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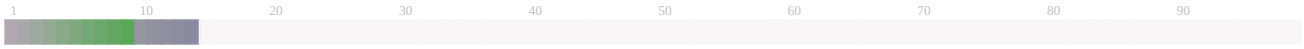

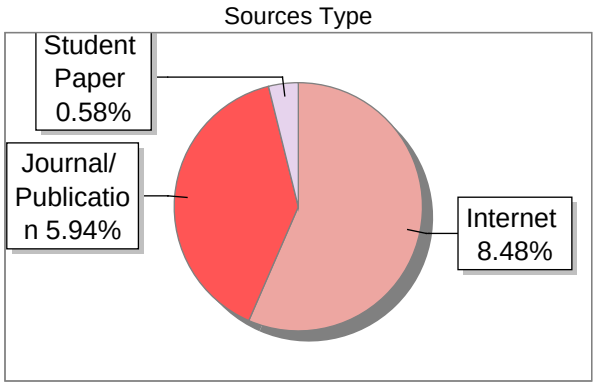

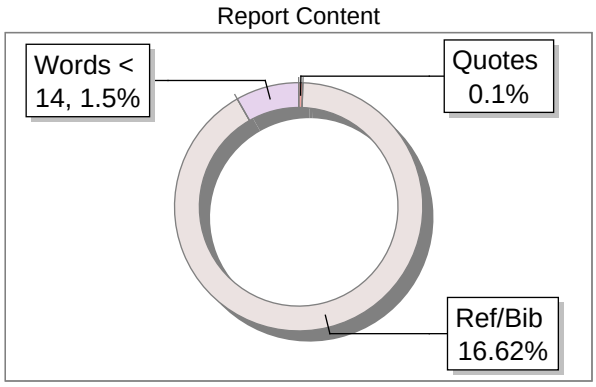

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In Silico Study of Purple Yam Anthocyanin Compounds (*Dioscorea alata* L.) As MAO-B and COMT Inhibitors in Parkinson's Disease

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ABSTRACT

The purple yam plant (*Dioscorea alata* L.) is an economically important staple food for millions of people in tropical and subtropical regions. Dioscorea spp. anthocyanin chemicals have been demonstrated to have antioxidant and neuroprotective properties. The purpose of this study was to explore the potency of anthocyanin compounds in purple yam as antiparkinsonian agents via the monoamine oxidase B (MAO-B) receptor (pdb: 2V5Z) and the catechol-O-methyltransferase (COMT) receptor (pdb: 6I3C) using a molecular docking technique. The study was divided into four stages: (1) pharmacokinetic and Lipinski Rule evaluation, (2) protein (receptor) and ligand preparation, (3) docking method validation, and (4) molecular docking for MAO-B and COMT proteins.

Pharmacokinetic prediction and Lipinski rule evaluation revealed that cyanidin, delphinidin, and delphinidin-3-glucoside had an ADMED profile and met Lipinski's rule. The docking results showed that the binding energy (ΔG) of the compounds cyanidin, delphinidin, and delphinidin-3-glucoside to the MAO-B receptor was lower (-9.50 kcal/mol) than that of the natural ligands (-4.79 kcal/mol). The Cys172, Leu 171, Ile198, Phe168, Pro104, Trp119 and the 'gatekeeper' residue Ile199 are the amino acids that are majoring involved in MAO-B inhibitors. At the COMT receptor, all the tested compounds had a higher binding energy than native ligands (> -4.79 kcal/mol) except for Cyanidin 3,5-diglucoside (-4.64 kcal/mol). The amino acids Trp143 and Pro174, ensure correct substrate orientation, Mg^{2+} ions, and cofactor SAM, as well as residues Lys144 and Glu199.

In conclusion, this study showed that based on the molecular docking approach, the active compounds of purple yam namely cyanidin, delphinidin, and delphinidin-3-glucoside have the potential to be developed as anti-parkinsonian agents through MAO-B and COMT

1. Introduction

Parkinson's disease is a motor function condition defined by dopaminergic function loss due to the loss of pigmented dopaminergic neurons and the presence of Lewy bodies (extrapyramidal system in the motor structure of the basal ganglia). There are roughly 6.1 million Parkinson's disease patients globally, and the prevalence increases with age, reaching 1% to 3% in the population over 65 years of age (Santos García et al., 2019). Parkinson's disease symptoms include tremors, bradykinesia, and muscle rigidity, as well as changes in gait and posture. Parkinson's disease is characterized by the loss

of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and depletion of dopaminergic levels in the striatum. The buildup of proteins is one of the most significant pathways implicated in the development of Parkinson's, including the accumulation of protein aggregates, failure of protein clearance pathways, mitochondrial damage, oxidative stress, excitotoxicity, neuroinflammation, and mutations (Maiti et al., 2017).

Levodopa is usually recognized as the most effective symptomatic treatment for Parkinson's disease and is required by nearly all patients at some time during their illness (Chen et al., 2016; Tambasco et al., 2018). Long-term use of levodopa, however, can induce motor difficulties such as wear and tear ('on-off') and dyskinesia. Dopamine agonists (DAs) or enzyme inhibitors, such as catechol-O-methyl-transferase (COMT) inhibitors and monoamine oxidase B (MAO-B) inhibitors, are commonly used as adjuvants to levodopa to ease motor difficulties. COMT inhibitors, such as entacapone and opicapone, diminish levodopa degradation in the peripheral nervous system, whereas MAO-B inhibitors cross the blood-brain barrier and limit central MAO activity in the CNS, thereby reducing dopamine degradation (Gershanik, 2015). MAO-B inhibitors have been shown to be extremely effective and safe in the early stages of Parkinson's disease. Therefore, MAO-B and COMT inhibitors are excellent strategies treatment. Many studies have explored potential anti-Parkinson agents, both from synthetic compounds and natural products (Mythri & Bharath, 2012).

A wide number of plant metabolites with the ability to inhibit one or both isoforms of MAO have been discovered through investigation of different diets and herbal treatments (Candeletori et al., 2014). Flavonoids found in plants, such as (+)-catechin, (+)-epicatechin, and naringenin, have been shown to inhibit MAO-B (Olsen et al., 2008). Piperine and its related chemicals found in long pepper plants (Piper longum) are known to be powerful MAO-B inhibitors (Lee et al., 2005). Anthocyanins, which are abundant in plants, such as cherry and red chicory, can block MAO-B. Anthocyanins are an intriguing phytochemical that has the potential to be developed as an anti-Parkinson medication by inhibiting MAO-B and COMT (Dreiseitel et al., 2009; Fang et al., 2020). Fruits and vegetables contain anthocyanins, which are responsible for the red, purple, and blue colors. One of the Indonesian natural plants that consists of purple pigment that is associated with the major anthocyanin constituent is Dioscorea spp.

The anthocyanin compounds found in *Dioscorea alata* L. are cyanidin 3-(6-synapyl gentiobioside), cyanidin-3-diglucoside, cyanidin-3,5-diglucoside, delfinidin-3-glucose-5-rutinoside, delfinidin-3-glucoside, and delfinidin-3,5-diglucoside (Adomėnienė & Venskutonis, 2022). Moreover it has been proved that extracts rich in anthocyanins exhibit greater neuroprotective activity than extracts rich in other polyphenols, and some anthocyanins impair rotenone neurotoxicity (Strathearn et al., 2014). Therefore, in this study, we investigated the potency of anthocyanin compounds of *Dioscorea alata* L as MAO-B and COMT inhibitors, an important enzyme in Parkinson's disease by molecular docking method. As part of the development of natural resources, *Dioscorea alata* L has been used in Parkinson's disease treatment. Molecular docking is an early step in drug discovery, where potential drugs are compared to inactive compounds by specific receptor affinity (Torres et al., 2019). This process creates a bond energy value that indicates the amount of energy required to form the desired bond between the ligand (a potential drug) and receptor (a target protein). The smaller the bond energy, the more constant is the relationship between the two molecules, meaning that the activity of the potential drug is likely to increase (Khaerunnisa et al., 2020).

In this study, as shown in Fig. 1, there were eleven compounds were used, consisting of eight anthocyanin compounds from *Dioscorea alata* L (a-h), curcumin (i) as an established natural anti-Parkinson compound, safinamide (j), and 3,5-dinitrocatechol (k) as the native ligand of MAO-B and COMT proteins.

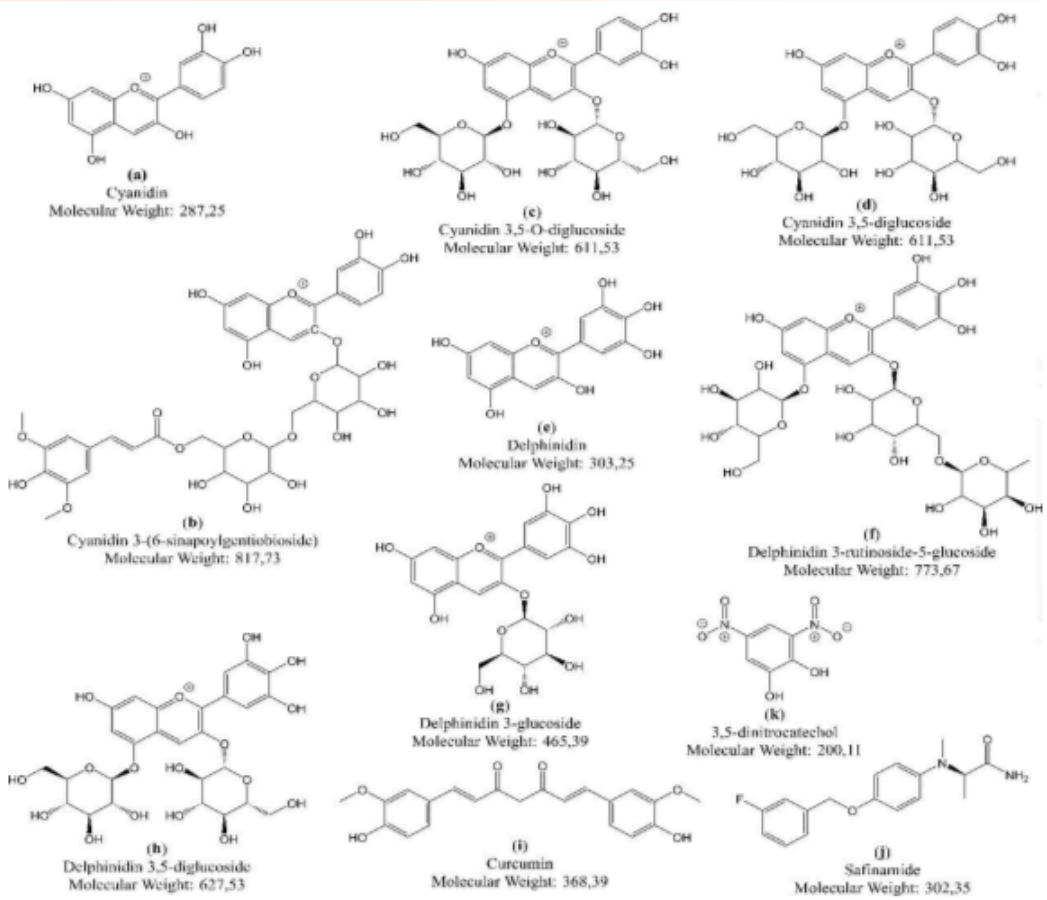

Fig. 1. The Structure of Tested Compounds. (a) Cyanidin, (b) Cyanidin 3-(6-sinapoylgentiobioside), (c) Cyanidin 3,5-O-diglucoside, (d) Cyanidin 3,5-diglucoside, (e) Delphinidin, (f) Delphinidin 3-rutinoside-5-glucoside, (g) Delphinidin 3-glucoside, (h) Delphinidin 3,5-diglucoside, (i) Curcumin, (j) safinamide and (k) 3,5-dinitrocatechol

2. Materials and Methods

2.4. Hardware

The hardware used was a ZYREX NoteBook with the Cruiser EM4100 model with Intel® Core™ i3-4030U CPU@ 1.90 specifications with 4 GB RAM, 500 GB SSD, Intel® HD Graphics 4400, and Windows 10 Pro 64 bit.

2.5. Software

Software used is Discovery Studio Visualizer v21.1.0.20298 , AutoDock 4.2, Lipinski Rule of Five (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp), and pkCSM (https://biosig.lab.uq.edu.au/pkcsm/prediction).

2.6. 2.3. Pharmacokinetic and toxicity prediction and Evaluation of Lipinski Rule

Pharmacokinetic and toxicity predictions were performed using pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction). The application of pkCSM is based on general compound qualities (molecular properties, toxicophores, and pharmacophores) as well as distance-based graph signatures. In the pkCSM, eight predictors describe the pharmacokinetic properties of a compound. The predictors were divided into the absorption of two predictors (intestinal absorption and P-glycoprotein substrate), distribution of two predictors (BBB permeability and CNS

permeability), metabolism of two predictors (CYP2D6 substrate and CYP3A4 substrate), excretion of two predictors (total clearance (log mL/min/kg) and renal OCT2 substrate), and toxicity of two predictors (mutagenic toxicity (AMES toxicity) and hepatotoxicity). The Lipinski Rule was evaluated by the Lipinski drug filter using the Lipinski Rule of Five in SCFBio (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp).

2.7. Receptor Preparation

In this study, the 2V5Z PDB protein was used as the MAO-B protein compound and the 6I3C protein as the COMT protein was downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/). Proteins were separated with water molecules and native ligands were separated from proteins using the Discovery Studio Visualizer v21.1.0.20298 and saved in ". pdb" format. In Autodock Tools 4.2, the receptor was set to only have polar hydrogen and the Kollman charge was added and saved in the ". pdbqt" file format.

2.8. Ligand Preparation

This study used ligand preparation where the test compound was downloaded at PubChem (https://pubchem.ncbi.nlm.nih.gov/), accessed on September 22, 2022. The test compounds used were purple yam (cyanidin, cyanidin 3-(6-synapoil gentiobioside), cyanidin-3-diglucoside, cyanidin-3,5-diglucoside, delfinidin, delfinidin-3-glucose-5-rutinoside, delfinidin-3-glucoside, and delfinidin-3,5-diglucoside) (Adomėnienė & Venskutonis, 2022) with the comparator curcumin. The ligand was set to only have polar hydrogen and added Gasteiger charge using Autodock Tools 4.2, then saved in ``. pdbqt" file format.

2.9. Molecular Docking Validation

Method validation was performed to ensure that the docking parameters were valid for the ligand docking process for the 2V5Z and 6I3C proteins. This validation was carried out by re-docking the native ligand, which had previously been separated into 2V5Z and 6I3C proteins. The 2V5Z redocking process was carried out using a grid box with a size of 60 × 60 × 60 with coordinates x = 15.427, y= 128,925, and z = 23.358, while 6I3C redocking was carried out using a grid box with a size of 40 × 40 × 40 with coordinates x = 2.562, y= -6.641, and z = 1.970. The docking parameters, including the Genetic Algorithm (GA) value, were set to 50, resulting in the Lamarckian GA output algorithm. Other docking parameters were set to their default values. Validation was adjusted using the RMSD value (less than 3 Å). The smaller the RMSD value, it indicates that the ligand position from the redocking results will be close to the ligand position from the crystallography results (Kontoyianni et al., 2004).

2.10. Protein-Ligand Docking

The grid box parameter setting was performed using Autodock-4. The x-, y-, and z-coordinates in the grid box were determined based on the coordinates of the native co-crystalline ligand from the receptor file used during validation. A docking process was then carried out between the test ligand and receptor using Autodock-4. The docking parameters used included the value of the Genetic Algorithm (GA) set at 100, and the Lamarckian GA was used as the output algorithm for the docking results. Other docking parameters were set to default parameters.

2.11. Analysis and Visualization of Molecular Docking Results

The conformation of the docked ligand (best pose) was determined by selecting the ligand with the lowest binding energy. The docking results with the best poses were then analyzed using Biovia Discovery Studio. The parameters analyzed included the binding energy (ΔG), inhibition constant (IC), amino acid residues, and bond interactions formed. The Biovia Discovery Studio software was used to visualize the 2D binding maps of the test compound to the protein.

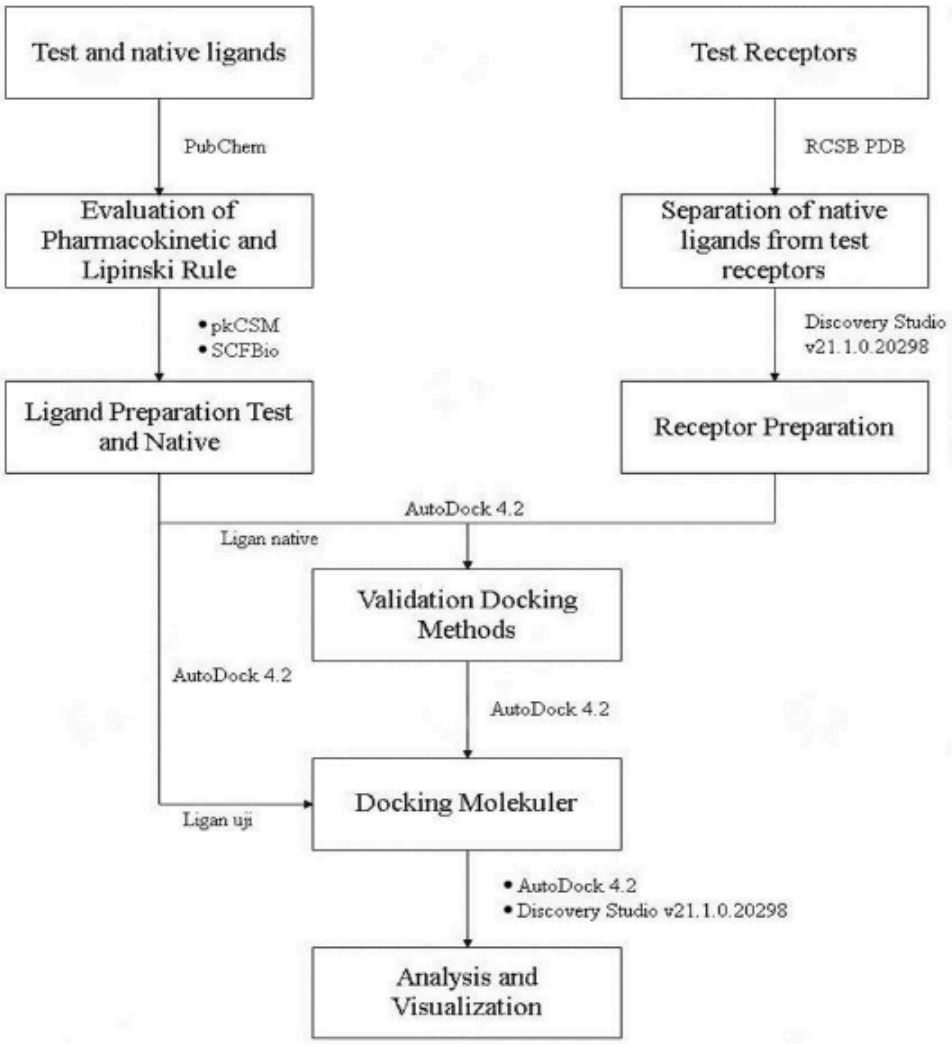

Fig.2. Research Procedure Flowchart

3. Results and Discussion

2.12.3.1. Prediction of pharmacokinetic and toxicity

Pharmacokinetics and toxicity were predicted for the eight compounds with the best scores in virtual screening via pkCSM. Several parameters have been observed in the prediction of pharmacokinetic parameters, such as absorption, distribution, metabolism, excretion, and toxicity. The categories of absorption observed were intestinal absorption and P-glycoprotein substrate, whether the distribution observed were the permeability of the blood-brain barrier (BBB permeability) and the permeability of the central nervous system (CNS permeability). Metabolism prediction was performed using CYP2D6 and CYP3A4 substrate parameters. The excretion prediction was presented as the total clearance (log ml/min/kg) and renal OCT2 substrate parameters. Mutagenic toxicity (AMES toxicity) and hepatotoxicity were considered as toxicity predictions.

Ta le 1. Predicted pharmacokinetic properties and toxicity

Compound	Intestinal Absorption (%)	P-glycoprotein substrate	BBB Permeability (logBB)	CNS Permeability (log PS)	CYP2D6 substrate	CYP3A4 substrate	Total Clearance (log mL/min/kg)	Renal OCT2 substrate	AMES Toxicity	Hepatoxicity
Curcumin	82.19	Yes	-0.562	-2.99	No	Yes	-0.002	No	No	No
Cyanidin	87.303	Yes	-1.234	-2.218	No	No	0.532	No	No	No
Cyanidin 3-(6-sinapoylgentiobioside)	19.663	Yes	-2.919	-5.347	No	Yes	0.897	No	No	No
Cyanidin 3,5-O-diglucoside	0	Yes	-2.366	-4.85	No	No	-0.164	No	No	No
Cyanidin 3,5-diglucoside	0	Yes	-2.366	-4.85	No	No	-0.164	No	No	No
Delphinidin	77.385	Yes	-1.62	-3.523	No	No	0.58	No	No	No
Delphinidin 3-rutinoside-5-glucoside	0	Yes	-2.982	-6.2	No	No	-0.439	Yes	No	No
Delphinidin 3-glucoside	32.504	Yes	-2.156	-4.45	No	No	0.507	No	No	No
Delphinidin 3,5-diglucoside	0	Yes	-2.725	-5.508	No	No	-0.181	No	No	No
Requirement Value	≥30	-	≥ -1	≥ -2	-	-	Higher is better	-	-	-

As shown in Table 1, three of the eight anthocyanin compounds had adequate absorption parameters (not less than 30%): cyanidin, delfinidin, delfinidin-3-glucoside, non-mutagenic, and hepatotoxic. poorly distributed in the brain because logBB < -1 (except curcumin) cannot penetrate the CNS because log PS < -2. Curcumin and Cyanidin 3-(6-sinapoylgentiobioside) are predicted to be metabolized in the liver by CYP3A4. In the excretion prediction, all eight tested compounds met the total clearance parameters. In addition, delphinidin 3- rutinoside-5-glucoside is predicted to bind with the renal organic cation transporter (Renal OCT2) enzyme. The toxicological prediction of the eight anthocyanin compounds were not mutagenic or hepatotoxic.

2.13.3.2 Evaluation of Lipinski Rule

The rules defined in the Lipinski rule were used to predict the physicochemical properties of the ligand by determining the hydrophobic/hydrophilic properties of the compound on the cell membrane through passive diffusion. The conditions that must be met in determining drug molecule candidate compounds that have been defined in the Lipinski rule are molecular weight < 500 Da to easily enter and penetrate the cell membrane, Log P value < 5 to be selective in binding to target proteins, number of donor hydrogen bonds < 5, number of acceptor hydrogen bonds <10, and reactive molar:40-130 (Sukmawaty et al., 2021). Candidate drug compounds have potential properties as new drugs if they meet two or more than 5 Lipinski provisions (Lipinski, 2004). Based on the observations in Table 2, the compounds cyanidin, delphinidin, and delfinidin-3-glucoside meet the minimum Lipinski standards that have been set. Therefore, these three active compounds have the potential to be developed into medicinal compounds.

Table 2. Lipinski Rule's Evaluation

Compound	Molecular Formula	Molecular Weight	Log P	Hydrogen Bond Donors	Hydrogen Bond Acceptor	Molar Refractivity	Lipinski Rule's
Curcumin	$C_{21}H_{20}O_6$	368.00	3.36990	2	6	102.02	+
Cyanidin	$C_{15}H_{11}O_6$	287.00	2.71889	5	6	73.71	+
Cyanidin 3-(6-sinapoylgentiobioside)	$C_{38}H_{41}O_{20}$	817.00	0.00329	11	20	193.20	-
Cyanidin 3,5-O-diglucoside	$C_{27}H_{31}O_{16}$	611.00	-2.33491	11	16	139.18	-
Cyanidin 3,5-diglucoside	$C_{27}H_{31}O_{16}$	611.00	-2.33491	11	16	139.18	-
Delphinidin	$C_{15}H_{11}O_7$	303.00	2.42449	6	7	75.38	+
Delphinidin 3-rutinoside-5-glucoside	$C_{33}H_{41}O_{21}$	773.00	-3.77751	14	21	172.06	-
Delphinidin 3-glucoside	$C_{21}H_{21}O_{12}$	465.00	-0.10241	9	12	108.11	+
Delphinidin 3,5-diglucoside	$C_{27}H_{31}O_{17}$	627.00	-2.62931	12	17	140.84	-

Notes: + = accepted; - = not accepted

Intestinal absorption in pharmacokinetics has a unique relationship with Lipinski s rule. Cyanidin, delfinidin, delphinidin-3-glucoside, and curcumin with an intestinal absorption value above 70% usually meet the Lipinski rule, especially in terms of molecular weight, log P, hydrogen donor, and acceptor. The number of hydrogen-bond donors is greater than 5, and the number of H-bond acceptors is greater than 10, even if only applied to compounds that are not substrates for active transporters (Benet et al., 2016). As the conclusion based on pharmacokinetic prediction and Lipinski rule selection, anthocyanin compounds from *Dioscorea alata* L have a chance to explore its activity to Parkinson's receptors by molecular docking.

2.14.3.3. Molecular Docking Study

The crystal structures of MAO-B and COMT receptors are presented in Fig. 3. The three-dimensional structure of MAO-B was obtained by X-ray diffraction with a resolution of (1.60 Å). Monoamine oxidase B crystallizes as dimers with 993 residues and 7911 atoms (Soufi et al., 2020). The COMT receptor with a resolution of 1.34 Å was containing 232 amino acids in a single chain and co-crystallized with cofactor $Mg2^+$, SAM, and 3,5-DNC inhibitor.

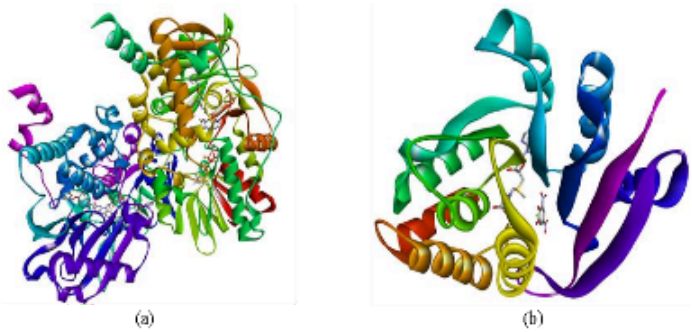

Fig 3. Receptor crystal form (a) MAO-B/2V5Z (b) COMT/6I3C

The docking process on the MAO-B and COMT receptors was validated by the redocking method using Autodock-4 on the active site of the co-crystal ligand. The results of re-docking on the MAO-B receptor showed the smallest RMSD value of 2.002 Å < 3 Å, and the COMT receptor showed the smallest RMSD value of 0.528 Å < 3 Å. This result indicated that the conformation of the ligand from the redocking results was highly similar to the crystallographic results (Fig.4.)

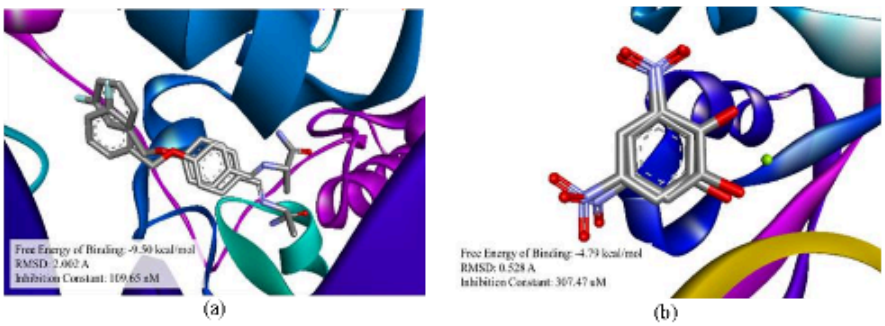

Fig 4. Molecular Docking Validation Results (a) MAO-B/2V5Z (b) COMT/6I3C

Molecular docking (reverse docking) is one of the initial stages of target identification and validation for identifying compounds that are potential/active as drug candidates from many inactive compounds. Molecular docking data indicated that the compound has an affinity for the target protein (Khaerunnisa et al., 2020).

The results obtained from docking of the test compounds with MAO-B and COMT receptors were in the form of bond energies, inhibition constants, and hydrogen bonds. The expected result was that the bond energy and inhibition constants of the tested compounds were lower than those of the native ligands. The binding energies of the tested compounds to the MAO-B receptor tend to show lower values compared to their native ligands (<-9.50 kcal/mol) except for curcumin and cyanidin 3-(6-sinapoylgentiobioside) and delphinidin 3-glucoside compounds whose bond energies are close to native ligands. Meanwhile, the binding energy of the tested compounds to the COMT receptor showed a higher value compared to the native ligand (>-4.79 kcal/mol) except for Cyanidin 3,5-diglucoside whose bond energy was close to that of the native ligand. The inhibition constant of the tested compounds towards the MAO-B receptor tended to be higher than that of the native ligands (>109.65 nM), except for curcumin. The inhibition constant of the test compound against the COMT receptor was lower than that of its native ligand (-307.47 µM), except for cyanidin 3,5-diglucoside, as shown in Table 3.

Furthermore, molecular docking visualization was performed to determine the interactions between the receptor and ligand. At the MAO-B receptor, hydrophobic interactions were formed by Cys172, Leu 171, Ile198, Phe168, Pro104, Trp119 and the 'gatekeeper' residue Ile199 (Dhiman et al., 2020). The COMT receptor was surrounded by "gatekeeping" residues Trp143 and Pro174, which ensure correct substrate orientation, Mg^{2+} ions, and cofactor SAM, as well as residues Lys144 and Glu199, which are involved in substrate binding (Cruz-Vicente et al., 2022). In general, the type and motif of the receptor interactions of the tested compounds were similar to those of native ligand. The visualization results are presented in Supplementary Material Table S1, Figure S1, and Figure S2.

All the tested compounds had a lower binding energy than the native ligands at the MAOB receptor (-9.50 kcal/mol); however, the cyanidin, definidin, and delphinidin-3-glucoside compounds had a modest variation in binding energy. The tested compounds possessed native ligand-like hydrogen bonds with Cys 172 and non-hydrogen bonds with Ile199. Except for Cyanidin 3-(6-sinapoylgentiobioside), all the tested compounds exhibited a greater inhibitor constant than the native ligand (> 109.65 nM). The tested chemical has a lower binding energy than the native ligand (-10.41 kcal/mol), similar hydrogen and non-hydrogen bonds, and a greater inhibitor constant (> 23.44 nM) than the native ligand, except for Cyanidin 3-(6-sinapoylgentiobioside), Delphinidin 3,5-diglucoside is less effective against the MAOB receptor due to differences in binding mode.

Table 3. Molecular Docking Result

Compound	MAO-B		COMT	
	Binding energy (kcal/mol)	Inhibitor Constant	Binding energy (kcal/mol)	Inhibitor Constant
Ligand Native	-9.50	109.65 nM	-4.79	307.47 uM
Curcumin	-10.41	23.44 nM	-8.12	1.12 µM
Cyanidin	-8.73	398.50 nM	-6.69	12.41 µM
Cyanidin 3-(6-sinapoylgentiobioside)	-13.01	291.72 pM	-8.69	428.78 nM
Cyanidin 3,5-O-diglucoside	-8.02	1.33 µM	-5.75	61.44 µM
Cyanidin 3,5-diglucoside	-7.65	2.48 µM	-4.64	491.26 µM
Delphinidin	-8.45	639.02 nM	-7.10	6.25 µM
Delphinidin 3-rutinoside-5-glucoside	-7.61	2.63 µM	-4.98	223.02 µM
Delphinidin 3-glucoside	-9.12	206.05 nM	-6.64	13.57 µM
Delphinidin 3,5-diglucoside	-5.54	87.33 µM	-5.19	157.16 µM

Table 4. Mechanisms related to antiparkinsonism in curcumin and anthocyanins

Compound	Mechanism	Literature
Curcumin	a. Curcumin has been found to inhibit the MAO-B enzyme, resulting in higher levels of dopamine in the brain. b. Curcumin has been found to have protective effects on the number of TH-positive neurons, as well as on the level of striatal dopamine and its metabolites. c. restores neuronal regeneration by stimulating Trk/PI3K signaling cellular cascade, reducing levels of tumor necrosis factor-α (TNF-α) and caspase activity, hence increasing levels of BDNF in 6-OHDA model of PD d. α7-nAChRs is a potential therapeutic target and curcumin would be the first natural agent which is reported to modulate nicotinic receptors in PD	(Nebrisi, 2021)
Anthocyanins	a. The presence of glycosylated B-ring structure in anthocyanin enhances its antioxidant activity, particularly when the B-ring is orthohydroxylated and methoxylated. b. The anthocyanin mixture reduced the level of intracellular ROS in a dose-dependent manner in human brain neuroblastoma SK-N-SH cells. c. The anthocyanins prevented the activation of apoptosis signal-regulating kinase 1 (ASK1)–JNK/p38 pathways, increased the expression of heme oxygenase 1, and upregulated the expression of sialidase 1 (also known as Neu1) gene.	(Khoo et al., 2017)

The tested compounds, with the exception of cyanidin 3,5-diglucoside (-4.64 kcal/mol), had a higher binding energy at the COMT receptor than native ligands (> -4.79 kcal/mol). Similar to the native ligand, the test compounds formed hydrogen bonds with Lys144 and Glu199, and non-hydrogen bonds with Pro174. Compared to native ligands, all compounds studied had a low Inhibitor Constant (307.47 uM). Exceptions included cyanidin 3,5-diglucoside and cyanidin 3-(6-sinapoylgentiobioside). The test compounds have a lower binding energy (-8.12 kcal/mol) than the native ligand, similar hydrogen bonds and non-hydrogen bonds, and a greater Inhibitor Constant (> 1.12 uM) than native ligands. Cyanidin 3,5-diglucoside is less potent against COMT receptors because its binding energy is lower than that of the native ligand and curcumin.

The ability of curcumin to modulate the function of several signal transduction pathways has been strongly associated with reduced disease progression by modulating and interacting with multiple cell and protein signaling pathways. This suggests that curcumin is an effective multitarget compound. The inhibitory effect of curcumin on MAO-B enzymes increases the level and availability of dopamine in the brain. Previous studies in animal models of 6-OHDA have demonstrated that curcumin enhances the life recovery of striatal fiber tyrosine hydroxylase and SNpc neurons, reduces abnormal turning behavior, and exerts neuroprotective properties, at least in part, through α7-nAChR-mediated mechanisms (Nebrisi, 2021).

Purple cauliflower anthocyanins have been shown to increase monoamine neurotransmitter content and inhibit monoamine oxidases (MAO) in the brain (Fang et al., 2020). Anthocyanin molecules, on the other hand, can alleviate Parkinson's symptoms owing to their neuroprotective properties. The neuroprotective function of anthocyanins is to lower the intracellular ROS levels in neuroblastoma cells. SK-N-SH Anthocyanins also suppress ROS-dependent activation of the apoptotic signal regulatory kinase 1 (ASK1)-JNK/p38 pathway, as well as upregulate heme oxygenase 1 expression and sialidase gene expression 1 (also known as Neu1) (Khoo et al., 2017). Furthermore, the limitations of this study were that it only focused on anthocyanin chemicals in purple yams. In light of the other phytochemical substances found in purple yam, molecular docking investigations of MAO-B and COMT were conducted.

4. Conclusion

In summary, based on pharmacokinetic prediction by PreADMET and Lipinski rule screening and molecular docking with MAO-B and COMT enzymes, three of eight anthocyanin compounds of *Dioscorea alata* L, namely, cyanidin, delphinidine, and delfinidin-3-glucoside, can be developed as anti-parkinsonian agents through MAO-B and COMT receptors using a molecular docking approach. Prior to the development of new drug compounds, further validation must be performed using in vitro and in vivo tests.

Supplementary Materials

The authors can provide supplementary files, such as figures or tables. Supplementary data can be written in Figure S1: title and Table S1: title.

Author Contributions: Muhammad Marwan Ramadhan and Dwi Utami conceived of and designed the study. Muhammad Marwan Ramadhan performed all data analysis. Muhammad Marwan Ramadhan, Dwi Utami, and Sapto Yuliani interpreted the result and revised the paper. Muhammad Marwan Ramadhan.Dwi Utami supervised the manuscript. All authors have read and approved the final manuscript

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Competing Interests

The authors declare no conflicts of interest.

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References

Adomėnienė, A., & Venskutonis, P. R. (2022). Dioscorea spp.: comprehensive review of antioxidant properties and their relation to phytochemicals and health benefits. *Molecules*, *27*(8), 2530. https://doi.org/10.3390/molecules27082530

B. Mythri, R., & M. Srinivas Bharath, M. (2012). Curcumin: a potential neuroprotective agent in parkinson's disease. *Current Pharmaceutical Design*, *18*(1), 91–99. https://doi.org/10.2174/138161212798918995

Benet, L. Z., Hosey, C. M., Ursu, O., & Oprea, T. I. (2016). BDDCS, the Rule of 5 and drugability. *Advanced Drug Delivery Reviews*, *101*, 89–98. https://doi.org/10.1016/j.addr.2016.05.007

Carradori, S., D'Ascenzio, M., Chimenti, P., Secci, D., & Bolasco, A. (2014). Selective MAO-B inhibitors: a lesson from natural products. *Molecular Diversity*, *18*(1), 219–243. https://doi.org/10.1007/s11030-013-9490-6

Chen, S., Chan, P., Sun, S., Chen, H., Zhang, B., Le, W., Liu, C., Peng, G., Tang, B., Wang, L., Cheng, Y., Shao, M., Liu, Z., Wang, Z., Chen, X., Wang, M., Wan, X., Shang, H., Liu, Y., … Xiao, Q. (2016). The recommendations of chinese parkinson's disease and movement disorder society consensus on therapeutic management of parkinson's disease. *Translational Neurodegeneration*, *5*(1), 12. https://doi.org/10.1186/s40035-016-0059-z

Cruz-Vicente, P., Gonçalves, A. M., Ferreira, O., Queiroz, J. A., Silvestre, S., Passarinha, L. A., & Gallardo, E. (2022). Discovery of small molecules as membrane-bound catechol-O-methyltransferase inhibitors with interest in parkinson's disease: pharmacophore modeling, molecular docking and in vitro experimental validation studies. *Pharmaceuticals*, *15*(1), 51. https://doi.org/10.3390/ph15010051

Dhiman, P., Malik, N., & Khatkar, A. (2020). Natural based piperine derivatives as potent monoamine oxidase inhibitors: an in silico ADMET analysis and molecular docking studies. *BMC Chemistry*, *14*(1), 12. https://doi.org/10.1186/s13065-020-0661-0

Dreiseitel, A., Korte, G., Schreier, P., Oehme, A., Locher, S., Domani, M., Hajak, G., & Sand, P. G. (2009). Berry anthocyanins and their aglycons inhibit monoamine oxidases A and B. *Pharmacological Research*, *59*(5), 306–311. https://doi.org/10.1016/j.phrs.2009.01.014

Fang, J.-L., Luo, Y., Jin, S.-H., Yuan, K., & Guo, Y. (2020). Ameliorative effect of anthocyanin on depression mice by increasing monoamine neurotransmitter and up-regulating BDNF expression. *Journal of Functional Foods*, *66*, 103757. https://doi.org/10.1016/j.jff.2019.103757

Gershanik, O. S. (2015). Improving L- dopa therapy: The development of enzyme inhibitors. *Movement Disorders*, *30*(1), 103–113. https://doi.org/10.1002/mds.26050

Khaerunnisa, S., Suhartati, & Awaluddin, R. (2020). *Penelitian in silico untuk pemula*. Airlangga University Press.

Khoo, H. E., Azlan, A., Tang, S. T., & Lim, S. M. (2017). Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits. *Food & Nutrition Research*, *61*(1), 1361779. https://doi.org/10.1080/16546628.2017.1361779

Kontoyianni, M., McClellan, L. M., & Sokol, G. S. (2004). Evaluation of docking performance: comparative data on docking algorithms. *Journal of Medicinal Chemistry*, *47*(3), 558–565. https://doi.org/10.1021/jm0302997

Lee, S. A., Hong, S. S., Han, X. H., Hwang, J. S., Oh, G. J., Lee, K. S., Lee, M. K., Hwang, B. Y., & Ro, J. S. (2005). Piperine from the Fruits of Piper longum with Inhibitory Effect on monoamine oxidase and antidepressant-like activity. *Chem. Pharm. Bull.*, *53*(7), 832—835.

Lipinski, C. A. (2004). Lead- and drug-like compounds: The rule-of-five revolution. *Drug Discovery Today: Technologies*, *1*(4), 337–341. https://doi.org/10.1016/j.ddtec.2004.11.007

Maiti, P., Manna, J., & Dunbar, G. L. (2017). Current understanding of the molecular mechanisms in Parkinson's disease: Targets for potential treatments. *Translational Neurodegeneration*, *6*(1), 28. https://doi.org/10.1186/s40035-017-0099-z

Nebrisi, E. El. (2021). Neuroprotective activities of Curcumin in parkinson's disease: a review of the literature. *International Journal of Molecular Sciences*, *22*(20), 11248. https://doi.org/10.3390/ijms222011248

Olsen, H. T., Stafford, G. I., van Staden, J., Christensen, S. B., & Jäger, A. K. (2008). Isolation of the MAO-inhibitor naringenin from Mentha aquatica L. *Journal of Ethnopharmacology*, *117*(3), 500–502. https://doi.org/10.1016/j.jep.2008.02.015

Santos García, D., de Deus Fonticoba, T., Suárez Castro, E., Borrué, C., Mata, M., Solano Vila, B., Cots Foraster, A., Álvarez Sauco, M., Rodríguez Pérez, A. B., Vela, L., Macías, Y., Escalante, S., Esteve, P., Reverté Villarroya, S., Cubo, E., Casas, E., Arnaiz, S., Carrillo Padilla, F., Pueyo Morlans, M., … Villar, M. D. (2019). Non-motor symptoms burden, mood, and gait problems are the most significant factors contributing to a poor quality of life in non-demented Parkinson's disease patients: Results from the COPPADIS Study Cohort. *Parkinsonism & Related Disorders*, *66*, 151–157. https://doi.org/10.1016/j.parkreldis.2019.07.031

Soufi, W., Merad, M., Hacene, F. B., & Ghalem, S. (2020). Study of monoamine oxidase-B and indole derivatives using two molecular docking programs: molegro and MOE. *International Journal of Scientific Research and Management*, *8*(09), 25–31. https://doi.org/10.18535/ijsrm/v8i09.c01

Strathearn, K. E., Yousef, G. G., Grace, M. H., Roy, S. L., Tambe, M. A., Ferruzzi, M. G., Wu, Q.-L., Simon, J. E., Lila, M. A., & Rochet, J.-C. (2014). Neuroprotective effects of anthocyanin- and proanthocyanidin-rich extracts in cellular models of Parkinson′s disease. *Brain Research*, *1555*, 60–77. https://doi.org/10.1016/j.brainres.2014.01.047

Sukmawaty, E., Susanti, S., & Masriany, M. (2021). Penambatan molekuler senyawa cendawan endofit Trichoderma sp. sebagai inhibitor protein low density lipoprotein, enzim lanasterol 14 demetilase dan lipase yang bertanggung jawab dalam dermatitis seboroik. *Jurnal Ilmiah Ibnu Sina (JIIS): Ilmu Farmasi Dan Kesehatan*, *6*(1), 98–107. https://doi.org/10.36387/jiis.v6i1.636

Tambasco, N., Romoli, M., & Calabresi, P. (2018). Levodopa in Parkinson's Disease: Current Status and Future Developments. *Current Neuropharmacology*, *16*(8), 1239–1252. https://doi.org/10.2174/1570159X15666170510143821

Torres, P. H. M., Sodero, A. C. R., Jofily, P., & Silva-Jr, F. P. (2019). Key topics in molecular docking for drug design. *International Journal of Molecular Sciences*, *20*(18), 4574. https://doi.org/10.3390/ijms20184574