Pharmacophore Modeling and Docking Studies of SNCA Receptor with Some Active Phytocompounds from Selected Ayurvedic Medicinal Plants Known for their CNS Activity

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Abstract. Neurodegeneration is an alarming problem all over the globe. The significant role of SNCA receptor has been well established in several neurodegenerative disorders including various types of progressive dementia—most commonly in Parkinson's disorder (PD) and Lewy body dementia. Phytocompounds selected from ayurvedic medicinal plants are thoroughly screened against the SNCA receptor (*in silico*). The gene receptor responsible for Parkinson's disorder (PD), SNCA, was taken for this work. Mutated mammalian SNCA implicated as one of the factors responsible for PD was taken from NCBI; templates as retrieved from BLAST were downloaded from PDB. The 3D structure of SNCA was modeled; the 3D structures of phytocompounds (unknown ligands) were taken from various online databases; phytocompounds were virtually screened against the SNCA receptor, and the best ligand was selected.

Keywords: Parkinson's disorder (PD) · SNCA · Pharmacophore · Modeling Ramachandran plot · Docking

1 Background

From very ancient days, different medicinal plants dealing with health care are part and parcel of major populations of India, and other Asian countries.

Parkinson's disorder (PD) is a movement disorder having well-expressed symptoms like slowing of movement, tremor, rigidity or stiffness, and balancing problems. As per Dr. Dickson, the typical patient with PD has Lewy bodies (aggregates of protein, alpha synuclein or SNCA) in the brain neurons. Research suggests that the above central nervous system (CNS) disorder, PD, is a combination of environmental factors and multi-gene mutation [1–6].

In the present study for the preliminary screening, the following medicinal plants have been selected to study the scope and activity of different compounds on CNS using the above-mentioned bioinformatic parameter. These are *Hydrocotyle asiatica/Centella*

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asiatica, *Bacopa monnieri*, *Convolvulus pluricaulis*, *Mucuna pruriens*, *Ocimum sanctum*, *Tinospora cordifolia*, *Curcuma longa, Nardostachys jatamansi, Gloriosa superba, Colchicum autumnale, etc*., especially considered in this work.

Mutations in the SNCA (alpha synuclein) receptor and is noted as causal factors for many CNS disorders is used in this work [7–9].

SNCA

Alpha synuclein is expressed in the brain and integrates presynaptic signals and membrane traffics, mutations and defects of are implicated in the pathogenesis of PD [10, 11]. Unconventionally spliced transcripts encoding different isoforms have been identified for this gene [12]. Researchers are still much unclear about the function of SNCA, though it is seen it generally maintains a supply of synaptic vesicles in presynaptic terminals by clustering synaptic vesicles and controls the release of dopamine which is an important neurotransmitter which critically controls the voluntary and involuntary movements [13].

In this work, the 3D structure of the SNCA receptor is modeled by homology modeling, using high-throughput screening (HTS), and its ligand is selected from Indian Ayurvedic Herbs.

2 Methodology

The 3D structure of the SNCA receptors was modeled using modeler software [14]. The SNCA receptor's amino acid sequence is downloaded from NCBI; its homologous templates were selected by BLAST (Table 1). The receptor and their corresponding templates were submitted to modeler software to model their 3D structure. Using Rampage Ramachandran plot server [15], the generated five models generated by modeler were evaluated and the selection of the best model was done (Table 2). The 3D structures of the unknown ligands (phytocompounds as in Table 3) were downloaded from various other online databases, and a phase database is generated [16]. Structure-based pharmacophore model is a unique procedure for generating energy-optimized e-pharmacophores. This was done by selecting the regular features of the 3D structure of SNCA receptor interacting with the known ligands; thus, phores were generated in the 3D structure of the SNCA receptor at the interaction sites with the above known ligands. Hence, these e-pharmacophores were used as queries for virtual screening [17, 18].

Docking was performed by PATCHDOCK server by selecting the best model (model 4) with the ligand selected by pharmacophore modeling, colchicine, to get the docked structure [19, 20].

3 Results and Discussions

3.1 Homology Modeling

The amino acid sequences of SNCA receptor were downloaded from NCBI (Table 1). Its homologous templates were selected by BLAST (Table 1).

Table 1. PD receptors with their GenBank accession number and homologous templates

Receptor	Accession number	Homologous templates
SNCA	P06241	2H8HA, 1Y57A, 1FMKA

The amino acid sequences of the receptors along with their homologous templates were submitted to modeler software for the generation of the 3D structures of the receptor using the principle of homology modeling [14]. Modeler generated five models for each receptor. The 3D models generated by modeler of SNCA (Table 3) are submitted to Rampage Ramachandran Plot server for model verification [15], and the best (Figs. 1 and 2) model was selected.

Table 2. Ramachandran plot analysis of SNCA receptor's modeler generated models

	Number of residues in favored region	Number of residues in allowed region	Number of residues in outlier region	
Model 1	493 (92.1%)	28 (5.2%)	14 (2.6%)	
Model 2	499 (93.3%)	27 (5.0%)	9 (1.7%)	
Model 3	497 (92.9%)	26 (4.9%)	12 (2.2%)	
Model 4	500 (93.5%)	26 (4.9%)	9 (1.7%)	Selected
Model 5	496 (92.7%)	28 (5.2%)	11 (2.1%)	

3.2 Structure-Based Pharmacophore

Pharmacophore sites were created in the SNCA receptor (model 4) using the known ligands, viz. phenothiazine, N-acylaminophenothiazine, N-alkylphenothiazine, stimovul, etorphine, propoxyphene, and pentazdine. The above ligands are established ligands for SNCA receptor [21, 22].

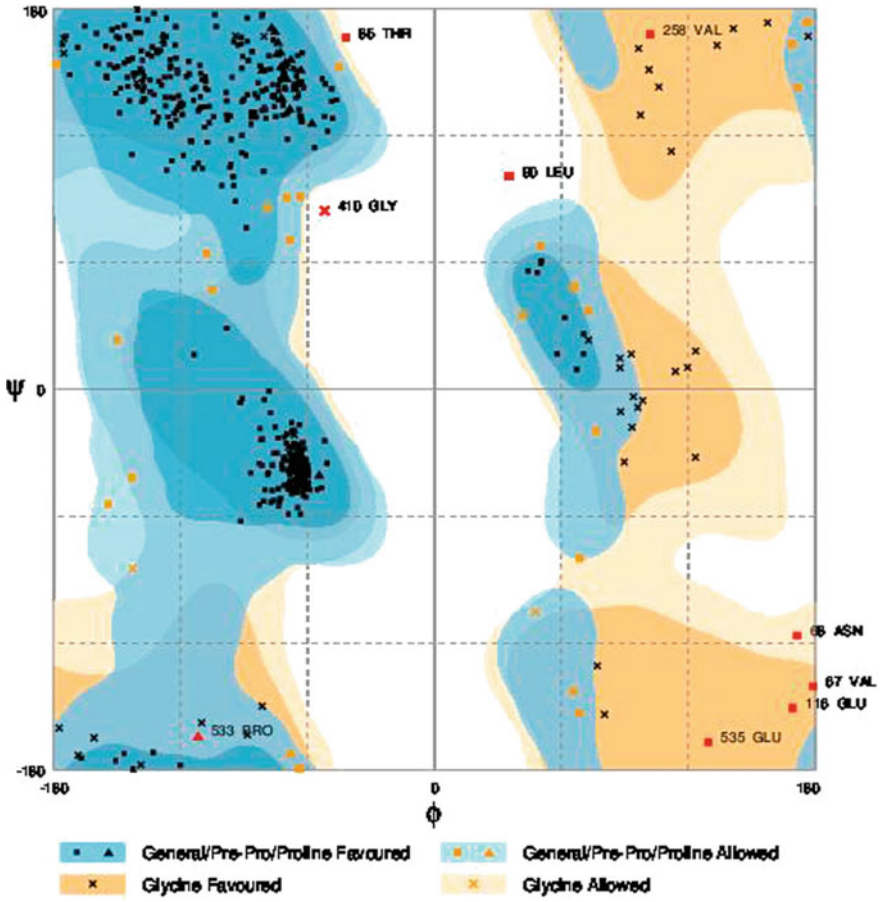

Fig. 1. Ramachandran plot analysis of SNCA receptor model 4

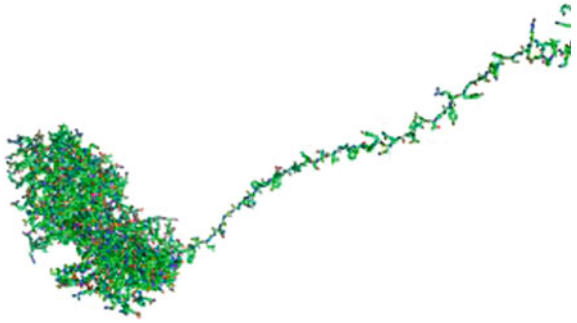

Fig. 2. 3D structure of SNCA receptor model 4

Based on preliminary screening, special emphasis is given on the following herbs having known phytocompounds as given in Table 3 were screened.

Table 3. Ayurvedic herbs (the source of phytocompounds) used in this work.

Source Natural remedies, Bengaluru, India, and Bhesaj Uddyan, Satsang, India
Plant Name/(with known phytocompounds)
Acorus calamus (acoradin)
Asparagus racemosus (racemosol)
Rauwolfia serpentina (rescinnamine)
Withania somnifera (withanone)
Andrographis paniculata (andrographolide)
Gloriosa superba (colchicine)
Colchicum autumnale (colchicine)
Centella asiatica (asiaticoside)
Convolvulus pluricaulis (shankhapushpine)
Ocimum sanctum (eugenol)

As per structure-based pharmacophore results, phytocompound having the fitness score 1.089598 was selected as the best fitted ligand (Fig. 3, Table 4) and the further docking studies were done using this phytocompound.

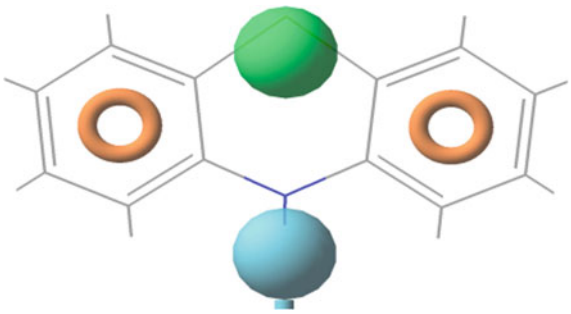

Fig. 3. Pharmacophore features of phenothiazine

Table 4. Results of pharmacophore modeling

Known ligand	Fitness score	Phytocompound	Plant name
Phenothiazine	1.089598	Colchicine	*Gloriosa superba and Colchicum autumnale*

3.3 Molecular Docking

SNCA receptor (model 4) was docked with the phytocompound using software PATCHDOCK [19, 20]. It was seen that SNCA receptor docks with the phytocompound, colchicine, with a docking score of −5566 kcal/mol (Fig. 4, Table 5).

From the above result is compared with the docking interactions of SNCA receptor

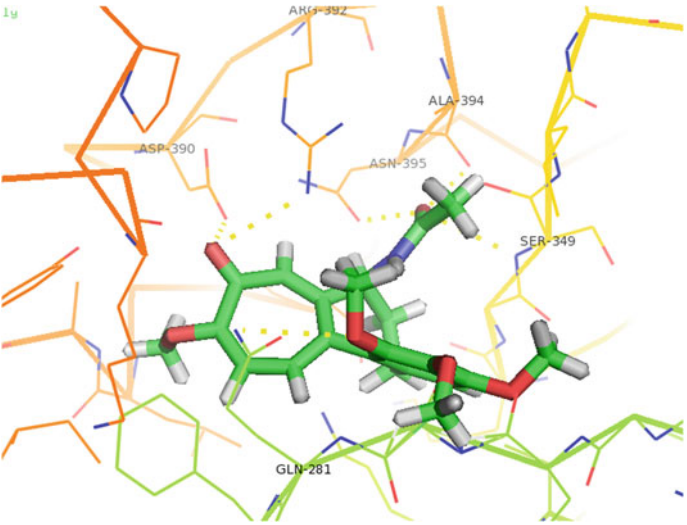

Fig. 4. Docked structure of SNCA receptor with phytocompound colchicine

Table 5. Docking results of SNCA receptor with phytocompound colchicine, jatamanin11, and bacopaside I

Phytocompound	Interacting amino acids	Docking score (in kcal/mol)	Docking
Colchicine	GLN281, ASP390, ARG392, ALA394, SER349, ASN395	−5566	Yes
Jatamanin11	ASP121, ASN122, GLU126, TYR125	−7.33	Yes
Bacopaside I	LEU350, LYS299, TYR420	5106	Yes

with known phytocompounds Jatamanin11 from *Valeriana jatamansi* (Fig. 5) [23, 24] and Bacopaside I from *Bacopa monnieri* (Fig. 6) [25] which were established as ligands for PD [23, 25] in our previous works.

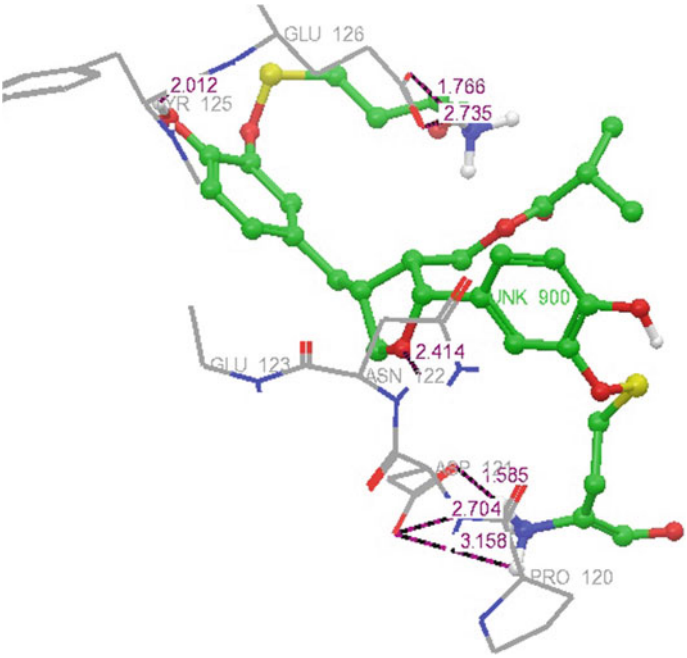

Fig. 5. Docked structure of SNCA receptor with phytocompound jatamanin11 [23, 24]

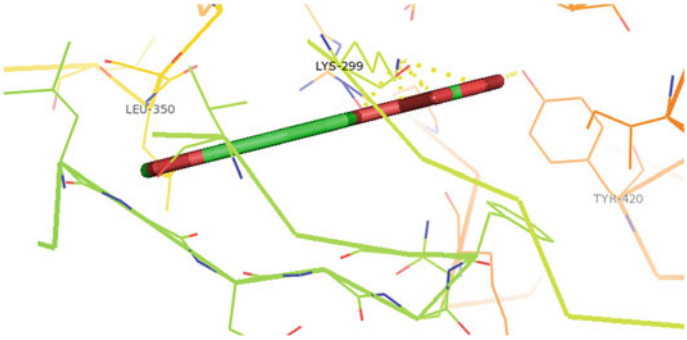

Fig. 6. Docked structure of SNCA receptor with phytocompound bacopaside I [25]

3.4 ADME Screening

ADME is an abbreviation for absorption, distribution, metabolism, and excretion. It is used to calculate the drug-like properties of the molecules [16].

QikProp generated the following output (Tables 6 and 7) [18, 23] for the phytocompound colchicine.

Table 6. QikProp prediction [18, 23]

Lead molecules	Molecular weight[a] (g/mol)	Molecular volume[b] (Å)	PSA[c]	HB[d] donors	HB[e] acceptors	Rotatable bonds[f]
Colchicine	399.443	1225.827	93.286	1.000	7.500	5.000

Table 7. QikProp prediction [18, 23]

Lead molecule	QP log P (o/w)[a]	QP log S[b]	QP PCaco[c]	QP log HERG[d]	QP PMDCK[e]	Human oral absorption[f]
Colchicine	2.545	−3.809	550	−3.180	483	91

4 Conclusion

As per Rampage Ramachandran Plot analysis, model 4 of SNCA receptor was selected as the best model. Further, pharmacophore and molecular docking studies prove that phytocompound colchicine can be used as ligand for SNCA receptor. Further, in vitro receptor–ligand binding studies can be performed on SNCA receptor with the above ligand to justify the selection of colchicine as the ligand for SNCA receptors and as a remedy for PD. Also, as per ADME studies, colchicine satisfies all drug-like properties which correlate with the results of Bagchi et al. [26].

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