ORIGINAL ARTICLE

In silico molecular docking analysis of selected phytoconstituents from *Psydrax dicoccos* (Gaertn.) against Parkinson's disease

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Abstract

Introduction: Parkinson's disease is a major neurodegenerative disorder that occurs due to the loss of dopamine in *Substantianigra* pars compacta. The disease can be treated by inhibiting α-synuclein protein, monoamine oxidase-B (MAO-B), a neurotransmitter (dopamine) pack in the synaptic vesicle, and inflammation. **Material and Methods:** Six phytoconstituents were identified from a plant *Psydrax dicoccos* of the family, Rubiaceae. Sequesterpenes and coumarins are found in this plant which is a source of neuroprotection. Ligands were analyzed for docking analysis using Autodock Vina software against the targets (α-synuclein, heat shock protein-70, matrix metalloprotease-3, synaptic vesicle protein, nitric oxide synthase, cannabinoid receptor type-2, MAO-B, and Nrf2 [nuclear factor erythroid 2-related factor-2]) of Parkinson's disease and compared with standards. Multiple targets were selected due to complexity of Parkinson's disease. It has a complex structure and a variety of molecular proteins affects the desired effect of the drug. Docking interactions are identified by Biovia Discovery Studio Visualizer 2021. *In silico* pharmacokinetics (ADME) was analyzed by Swiss ADME, ADMET lab. The effectiveness of the ligands was predicted by Molinspiration studies. **Result:** The results showed that that the anti-Parkinson compounds activity was due to their action on multiple targets. Examining all the parameters, it shows that *P. dicoccos* has the potential to cure Parkinson's disease. **Conclusion:** In this study, it was concluded that all six ligands scored well compared to those of standards. All ligands exhibited good pharmacokinetics low solubility, optimal ($CaCo_2$ permeability, volume of distribution, and plasma protein binding), and BBB tolerant.

KEYWORDS: *Psydrax dicoccos*, Autodock Vina, ADMET lab, Swiss ADME, Molinspiration, Neuroprotection

INTRODUCTION

Psydrax dicoccos Gaertn., the species, belongs to the family Rubiaceae, commonly known as Ceylon Box wood. Synonyms used for this plant are *Canthium cymosum* (Poir.) *Pers.*, *Canthium dicoccum* (Gaertn.) *Merr.,* and *Webera cymosa*. In India, it is known as Tupa, Arsul, and Earkollimaram. It is a smooth shrub 3–4 m high. It is distributed in low-altitude areas, found from South East China to Tropical Asia. The bark leaves and roots are used. Fruit pulp is reported to be edible.[1] Plant contains phytoconstituents such as alkaloids, tannins, flavonoids, saponins, coumarins, sequesterpenes, and terpenes which have antifungal, anti-diarrheal, febrifuge, antibacterial, anti-inflammatory, antidiabetic, arthritic, nephroprotective, and hepatoprotective properties. The bark of the plant is used to treat fever and the decoction of roots is used to treat diarrhea.[2]

Natural remedies have been shown to be effective as that of allopathic in the treatment of the disease. Herbal remedies have fewer side effects, less expensive and can be made available to everyone. Many of the existing plants around us such as neem, tulsi, and hibiscus are useful as a remedy for a number of ailments.[3] With the emergence of the coronavirus,

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it is 100% true that naturopathic is equivalent to allopathic in the present case. The ethanolic plant extracts contain coumarins and sequesterpenes such as 7-Ethoxy Coumarin, caryophyllene oxide, Cedr-8-en-13-ol, spathulenol, ledene oxide, and scopoletin.[4] Coumarins and sequesterpenes present are potential resource for neuroprotection in many studies by interacting with various proteins such as monoamine oxidase-B (MAO-B) and nuclear factor erythroid 2-related factor-2 (Nrf2) and exhibit various activities such as antidepressant, antiepileptic, and antioxidative. They, therefore, act as an arena to achieve better bioactivity in the treatment of PD.[5]

Parkinson's disease is one of the most progressive neurodegenerative diseases, caused by a decrease in the level of dopamine in *Substantia nigra* pars compacta. It affects mainly the population above the age of 50.[6] There are two mechanisms of the disease: Early onset of Parkinson's disease and late onset of Parkinson's disease.[7] There is no ideal treatment for the disease, with the present medications such as levodopa, dopamine agonists, MAO-B inhibitors, and catechol o-methyl transferase inhibitors relieve the symptoms and prevent the progression of the disease for a limited period. New technologies such as deep brain simulation are also be used to manage the condition.[8]

The mechanisms involved in the pathophysiology of the disease include modification of regulatory proteins such as α-synuclein, hyperphosphorylation of Tau protein, genetic modifications – SNCA, PARK, LRRK2, DJ-1, mitochondrial dysfunction, oxidative stress, excitotoxicity, natural pesticides, and chemicals such as MPTP and neuroinflammation.[9]

Molecular docking is an important tool in drug discovery and development of the current scenario. Through the use of the docking studies, binding affinity of small molecules in their protein targets such as receptors, enzymes, and transporters is identified. It is mainly used to predict bonds and strength between the molecules. The aim of the docking studies is to eliminate all the free energy between the molecules and the corresponding alignment between the ligand and the protein to produce and build stable structures.[10] Molecular docking makes the interaction of biocells and predicts the binding sites between ligand and receptor. Lesser the free energy, more intense the binding site. Free binding energy (ΔG) is defined in various parameters such as hydrogen bonds, hydrophobic interactions, and ionizability.[11]

Specific diseases such as Parkinson's, cancer, and Alzheimer's have complex structure and function that contain a variety of cells. In the olden days, single-targeted drugs were available to avoid unwanted side effects. Nowadays, there are many aspects of the emergence of the disease, in which the compounds screened have to achieve many targets to define the desired effect of the treatment.[12] Novel targets are identified for the treatment of the disease such as GPR109A (hydroxycarboxylic acid receptor 2 and niacin receptor 1), C-abl, synaptic vesicle protein 2c (SV2C), non-tyrosine kinases, and molecular chaperones (HSP-70, HSP-90, and Bcl), which help to provide new information on the treatment of this disease.[13]

In recent years, plants have come a long way in treating various ailments. The secondary metabolites in the plant act as an active ingredient in medicinal plants.[14] Current research is aimed at predicting the binding affinities of the constituents with the target proteins (proteins, receptors, and enzymes) of the disease.

METHODOLOGY

All computational studies were conducted using VIAO, a Sony company with OS name features: Microsoft Windows 10 pro with a version 10.0.19042, x64-based PC, with processor Intel(R) Core™ iS-3210M CPU@ 2.50 GHz, 2501 MHz, 2 core(s), with 8 GB RAM.

Software's and online websites used for the study AutoDock MGL tools, Pymol, AutoDock VINA from the Scripps Research Institute, Biovia Discovery Studio Visualizer 2021, Swiss ADME, ADMET lab, Molsoft, Molinspiration.

Selection of Phytochemicals

The phytochemicals in the present study were obtained from a plant *P. dicoccos*, belong to the family Rubiaceae. Six phytochemicals were identified from the plant which is coumarins and sequesterpenes.[15]

Drug-Likeliness Test of Phytochemicals Based on Lipinski's Rule

Drug-likeliness of the ligands Log P, number of atoms, deviations, TPSA, Volume, no. of rotatable bonds, HBA, and HBD is made using ADMET lab (http://admet.scbdd.com/calcpre/calc_rules/) and Molsoft (https://molsoft.com/mprop/). These properties are known as the molecular descriptors of the ligand. Here, the descriptors of the ligand were analyzed based on the law of Lipinski, Veber's, Opera, and Ghose.[16]

Docking Studies

Protein preparation

A total of six proteins are involved in the study. Crystalline protein structures were downloaded from Protein Data Bank (PDB) site (https://www.rcsb.org/) [Table 1]. The protein was prepared using AutoDockTools (ADT) and stored in PDB format. The proteins are formed by addition of polar

Table 1: Targets with their PDB ID[13,18,19]

Targets	Abbreviation	PDB ID
Alpha synuclein	α-syn	3Q27
Heat Shock Protein-70	HSP-70	1S3X
Synaptic Vesicle Protein	SV2C	5JLV
Nitric Oxide Synthase	NOS	1M9M
Matrix Metalloproteinase-3	MMP-3	1HY7
Cannabinoid Receptor-2	CBR_2	5ZTY
Monoamine Oxidase-B	MAO-B	2BK4
Nuclear factor erythroid 2 related factor-2	Nrf2	1X2R

hydrogens, deletion of water molecules, and inclusion of Kollman charges. AutoDockTools stores the protein in PDBQT format.[17]

Ligand preparation

The ligands were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and the ligand preparation took place in AutoDockTools (\The Scripps Research Institute\Vina) by removing bonds, addition of torsions. The compounds were converted form SDF format to PDB format using Pymol software (https://pymol.org/2/).[20]

Docking Protocol

AutoDock VINA was used to conduct molecular docking research. The AutoGrid system is used to set grid points and spaces. Grid map 20 × 20 × 20 A˙ grid points and 0.375 A˙ spaces created. The configuration file is made using a note pad that contains information about grid points, grid spaces, and dimensions such as X, Y, and Z. A grid file is also created where it contains information of protein bindings. The pose with the lowest binding affinity is taken and the interactions were visualized.[21]

Analysis and Visualization

Binding sites were visualized using Biovia Discovery Studio Visualizer 2021 (https://discover.3ds.com/discovery-studio-visualizer-download) and ligand-receptor interactions were analyzed using AutoDockTools.[22]

ADME predictions

The pharmacokinetic properties of the ligands were predicted using Swiss ADME (http://www.swissadme.ch/), ADMET lab (http://admet.scbdd.com/).[23]

Bioactive scores prediction

All drugs have a very high number of targets that predict the drug-likeliness. Common targets such as GPCR ligands, ion channel modulator, kinase inhibitors, nuclear receptor ligands, and protease inhibitors were considered to predict the bioactivity of the drug, that is, mechanism of action. Bioactive scores for ligands are predicted by Molinspiration (https://www.molinspiration.com/cgi-bin/properties).[24]

RESULTS AND DISCUSSION

More than 60 million deaths are due to neurological disorders, the second of which is Parkinson's disease. Many drugs with a new way are designed for the treatment of PD [Figures 1-6]. Several plants have neuroprotective properties of treatment of CNS disorders.[25]

Drug-Likeliness

In this study, docking studies were performed on six phytoconstituents obtained from *P. dicoccos* against targets for PD. The physicochemical properties of ligands according to the rules of drug-likeliness are represented in Table 2 and molecular descriptors are described in Table 3. Drug-likeliness of the ligands is made as log P, MW, HBD, HBA, deviations, and rotatable bonds in which all ligands comply with Lipinski's, Veber's, and Ghose rule. There is no deviation from the ligands.

Molecular Descriptors

Molecular Docking

Molecular docking studies were performed for 15 ligands with targets such as α-synuclein, HSP-70, SV2C, MMP-3, and NOS [Figures 7 and 8]. Docking interaction results of the ligands with α-synuclein are represented in Table 4. In all ligands, ledene oxide exhibits highest binding affinity of −7.9 Kcal/Mole, which is free of amino acid residues interacting with hydrogen bonds [Figure 9b].

The docking interaction results of the ligands with HSP-70 are represented in Table 5. Spathulenol exhibits highest binding affinity of −7.2 Kcal/Mole and shown hydrogen bond interactions with ARG A: 72 [Figure 10b].

The docking interaction results of the ligands with SV2C are represented in Table 6. Scopoletin exhibits highest binding score of −6.3 Kcal/Mole and shown hydrogen bond interactions with LYS B: 1187 and LEU B: 1296 [Figure 11b].

The docking interaction results of the ligands with NOS are represented in Table 7. Spathulenol exhibits highest binding score of −7.5 Kcal/Mole and shown hydrogen bond interactions with PHE B: 468 and ARG B: 474 [Figure 12b].

The docking interaction results of the ligands with MMP-3 are represented in Table 8. Spathulenol exhibits highest

Table 2: Drug-likeliness analysis according to LIPINSKI rule of 5

Ligands	PubChem CID	Lipinski rules of five parameters				
		MW	Log P	HBA	HBD	nRB
7-Ethoxy coumarin	35703	190.20	2.42	3	0	2
Caryophyllene oxide	1742210	220.356	3.9	1	0	0
Cedr-8-en-13-ol	519545	220.35	3.3	1	1	1
Spathulenol	92231	220.35	3.3	1	1	0
Ledene oxide	91753473	220.35	3.6	1	0	0
Scopoletin	5280460	192.17	1.5	4	1	1

Table 3: Molecular descriptors of ligands

Ligands	Vol	Den	TPSA	MR	nA	nHet	fchar	nD
7-Ethoxy coumarin	170.93	0.975	39.45	53.65	24	3	0	0
Caryophyllene oxide	234.01	0.886	12.53	66.2	40	1	0	0
Cedr-8-en-13-ol	232.73	0.892	20.23	65.9	40	1	0	0
Spathulenol	233.07	0.913	20.23	65.9	40	1	0	0
Ledene oxide	228.53	0.754	12.53	64.1	40	1	0	0
Scopoletin	162.15	1.03	59.67	50.7	22	4	0	0

MW: Molecular weight; HBA: Hydrogen bond acceptor, HBD: Hydrogen bond donor; Vol: Volume; nRB: Number of rotatable bonds; MR: Molecular refractivity; nD: Deviations; nA: Number of atoms; Den: Density; TPSA: Topological surface area; nHet: Number of hetero atoms; fchar: Formal charge

Table 4: Interacting amino acid residues of alpha-synuclein with ligands

Ligands	Binding energy Δ G (Kcal/mol)	Binding interactions	
		Hydrogen bonds	Hydrophobic bonds
7-Ethoxy coumarin	−6.5	GLU A: 310, 311 VAL A: 303	ALA A: 302, TYR A: 91 ILE A: 318
Caryophyllene oxide	−7.5	--	ILE A: 318
Cedr-8-en-13-ol	−7.4	--	ILE A: 318, TYR A: 308, VAL A: 303
Spathulenol	−7.4	GLU A: 154	TYR A: 211
Ledene oxide	−7.9	--	ILE A: 318, ALA A: 302, VAL A: 303
Scopoletin	−6.7	SER A: 338, ARG A: 67	TYR A: 342
Levodopa (Standard)	−7.0	SO A: 4401, LYS A: 43, ASN A: 13, GLC B: 1	TYR A: 211

Table 5: Interacting amino acid residues of HSP-70 with ligands

Ligands	Binding energyΔG (Kcal/mol)	Binding interactions	
		Hydrogen bonds	Hydrophobic bonds
7-Ethoxy coumarin	−6.2	HIS A: 227, ARG	--
Caryophyllene oxide	−6.9	A: 72	VAL A: 59, ARG A: 264
Cedr-8-en-13-ol	−6.3	ARG A: 261	ARG A: 264
Spathulenol	−7.2	--	PHE A: 68
Ledene oxide	−7.0	ARG A: 72	CA A: 385
Scopoletin	−6.6	ARG A: 72	VAL A: 59, ARG A: 264
Levodopa (Standard)	−6.0	ARG A: 261, GLY A: 202, LYS A: 56, TYR A: 41	--

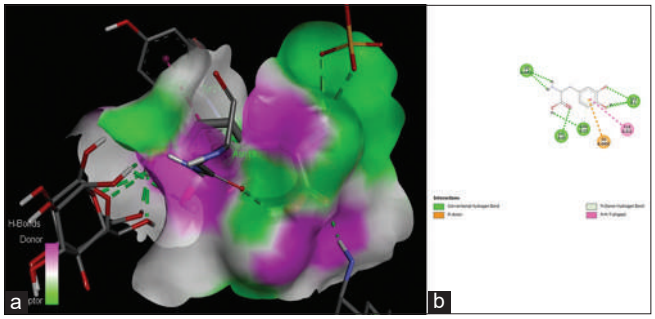

Figure 1: Interactions of levodopa (standard) with alpha-synuclein (a): 3D interactions (b): 2D interactions

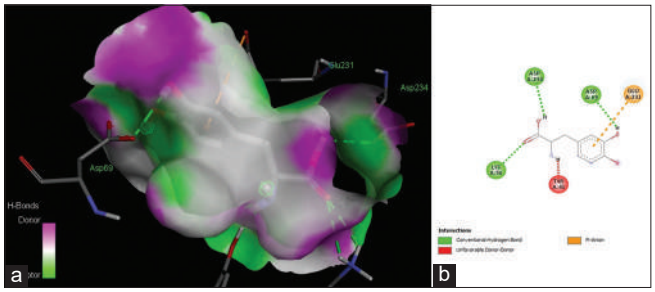

Figure 2: Interactions of levodopa (standard) with HSP-70 (a): 3D interactions (b): 2D interactions

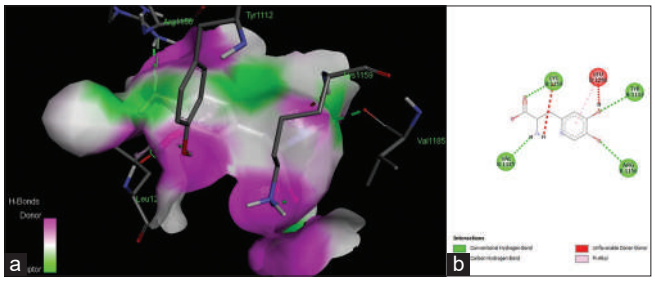

Figure 3: Interactions of levodopa (standard) with SV2C (a): 3D interactions (b): 2D interactions

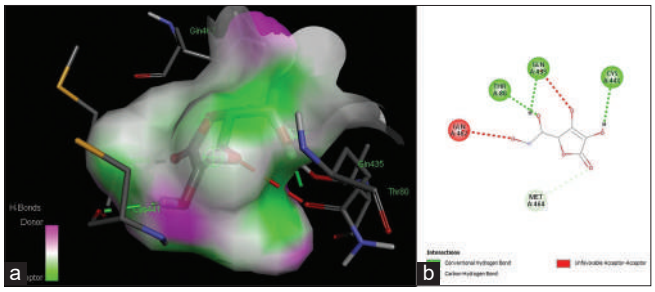

Figure 4: Interactions of ascorbic acid with NOS (a): 3D interactions (b): 2D interaction

binding score of −7.2 Kcal/Mole and shown hydrogen bond interactions with HIS A: 179, VAL A: 102, and VAL B: 648 [Figure 13b].

The docking interaction results of the ligands with CBR_2 are represented in Table 9. Caryophyllene oxide exhibits highest binding score of −6.1 Kcal/Mole with no hydrogen bond interactions [Figure 14b].

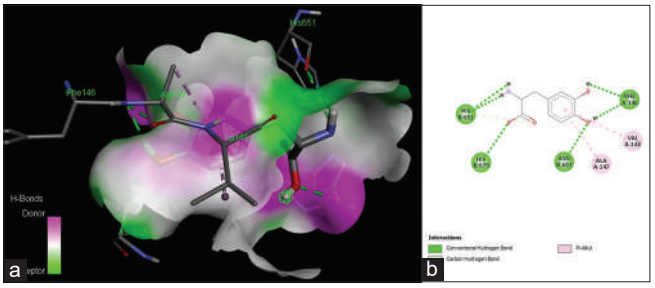

Figure 5: Interactions of levodopa (standard) with MMP-3 (a): 3D interactions (b): 2D interactions

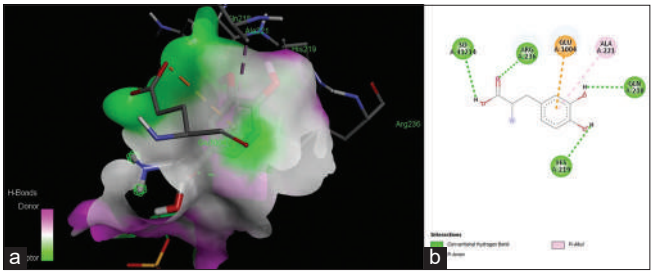

Figure 6: Interactions of levodopa (standard) with CBR_2 (a): 3D interactions (b): 2D interactions

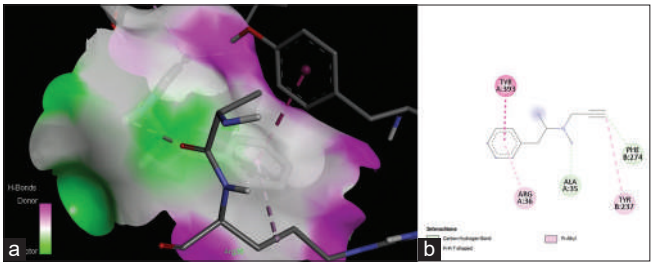

Figure 7: Interactions of selegiline with MAO-B (a): 3D interactions (b): 2D interactions

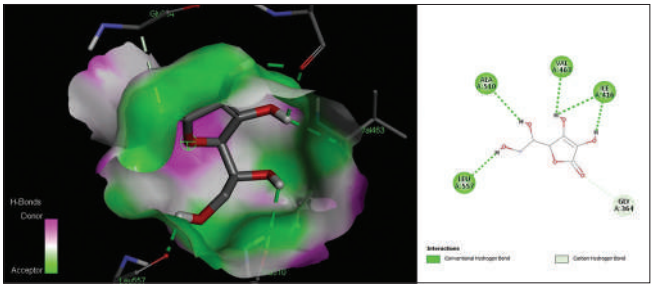

Figure 8: Interactions of ascorbic acid with Nrf2 (a): 3D interactions (b): 2D interactions

The docking interaction results of the ligands with MAO-B are represented as Table 10. Ledene oxide exhibits highest binding score of −6.5 Kcal/Mole and shown hydrogen bonding interactions with GLN A: 392 and TYR A: 393 [Figure 15b].

The docking interaction results of the ligands with Nrf2 are represented in Table 11. Cedr-8-en-13-ol exhibits highest binding score of −7.5 Kcal/Mole and shown hydrogen bond interactions with VAL A: 512, 465 [Figure 16b]. All targets SV2C, NOS, MMP-3, HSP-70, α-synuclein, CBR_2, MAO-B,

Table 6: Interacting amino acid residues of SV2C with ligands

Ligands	Binding energy∆G (Kcal/mol)	Binding interactions	
		Hydrogen bonds	Hydrophobic bonds
7-Ethoxy coumarin	–5.7	HIS A: 1064 LYS C: 558	--
Caryophyllene oxide	–6.0	ASN B: 1188	--
Cedr-8-en-13-ol	–5.7	LYS B: 1187	LEU B: 1296
Spathulenol	–6.1	GLY B: 1157	LEU B: 1296
Ledene oxide	–6.1	TYR B: 1112	LEU B: 1296
Scopoletin	–6.3	TYR B: 1112, LEU B: 1296, LYS B: 1187	VAL B: 1186, ALA B: 1158
Levodopa (Standard)	V5.9	LYS B: 1159, VALB: 1185, TYR B: 1112, ARGB: 1156	--

Table 7: Interacting amino acid residues of NOS with ligands

Ligands	Binding energy∆G (Kcal/mol)	Binding interactions	
		Hydrogen bonds	Hydrophobic bonds
7-Ethoxy coumarin	–6.7	SER A: 78, GLN A: 462	VAL A: 71,465, LEU A: 431
Caryophyllene oxide	–7.2	ASN B: 466	PRO B: 182
Cedr-8-en-13-ol	–7.0	ARG B: 183, ASN B: 466	PRO B: 182
Spathulenol	–7.5	--	PHE B: 468, ARG B: 474
Ledene oxide	–7.4	--	ARG B: 183, TYR B: 475
Scopoletin	–6.9	TYR B: 475, ASP B: 444, ASN B: 466	ARG B: 474, PRO B: 182
Ascorbic acid (Standard)	–6.5	THR A: 80, GLN A: 435, CYS A: 441	--

Table 8: Interacting amino acid residues of MMP-3 with ligands

Ligands	Binding energy∆G (Kcal/mol)	Binding interactions	
		Hydrogen bonds	Hydrophobic bonds
7-Ethoxy coumarin	–6.7	HIS A: 179	VAL A: 102, VAL B: 648
Caryophyllene oxide	–7.0	--	--
Cedr-8-en-13-ol	–6.9	--	VAL A: 102, MET A: 343, VAL B: 648
Spathulenol	–7.2	--	HIS A: 179, VAL A: 102, VAL B: 648
Ledene oxide	–7.0	HIS A: 179, SER A: 145	VAL B: 648, VAL A: 102
Scopoletin	–6.5	HIS A: 179, ASN A: 103	VAL B: 648, VAL A: 102
Levodopa (Standard)	–6.2	HIS A: 651, HIS B: 679, ASN B: 603, PHE A: 146	ALA A: 147, VAL A: 148

and Nrf2 are docked with their respective standards (ascorbic acid, levodopa, and diclofenac) and showed lesser binding affinity compared to selected phytochemicals.

The ligands docked are bounded at the same active site but their interactions with amino acids are different. The interactions (hydrogen and hydrophobic) between molecules are shown as amino acid residues.[26] The key amino acids involved in α-synuclein interactions are ILE A: 318 and TYR A: 211. Amino acids involved in HSP-70 are VAL A: 59 and ARG A: 264. The amino acids involved in the interactions of SV2C are LYS B: 1187, TYR B: 1112,

Table 9: Interacting amino acid residues of CBR2 with ligands

Ligands	Binding energy Δ G (Kcal/mol)	Binding interactions	
		Hydrogen bonds	Hydrophobic bonds
7-Ethoxy coumarin	–5.7	ARG A: 1007	ILE A: 1008
Caryophyllene oxide	–6.1	--	LEU A: 133,145,153
Cedr-8-en-13-ol	–5.3	--	LEU A: 125,126,201
Spathulenol	–5.4	--	MET A: 157
Ledene oxide	–5.7	--	ALA A: 252, LEU A: 251
Scopoletin	–5.5	SO A: 41215	OLC A: 1205
Levodopa (Standard)	–5.6	SO A: 41214, ARG A: 236, GLN A: 218, HIS A: 219	OLC A: 1205, ILE A: 206, ILE A: 1008, ARG A: 1007 ALA A: 221

Table 10: Interacting amino acid residues of MAO-B with ligands

Ligands	Binding energyΔG (Kcal/mol)	Binding interactions	
		Hydrogen bonds	Hydrophobic bonds
7-Ethoxy coumarin	–6.2	LYS B: 648	ALA B: 325, LEU B: 167, 345
Caryophyllene oxide	–6.3	ASP A: 37	ARG A: 36
Cedr-8-en-13-ol	–6.4	--	PRO A: 234
Spathulenol	–6.1	--	ARG A: 36, TYR A: 393, PROB: 277
Ledene oxide	–6.5	GLN A: 392, TYR A: 393	PRO B: 277
Scopoletin	–6.0	GLU B: 320	ALA B: 325, LEU B: 167
Selegiline (Standard)	–4.9	--	ARG A: 36, TYR B: 237

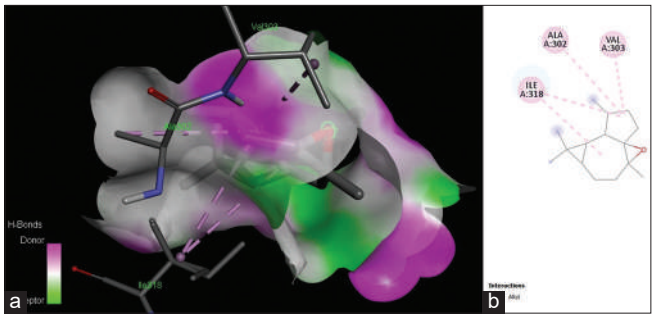

Figure 9: Interactions of ledene oxide with alpha-synuclein (a): 3D interactions (b): 2D interactions

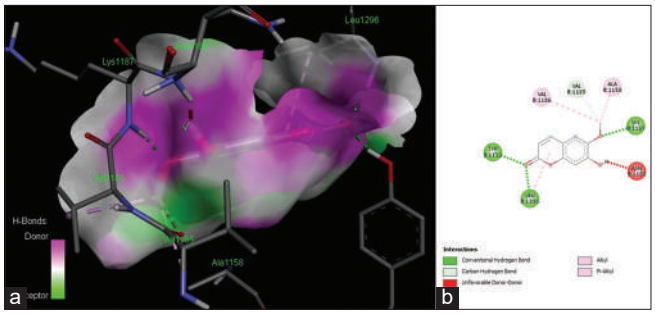

Figure 11: Interactions of scopoletin with SV2C (a): 3D interactions (b): 2D interactions

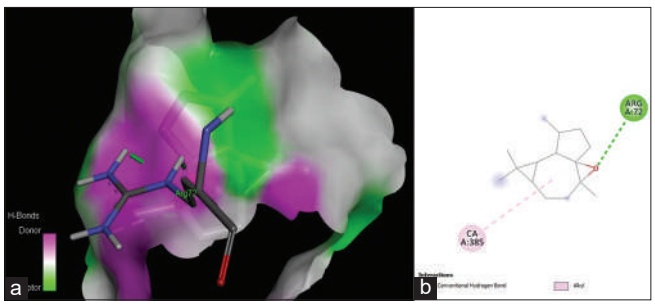

Figure 10: Interactions of spathulenol with HSP-70 (a): 3D interactions (b): 2D interactions

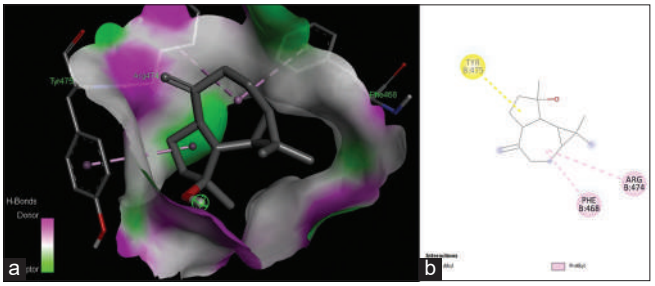

Figure 12: Interactions of spathulenol with NOS (a): 3D interactions (b): 2D interactions

Table 11: Interacting amino acid residues of Nrf2 with ligands

Ligands	Binding energy ΔG (Kcal/mol)	Binding interactions	
		Hydrogen bonds	Hydrophobic bonds
7-Ethoxy coumarin	–6.8	VAL A: 606, GLY A: 367	ALA A: 366, ARG A: 415
Caryophyllene oxide	–7.3	--	ALA A: 366
Cedr-8-en-13-ol	–7.5	VAL A: 512, 465	ALA A: 366
Spathulenol	–6.9	--	VAL A: 606, 366
Ledene oxide	–6.7	--	ALA A: 366
Scopoletin	–7.1	GLY A: 367, VAL A: 606	--
Ascorbic acid (Standard)	–6.8	ALA A: 510, LEU A: 557, VAL A: 463, ILE A: 416	--

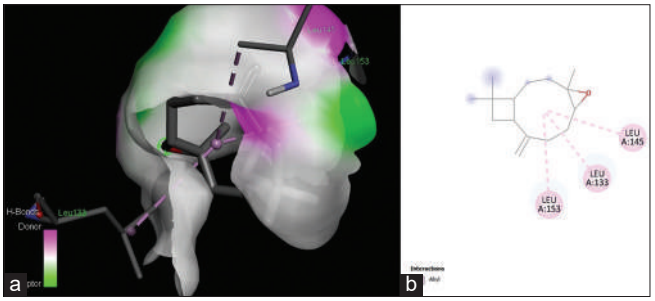

Figure 13: Interactions of caryophyllene oxide with CBR_2 (a): 3D interactions (b): 2D interactions

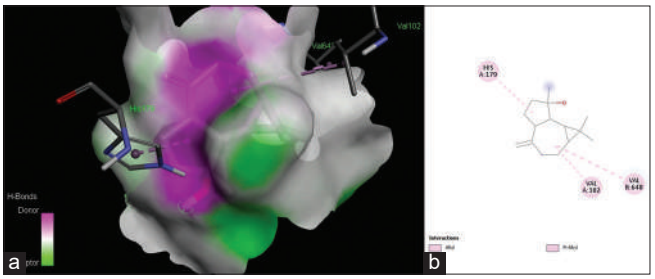

Figure 14: Interactions of spathulenol with MMP-3 (a): 3D interactions (b): 2D interactions

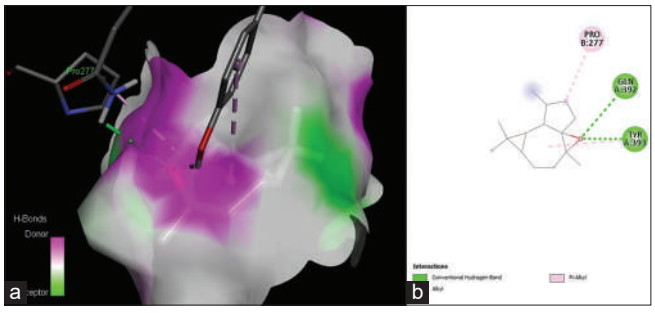

Figure 15: Interactions of ledene oxide with MAO-B (a): 3D interactions (b): 2D interactions

and LEU B: 1296. ASN B: 466, PRO B: 182, and VAL A: 449 are the key amino acids involved in the interactions of NOS. The amino acids involved in case of MMP-3 are

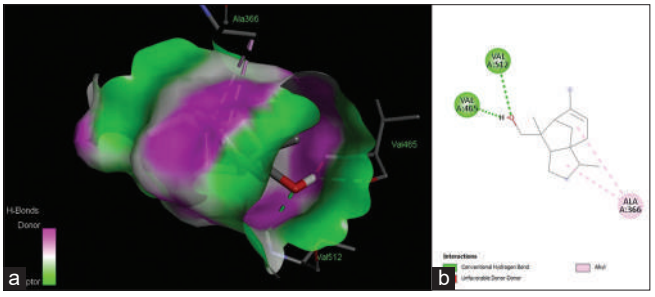

Figure 16: Interactions of Cedr-8-en-13-ol with Nrf2 (a): 3D interactions (b): 2D interactions

HIS A: 179 and VAL B: 648. The key amino acids involved in the interactions of CBR2 are ILE A: 1008 and OLC A: 1205. Amino acids of MAO-B are ALA B: 325, LEU B: 167, and PRO B: 277. The amino acids of Nrf2 involved are VAL A: 463 and ALA A: 366.

Bioactive Scores of Ligands

The biological activities of the compounds on common targets are shown in Table 12. Caryophyllene oxide and Cedr-8-en-13-ol act as a nuclear receptor ligand and exhibit enzyme inhibitory activity. Spathulenol acts as a nuclear receptor ligand.

ADME

Pharmacokinetic properties of ligands (ADME) were predicted and shown in Table 13, intestinal absorption, BBB permeable. The CYP450 enzymes (1A2, 3A4, 2C9, 2C19, and 2D6) are all the non-inhibitors. Half-life is low with <3 h. Clearance is also low at a rate of <5 ml/kg/min. All the compounds are lipophilic where they easily cross the cell membrane to show their action. Log P and TPSA are the two parameters defining lipophilicity (Log p <5, topological polar surface area [TPSA] <140).

Table 12: Bioactive scores of ligands

Ligands	GPC ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
7-Ethoxy coumarin	−1.15	−0.77	−1.22	−0.87	−1.18	−0.45
Caryophyllene oxide	−0.08	0.14	−0.86	0.62	0.00	0.57
Cedr-8-en-13-ol	−0.18	−0.01	−0.70	0.34	−0.48	0.55
Spathulenol	−0.42	−0.28	−0.68	0.28	−0.36	0.06
Ledene oxide	−0.48	−0.36	−0.89	−0.24	−0.25	−0.13
Scopoletin	−1.00	−0.65	−0.95	−0.81	−1.16	−0.24

Table 13: Pharmacokinetic profile of ligands

Pharmacokinetic property	Ligands					
	7-Ethoxy coumarin	Caryophyllene oxide	Cedr-8-en-13-ol	Spathulenol	Ledene oxide	Scopoletin
BBB Permeable	+	+	+	+	+	+
HIA (%)	+	+	+	+	+	+
P-glycoprotein I	I	NI	NI	NI	I	NI
P-glycoprotein S	NS	NS	NS	NS	NS	NS
CYP1A2 I	I	NI	NI	NI	NI	I
CYP2C19I	NI	NI	NI	NI	NI	NI
CYP2C9 I	NI	NI	NI	NI	NI	NI
CYP2D6 I	NI	NI	NI	NI	NI	NI
CYP3A4 I	NI	NI	NI	NI	NI	NI
CL (ml/min/kg)	10.35 (M)	15.5 (H)	17.79(H)	14.582 (H)	19.53(H)	13.32 (M)
$T_{½}$ (h)	0.452 (S)	0.083 (S)	0.153 (S)	0.064 (S)	0.068 (S)	0.85 (S)

+: Positive effect, BBB: Blood–brain barrier, HIA : Human intestinal absorption, I: Inhibitor, NI: Non-inhibitor, NS: Non-substrate, S: Substrate, CYP (1A2, 2C19, 2C9, 2D6, 3A4): Cytochrome P450 metabolizing enzymes, CL: Clearance, $T_{1/2}$: Half-life, M: Medium, H: High, S: Short

CONCLUSION

In the *in silico* docking study, phytoconstituents are docked against targets of PD. Selected phytoconstituents, coumarins and sequesterpenes have anti-inflammatory, immunomodulatory, antifungal, anticancer, and antioxidant activities, used as the source of the work. The targets selected for the study cover the entire pathophysiology of the disease. Initially, an analysis of drug-likeliness was made in the information about the better output of ligands. Molecular docking, ADMET predictions, and bioactivities of ligands were performed. All the compounds comply with Lipinski's drug-likeliness, show intestinal absorption and BBB permeability. The compounds such as caryophyllene oxide, Cedr-8-en-13-ol, and spathulenol act as a nuclear receptor ligand and have an enzyme inhibitory activity. The results showed that the anti-Parkinson activity of the compounds was due to their action on multiple targets. Examining all the parameters shows that *P. dicoccos* has the potential to cure Parkinson's disease.

REFERENCES

1. Malakafe, *Psydrax dicoccos*. Ceylon Box Wood: Philippine Medicinal Herbs/Alternative Medicine. Stuartxchange Organization; 2018. Available from: http://www.stuartxchange.org/Malakafe.html [Last accessed on 2018 Jul 24].
2. Rao PS, Kumar VR. *In vitro* anti-oxidant and anti-helminthic potential of *Psydrus dicoccos*. World J Pharm Pharm Sci 2019;8:725-32.
3. Verma J, Mangal G, Garg G. Parkinson's disease: Treatment approach through Ayurveda. Int J Res Anal Rev 2019;6:454-65.
4. Rajeswari NR, Ramalakshmi S, Muthuchelian K. GC-MS Analysis of bioactive compounds from the ethanolic leaf extract of *Canthium dicoccum* (Gaertn.) Teijsm and Binn. J Chem Pharm 2011;3:792-8.
5. Tao D, Wang Y, Bao XQ, Yang BB, Gao F, Wang L, *et al*. Discovery of coumarin Mannich base derivatives as multifunctional agents against monoamine oxidase B and neuroinflammation for the treatment of Parkinson's disease. Eur J Med Chem 2019;173:203-12.
6. Marvanova M. Introduction to Parkinson's disease (PD) and its complications. Ment Health Clin 2016;6:229-35.
7. Ferguson CW, Rajput AH, Rajput A. Early-onset vs. Late-onset Parkinson's disease: A clinical pathological study. Can J Neurol Sci 2015;43:113-9.
8. Stoker TB, Barker RA. Recent developments in the treatment of Parkinson's disease. F1000Res

2020;9:F1000 Faculty Rev-862.
9. Malti P, Manna J, Dunbar GL. Current understanding of the molecular mechanisms in PD: Targets for potentials treatments. Transl. Neurodegener 2017;6:28.
10. Supriya T, Shankar M, Lalitha SK, Dastagiri J, Babu MN. An over view on molecular docking. Asian J Biochem Pharm Res 2016;3:83-9.
11. Par AM, Mir S. Molecular docking: Approaches, types, applications and basic challenges. J Anal Bioanal Tech 2017;8:356.
12. Ramsay RR, Popovic-Nikolic MR, Bolognesi ML. A perspective on multi-target drug discovery and design for complex diseases. Clin Transl Med 2018;7:3.
13. Rai SN, Singh P, Varshney R, Chaturvedi VK, Vamanu E, Singh MP, *et al*. Promising drug targets and assosciated therapeutic interventions in Parkinson's disease. Neural Regen Res 2021;16:1730-9.
14. Gurria, Kaur I, Sharma S, Bhardwaj K. Wonders of phytomedicine in the management of neurological disorders. Eur J Mol Clin Med 2020;7:2899-914.
15. Umaiyambigai D, Kumar KS, Raj GA. Phytochemical profile and anti-fungal activity of leaves methanol extract from the *Psydrax dicoccos* (Gaertn) Teys. and Binn. *Rubiaceae* family. Int J Pharmacol Phytochem 2017;7:53-61.
16. Prasanth D, Panda SP, Rao AL, Chakravarthi G, Teja N, Vani VB, Sandhya T. *In-silico* strategies of some selected phytoconstituents from *Zingiber officinale* as SARS CoV-2 main protease (Covid-19) inhibitors. Indian J Pharm Educ Res 2020;54:S699-75.
17. Muhammad S, Hassan SH, AI-Sehemi AG, Shakir HA, Khan M, Irfan M, *et al*. Exploring the new potential antiviral constituents of *Moringa oliefera* for SARS-COV-2 pathogenesis: An *in silico* molecular docking and dynamic studies. Chem Phys Lett 2021;767:138379.
18. More SV, Choi DK. Emerging preclinical pharmacological targets for Parkinson's disease. Oncotarget 2016;7:29835-63.
19. Abellanas MA, Aymerich MS. Cannabinoid receptor Type 2 as a therapeutic target for Parkinson's disease. In: Diagnosis and Management in Parkinson's Disease. Vol. 1., Ch. 33. Cambridge, Massachusetts: Academic Press; 2020. p. 557-73.
20. Seeliger D, de Groot BL. Ligand docking and binding site analysis with PyMOL and Autodock/Vina. J Comput Aided Mol Des 2010;24:417-22.
21. Azam SS, Abbasi SW. Molecular docking studies for the identification of novel melatoninergic inhibitors for acetyl serotonin-O-methyltransferase using different docking routines. Theor Biol Med Model 2013;10:63.
22. Bakr RO, Fayed MA, Salem MA, Hussein AS. Tecoma stans: Alkaloid profile and anti-microbial activity. J Pharm Bioallied Sci 2019;11:341-7.
23. Dong J, Wnag NN, Yao ZJ, Zhang L, Cheng Y, Quyang D, *et al*. ADMET lab: A platform for systemic ADMET evaluation based on a comprehensively collected ADMET database. J Cheminform 2018;10:29.
24. Jyothi P, Yellamma K. Molecular docking studies on the therapeutic targets of Alzheimer's disease (AChE and BChE) using natural bioactive alkaloids. Int J Pharm Pharm Sci 2016;8:108-12.
25. Amoateng P, Quansah E, Karikari TK, Asase A, Osei-Safo D, Kukuia KK, *et al*. Medicinal plants used in the treatment of mental and neurological disorders in Ghana. Evid Based Complement Altern Med 2018;1:1-14.
26. Drwal MN, Banerjee P, Dunkel M, Wettig MR, Preissner R. Pro Tox: A web server for the *in silico* prediction of rodent oral toxicity. Nucleic Acids Res 2014;1:w53-8.

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