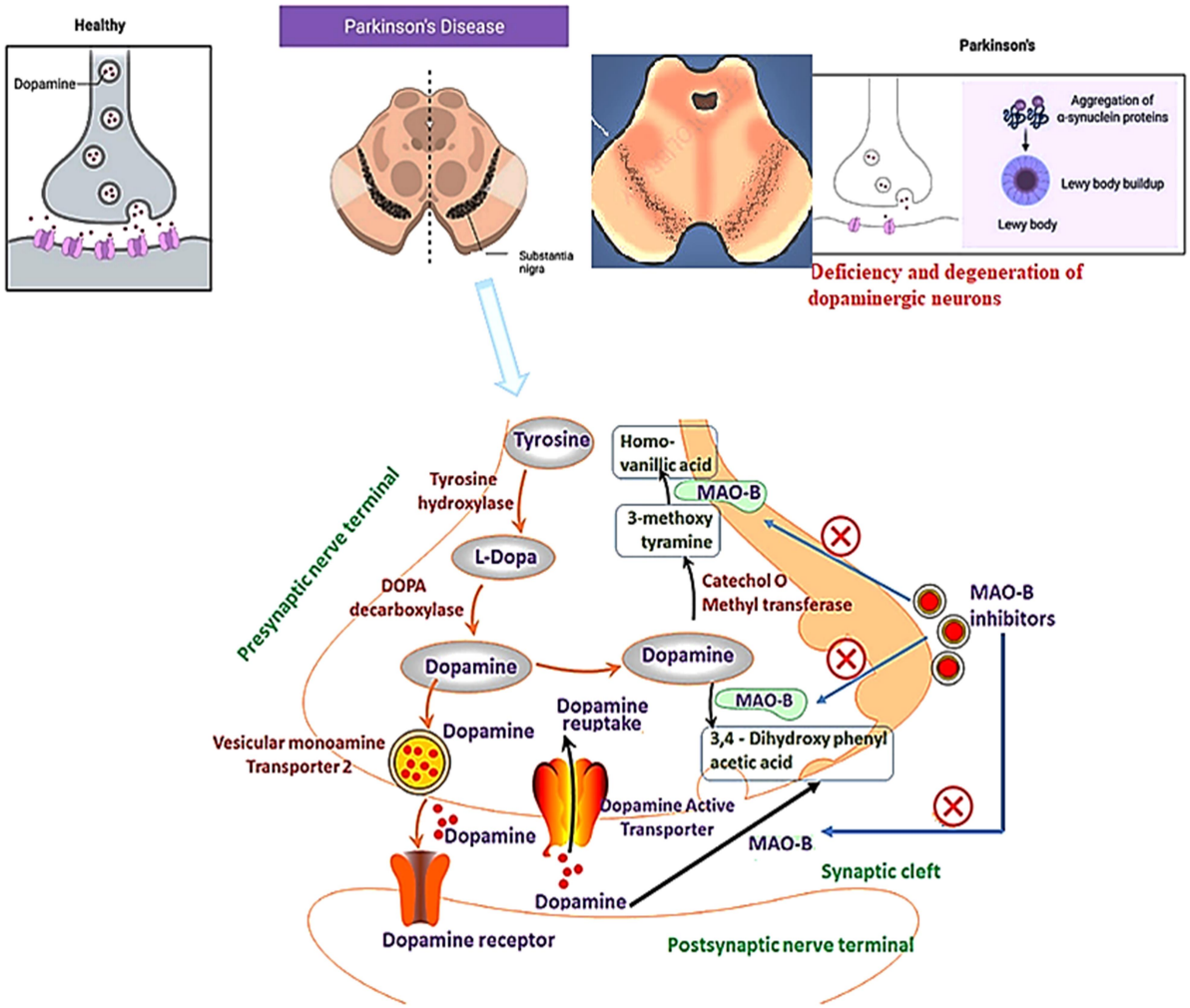

Fig. 1: Pathological features of PD characterised by the accumulation of Lewy bodies and the degeneration of dopaminergic neurons (adapted from Jost, 2022).

In several studies, MAO-B inhibitors, such as selegiline and rasagiline, have been shown mild relieve of symptomatic effects in PD, delay the onset of levodopa use, and reduce the frequency of motor fluctuations. Though the symptomatic efficacy of selegiline and rasagiline is inferior relative to dopamine agonists and levodopa, MAO-B inhibitors have fewer side effects. Contrary to their competitors, MAO-B inhibitors may furthermore provide a chance for disease modification, which so far remains the main unmet need in the treatment of PD and essentially makes them the right drug candidates for the early management of PD (Löhle and Reichmann 2011). Selegiline and rasagiline have been reported to have various side effects like hallucinations and confusion (Gu et al. 2018; Tan et al. 2022), light-headedness, nausea, mild headaches, and joint or neck pain (Baweja et al. 2023). In effect, there is an urgent need to search for novel drug candidates with no side effects that can be used in the treatment of PD. Notwithstanding the limited efficacy of synthetic agents as possible functional drugs against PD, major limiting factors such as pharmacokinetics and safety concerns remain challenging (Ayaz et al. 2019). Unfortunately, the currently available drugs only give symptomatic relief and do not halt neurodegeneration, making novel drug discoveries imperative.

Plant-derived bioactive compounds might offer effective and safe pharmacodynamic features in neurodegenerative disorders. Nevertheless, the number of biological axes and proteins involved in the pathogenesis of PD and the complexity of the brain remain serious obstacles towards drug development for PD (Morofuji and Nakagawa 2020). Natural products from plants as well as their bioactive molecules have been widely studied in recent times for their possible therapeutic action in a range of neurodegenerative diseases, including PD (Bui and Nguyen 2017; Rahman et al. 2021). Among numerous molecules, morin, piceatannol, resveratrol, and gallic acid are slated to have an excellent neuroprotective profile based on the reports of several epidemiological studies (Maher 2019). Morin is expressed in the stems, leaves, and fruits of members of the Moraceae family (Rajput et al. 2021). Studies have

revealed that morin possesses antioxidant and anti-inflammatory actions (Gong et al. 2011; Sinha et al. 2016). Morin has been shown to have neuroprotective properties and an antipsychotic-like therapeutic effect via modulation of oxidative/nitrergic, cholinergic actions, and neuroprotection in the ketamine model of schizophrenia (Ben-Azu et al. 2018b), improvement of GABAergic neurotransmission and neurotrophic factor, and downregulation of NADPH-oxidase-induced oxidative damage in mice (Ben-Azu et al. 2018a), and inhibition of pro-inflammatory mediators release and suppression of degeneration of cortical pyramidal neurons in lipopolysaccharide-, and ketamine- induced schizophrenic-like symptoms in mice (Ben-Azu et al. 2019). Furthermore, its low toxicity levels *in vivo* show chronic morin administration is feasible (Caselli et al. 2016; Hong et al. 2020). Two studies showed that morin's anti-inflammatory effects resulted in neuroprotection in PD mice, and that morin improved motor dysfunction and inhibited dopaminergic neuron loss in an acute PD model (Lee et al. 2016; Rajput et al. 2021). However, the potential inhibitory role of morin against MAO-B is not known.

Piceatannol (3,3',4',5-tetrahydroxy-trans-stilbene), a naturally occurring stilbene, and a subclass of phenolic compounds showed antioxidant (Hao et al. 2019), anti-inflammatory (Li et al. 2017), and neuroprotective (Zhang et al. 2018) activities. Temsamani et al. (2016) reported that piceatannol prevented the formation of α-synuclein fibrils and destabilised preformed filaments. Further arguing that piceatannol induced the formation of small soluble complexes that protect membranes against α-synuclein-induced damage. Even though another study have shown that piceatannol could decrease neurological deficits and behavioural disorders in animal models (Zhang et al. 2018), the neuroprotective mechanism of piceatannol through inhibition of MAO-B remains unclear.

Resveratrol (3,4′,5-trihydroxy-trans-stilbene) is another stilbene found in peanuts, raspberries, blueberries, and grapes. This stilbene is made up of a 144-carbon basic skeleton and two phenyl groups joined by an ethene double bond (Fig. 3) (He and Yan 2013; Tsai et al. 2017). It is shown that stilbenoids, such as resveratrol, possess anti-oxidant and anti-inflammatory properties, leading to neuroprotection (Arbo et al. 2020). The administration of resveratrol has been shown to be beneficial in rodent PD models. Zhao et al. (2017) revealed that administration of resveratrol significantly protected mice from rotenone-induced motor coordination impairment, elevated iron levels, and dopaminergic neuronal loss. In this study, we investigated the potential inhibitory action of resveratrol against MAO-B. In the same vein, the chemical structure of gallic acid, 3,4,5-trihydroxybenzoic acid, has been found to be abundant in numerous fruits, vegetables, and herbs (Yoon et al. 2013). It is a naturally occurring phytochemical of plant origin and has been shown to have cardio-protective, hepato-protective, anxiolytic, and neuroprotective properties (Rasool et al. 2012; Dhingra et al. 2012; Umadevi et al. 2012). Essentially, gallic acid has been shown to protect neuronal cells against 6-hydroxydopamine -induced neurotoxicity via the prevention of oxidative stress and apoptosis (Chandrasekhar et al. 2018). The main objective of this study was to evaluate the potential inhibitory role of the selected phytochemicals against MAO-B using the molecular docking paradigm.

MATERIALS AND METHODS

Ligands and Proteins Retrieval

In this study, the crystal structure of MAO-B was retrieved from the protein data bank (http://www.rcsb.org). For the MAO-B protein data bank (PDB) code: 2C65; human MAO-B in complex with 4CR (4-(N-methyl-N-ethyl-carbamoyloxy)-N-methyl-N-pro-pargyl-1(R)-aminoindan) (Fig. 2), resolution 1.70 A˚, binding sites GLN 206, LEU 171, TYR 326, ILE 316, ILE 199, ILE 198, PHE 343, and TYR 398 (Gnanaraj et al. 2022). The structure was cleaned by the removal of water molecules and inhibitors, as well as all non-interacting ions. Furthermore, polar hydrogen atoms were added to the prepared protein before use for the molecular docking studies using Discovery Studio 2020. Rasagiline and selegiline, the standard drugs that inhibit the activity of MAO-B, were used alongside morin, the test compound. The structure data file format of the test compounds (Fig. 3) was obtained from the PubChem database. Energy minimization and the PDBQT format of the structure data files were prepared using OpenBabel in PyRx 0.8 software.

Virtual Screening

Docking-based virtual screening of ligands (rasagiline, selegiline, and morin) against the target protein, 2C65, was done using Autodock Vina in PyRx. This was performed in order to gain more insight into the binding mode of the compounds. The auto-dock Vina grid box was set to incorporate the entire active site of the protein structure of MAO-B (with coordinates of x = 51.606905; y = 154.886381 27; z = 27.498619). The protein-ligand docked interactions were visualised and analysed with Discovery Studio 2020 software.

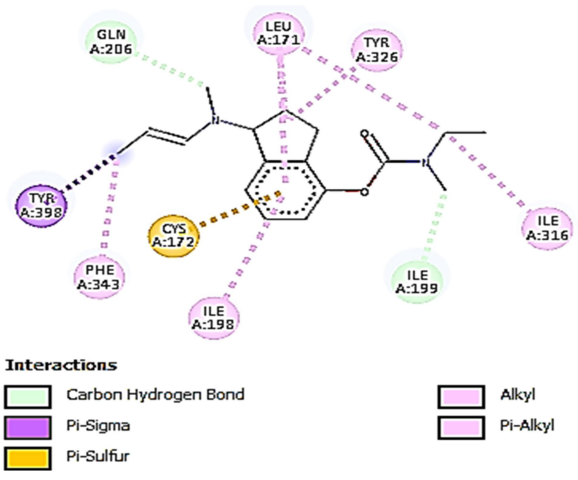

Fig. 2: Binding site prediction (Gnanaraj et al. 2022)

Rigid Docking Interactions

The four suspected inhibitors of MAO-B were rigidly docked into the binding pocket of MAO-B with interactions presented in 3D and 2D views. The binding energies of the hit compounds and standard drugs were shown in the range of -10.0 and -6.30 kcal/mol. The docking structure or conformation found at the end of molecular docking, the binding energies of these docked structures, and their similarities to each other were the key results in a docking log file. The docking log file revealed the docked binding energies, orientations, and conformations. The relationship between docked structures was assessed by computing the root-mean-square deviation between the coordinates of the chosen molecular conformation and the molecular conformation with the lowest binding energy, which is ranked at the top

ADMET Screening

The properties of morin, such as absorption, distribution, metabolism, excretion, and toxicity (ADMET), were determined by the *in silico* integrative SwissADME web server. Compounds that followed Lipinski's rules and other important SwissADME predictions were considered and utilised for docking and for the establishment of potential therapeutic interventions against Parkinson's disease.

RESULTS

Rigid Docking Interactions

The binding energies of the selected phytochemicals were plotted in the graph. The binding energies of all the active sites were revealed, and among the compounds, the best potency in all the active sites was morin, followed by piceatannol, and gallic acid (Fig. 4). The amino acid types and amino acid residues that interacted with selected phytochemicals following rigid receptor docking are provided in Figures 5-8.

Pharmacokinetic

The molecular weight and topological polar surface area of the test compounds were considerably low (Table 1). Furthermore, gastrointestinal absorption for all the test compounds have high possibility of gastrointestinal absorption after oral administration. All the test compounds except resveratrol do not have the possibility of crossing the blood-brain barrier.

Morin and piceatannol have inhibitory action on CYP2D6 and CYP3A4. Conversely, resveratrol and gallic acid showed inhibitory action on CYP3A4 but not on CYP2D6. Conversely, resveratrol and gallic acid have inhibitory action on CYP3A4 but not on CYP2D6. All the test compounds were soluble and possess considerably high bioavailability scores which could be associated with high gastrointestinal absorption of the test compounds.

The consensus Log P of all the test compounds was positive, with gallic acid presenting the lowest positive Log P value.

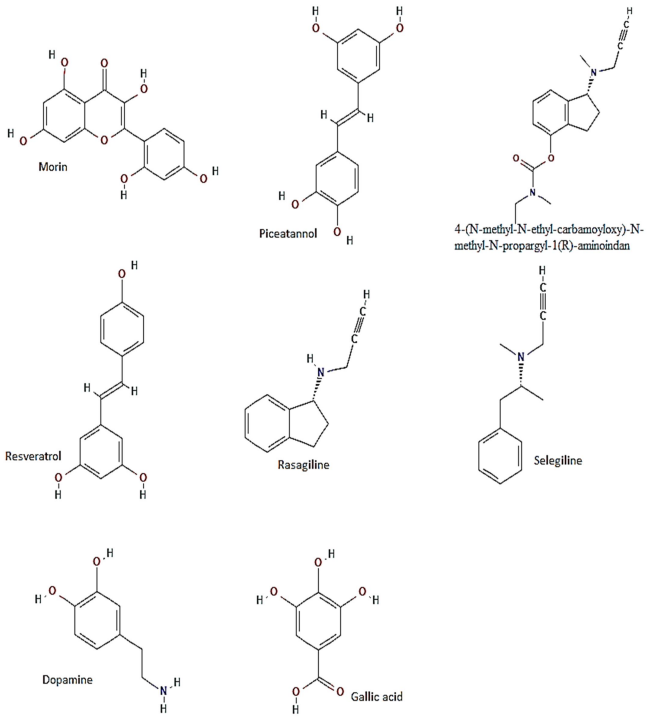

Fig. 3: 2D structures of test compounds and standard drugs as retrieved from PubChem 2023

DISCUSSION

The pharmacokinetics of a drug involved the kinetics ADMET. For a drug to possess a drug-like property, it must have a molecular weight of less than 500 DA, adequate water solubility to be distributed and dissolved in aqueous media, and associated lipophilic properties. The absorption, distribution, and metabolism of any test compound or drug are influenced by its physicochemical properties. For instance, the higher the topological polar surface area and the molecular weight of a drug, the lower the rate of pene-

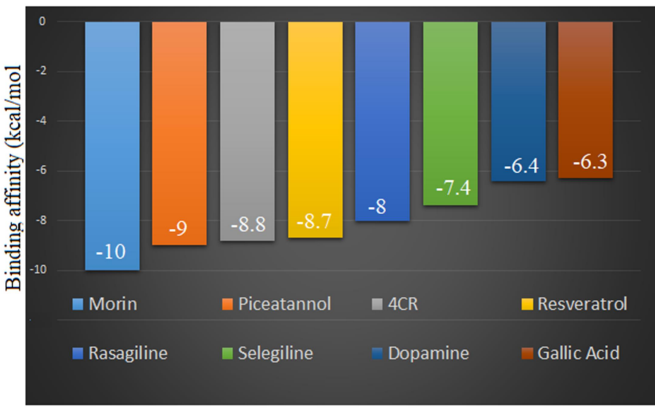

Fig. 4: Molecular docking score (kcal/mol) of test compounds with two standard drugs (rasagiline and selegiline) against MAO-B (2c65). 4CR = 4-(N-methyl-N-ethyl-carbamoyloxy)-N-methyl-N-propargyl-1(R)-aminoindan

tration through the biological barrier. In this study, the molecular weight and TPSA of the test compounds were considerably low. An indication that tests agents will penetrate biological membrane faster. This observation is supported by the high gastrointestinal absorption of molecules predicted in this study.

The physicochemical, drug-likeness, and ADMET properties of selected phytochemicals revealed that morin, piceatannol, resveratrol, and gallic acid appeared to follow all five of Lipinski's drug-likeness criteria. According to the data gotten from DruliTo software, the selected phytochemicals also passed Veber's rule for the unweighted quantitative estimate of drug-likeness and the weighted quantitative estimate of drug-likeness. Other phytochemcals except resveratrol failed the blood-brain barrier likeness rule. All of the above findings reveal that these bioactive compounds are good potential drug-like molecules and useful therapeutic agents against a variety of neurodegenerative diseases, including PD. The ADMET properties of morin, piceatannol, resveratrol, and gallic acid were evaluated using the online vNN ADMET webserver. All of the ADMET results and drug-likeness characteristics were consistent with those obtained from other tools, such as SwissADME and AdmetSAR. Overall, the ADMET properties indicate that all the selected phytochemicals are safe for therapeutic use (Daina et al. 2017). Although the blood-brain barrier-permeant property of resveratrol appears to make it a better candidate for PD management than others,

The solubility of a drug is one of the pre-formulation characteristic that regulates the desired concentrations in the drug's biological environment: The higher the solubility, the higher the bioavailability. All the test compounds were soluble and possess considerably high bioavailability scores, which could be associated with high gastrointestinal absorption of the test compounds.

Lipophilicity, also known as Log P is the logarithm of the partition coefficient of a drug molecule in a liquid or an organic phase. Lipinski's rule of five says that the partition coefficient should be positive, but less than ≤ 5. A drug with an increased lipophilicity (Log P) means increased possibility of the drug binding to unwanted cellular targets and lowered degradation rate of drug compounds in the body. The consensus Log P of all the test compounds was positive, with gallic acid presenting the lowest positive Log P value. An indication that, the probability that gallic acid

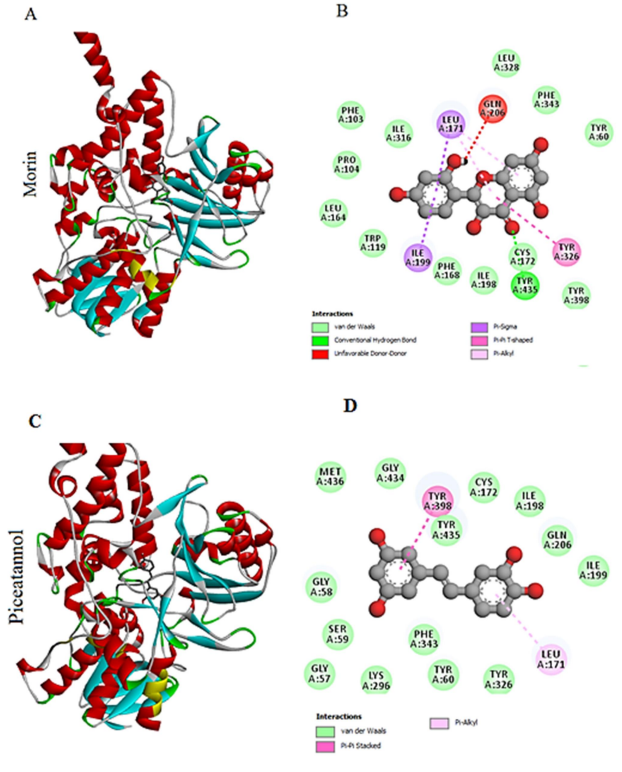

Fig. 5: 3D orientation and 2D orientation of molecular interaction of natural morin (A and B respectively) and piceatannol (C and D respectively) in the active site of MAO-B (PDB ID: 2C65) during molecular docking (AutoDock). The 2D depiction of morin and piceatannol in the active site of the MAO-B enzyme shows the residues involved in hydrogen bonding or polar interactions, van der Waals and hydrophobic interactions in coloured circles/legends in all 2-dimensional figures

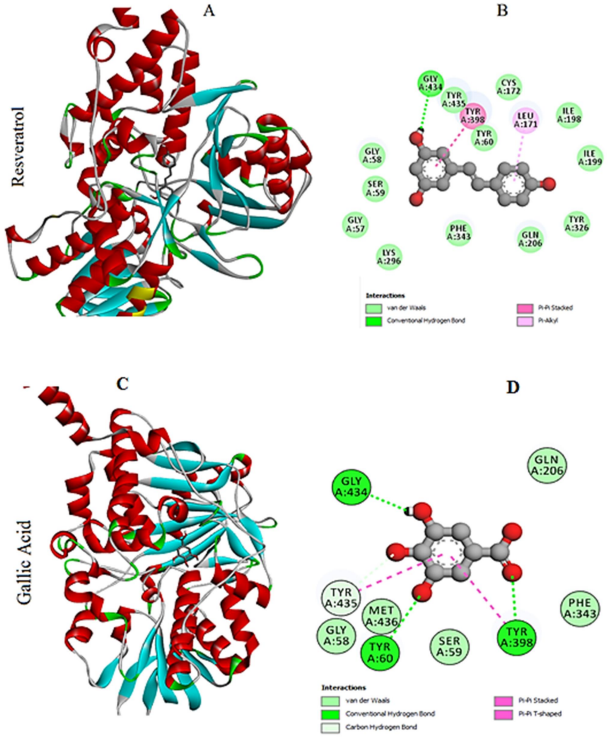

Fig. 6: 3D orientation and 2D orientation of molecular interaction of resveratrol (A and B respectively) and gallic acid (C and D respectively) in the active site of MAO-B (PDB ID: 2C65) during molecular docking (AutoDock). The 2D depiction of resveratrol and gallic acid in the active site of the MAO-B enzyme shows the residues involved in hydrogen bonding or polar interactions, van der Waals and hydrophobic interactions in coloured circles/legends in all 2-dimensional figures

will bind to undesirable cellular targets is lowest relative to other test compounds.

Lipinski's rule of five is an operative evaluator of drug likeness in drug discovery. This rule summarizes the features of a suitable drug candidate. This rule entails that drug agents must possess the following characteristics: a molecular weight of ≤500, a number of hydrogen bond donors of ≤5, a number of hydrogen bond acceptors of ≤10, and a log P (lipophilicity) of ≤5. All the test compounds in this study obeyed Lipinski's rule of five rule of five.

As per the AutoDock software, the docking score is often expressed using a negative value, where a higher negative value means better drug potency (Pokhrel et al. 2021). This is depicted in the *in silico* results of morin, piceatannol, resveratrol, and gallic acid against PD, where the individual ligand docking score against MAO-B protein predicts the biological activity of each compound. This study showed that morin exhibited a docking score of -10 kcal/mol against the target protein, MAO-B, while piceatannol, resveratrol, dopamine, and gallic acid respectively, exhibited -9, -8.7, -6.4, and -6.3 kcal/mol. It can be observed from these results that the highest potency was seen in morin against MAO-B (PDB ID: 2c65) with a docking score of -10.0 kcal/mol, while the lowest was gallic acid, -6.3 kcal/mol against MAO-B (PDB ID: 2c65). The inhibitory action of morin against MAO-B, according to this study, may partly explain the ameliorative action of morin in motor dysfunction observed in PD. For instance, Lee et al. (2016) reported the neuroprotective roles of morin in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of PD through amelioration of motor dysfunction, protection of the substantia nigra and striatum against dopaminergic neuronal loss, and alleviation of MPTP-induced astrocyte activation. Furthermore, Ishola et al. (2022) also lent credence to the neuroprotective effects of morin on rotenone-induced PD via improvement of antioxidant defence and anti-inflammatory mechanisms. This study shows that apart from morin working through anti-inflammatory and anti-oxidative pathways, one potential therapeutic action of morin against PD is via inhibition of MAO-B. The standard drugs, rasagiline and selegiline, exhibited docking scores of -8.0 and -7.4 kcal/mol, respectively, against MAO-B (PDB ID: 2c65). These results show that the selected phytochemicals have a better potency than the standard drugs and even dopamine (-6.4 kcal/mol), the main agonist of MAO-B.

The progression of PD involves the death of dopaminergic neurons and rapid oxidation of dopamine in the synaptic cleft of dopaminergic neurons, since most of the palliative treatments for PD involve the administration of MAO-B inhibitors, including rasagiline and selegiline, which impede

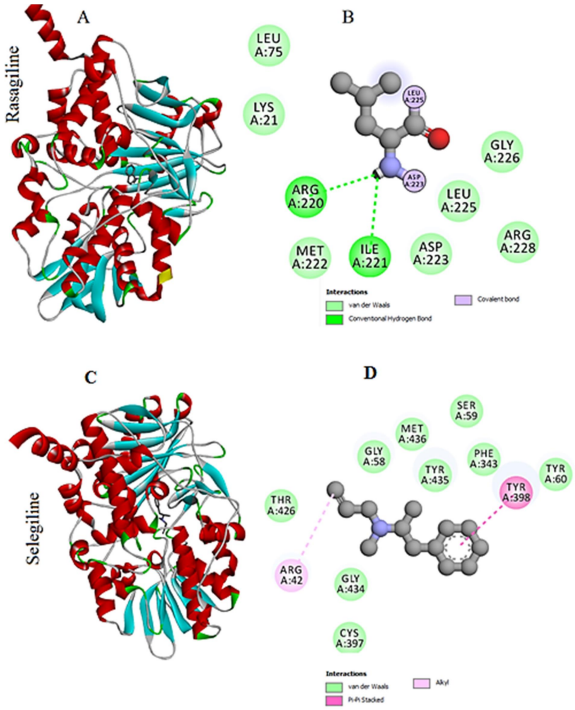

Fig. 7: 3D orientation and 2D orientation of molecular interaction of rasagiline (A and B respectively) and slegililne (C and D respectively) in the active site of MAO-B (PDB ID: 2C65) during molecular docking (AutoDock). The 2D depiction of rasagiilne and selegiline in the active site of the MAO-B enzyme shows the residues involved in hydrogen bonding or polar interactions, van der Waals, and hydrophobic in coloured circles or legends in all 2-dimensional figures

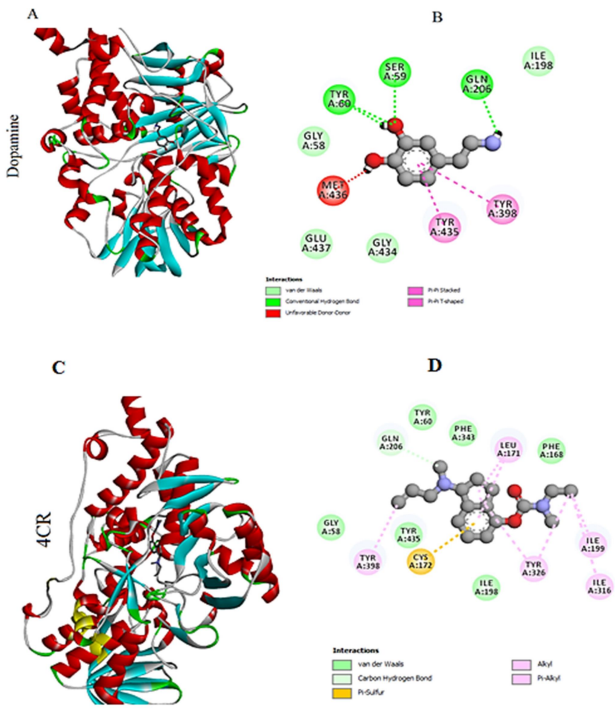

Fig. 8: 3D orientation and 2D orientation of the molecular interaction of dopamine (A and B, respectively) and 4CR (C and D, respectively) in the active site of MAO-B (PDB ID: 2C65) during molecular docking (AutoDock). The 2D depiction of dopamine and 4CR in the active site of the MAO-B enzyme shows the residues involved in hydrogen bonding or polar interactions, van der Waals, and hydrophobic interactions in coloured circles or legends in all 2-dimensional figures.

Table 1: Physicochemical and drug-likeness properties of test compounds

Property	Result (vNN-ADMET, SwissADME and admetSAR Tools)			
Compound	Morin	Piceatannol	Resveratrol	Gallic Acid
Molecular formula	$C_{15}H_{10}O_7$	$C_{14}H_{12}O_4$	$C_{14}H_{12}O_3$	$C_7H_6O_5$
Molecular weight	302.24	244.24	228.24	170.12
Hydrogen bond donors	7	4	3	4
Hydrogen bond acceptors	5	4	3	5
Rotatable bonds	1	2	2	1
Consensus Log P	1.2	2.14	2.48	0.21
Topological polar surface area	131.36 Å²	80.92 Å²	60.69 Å²	97.99
Lipinski's rule of five	Passed	Passed	Passed	Passed
GI absorption	High	High	High	High
CYP2D6 inhibitors	Yes	Yes	No	No
CYP3A4 inhibitors	Yes	Yes	Yes	Yes
BBB permeant	No	No	Yes	No
Synthetic Accessibility	3.25	2.09	2.02	1.22
PAINS alerts	0	1	0	1
Bioavailability score	0.55	0.55	0.55	0.56

the action of monoamine oxidase-B, which breaks down dopamine into homovanillic acid and 3,4-dihydroxyphenylacetic acid (Sung et al. 2022). The major therapeutic approach to managing PD before the commencement of levodopa is via enhancement of dopamine neurotransmission by preventing dopamine breakdown by MAO-B, which in turn maintains the brain's dopamine levels to compensate for the loss of functioning brain cells. In MAO-B (PDB ID: 2c65), the investigated standard drugs showed docking scores between -8.0 and -7.4 kcal/mol, while selected phytochemicals, except gallic acid exhibited better docking scores comparatively. Based on this conjecture and the fact that there are no or minimal side effects attributable to the selected phytochemicals, it is suggested that these phytochemicals, especially morin's ability to improve motor dysfunction and inhibit dopamine depletion in an acute PD model as demonstrated by Lee et al. (2016), Rajput et al. (2021), and Ishola et al. (2022), could be through inhibition of MAO-B rather than just through anti-inflammatory action. Hence, morin is suggested to be a better therapeutic approach in the management of PD.

Conclusion

The least binding energy was found to be -10.0 kcal/mol and corresponded to the phytochemical morin, with maximum potency among the drug candidates under study. Keeping the above study under consideration, further modifications can be made using morin as the reference of choice for better MAO-B inhibitory activity.

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No funding was received.

Conflict of Interest
None declared.

Authors' Contribution
Conception: POA; Writing of manuscript: POA, BVO, NOA, and NHA; Literature search and data collection: POA, BVO, NOA, and NHA.

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