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Research Paper

Beyond the Bioavailability Barrier: Comparative In-Silico ADMET Profiling and Molecular Docking of Ayurvedic Phytoconstituents vs. Allopathic Alternatives for Neurodegenerative Disorders

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ABSTRACT

Neurodegenerative diseases like Alzheimer's disease and Parkinson's disease are among the most common diseases of progressive cognitive and motor dysfunction in the world. There are some allopathic drugs available for symptomatic treatment, but they are not always effective and have adverse effects in long-term use, and are low bioavailable. In the present study, comparative in-silico analysis of Ayurvedic phytoconstituents and allopathic drugs was performed by using molecular docking and ADMET profile to find out the safer and better therapeutic molecules for the neurodegenerative disorders. Some of the phytoconstituents that were selected such as curcumin, bacoside A, withanolides and ginkgolides were screened against target proteins involved in neurodegeneration and standard allopathic drugs served as the reference compounds. To assess binding affinity, molecular interactions and stability inside the active site of target proteins, molecular docking was conducted. In addition, computational ADMET analysis was performed to evaluate the absorption, distribution, metabolism, excretion, toxicity, gastrointestinal absorption, permeability to the blood-brain barrier, cytochrome P450 interactions, and drug-likeness properties were assessed. The results indicated that some phytoconstituents were strongly binding to the neurodegenerative targets with a favorable safety profile and toxicity profile. Some compounds were less soluble in water and had low oral bioavailability, however. Allopathic drugs on the other hand, showed documented pharmacological efficacy and increased risk of hepatotoxicity and metabolic interactions. The study paves the way for newer drug discovery strategies using traditional Ayurvedic compounds in combination with computational tools in the field of neuroprotective drug development. In addition, the work leads to formulations and devices that can be optimized to successfully cross the bioavailability barrier to increase therapeutic efficacy in the treatment of neurodegenerative diseases. These results could be helpful in developing future evidence-based safer neuroprotective

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therapeutic alternatives.

INTRODUCTION

Neurodegenerative disorders are chronic and progressive conditions, with irreversible damage of central nervous system neurons, which causes the loss of various functions, including cognitive, sensory, behavioral, and motor functions. Of these, Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common and significant health problems worldwide. While the synuclein is associated with AD and forms amyloid- β plaques, tau protein aggregates, oxidative stress, and neuronal death leading to memory and cognitive decline, the degeneration of dopaminergic neurons in the substantia nigra occurs in PD, leading to tremors, rigidity, bradykinesia, and postural instability. Other factors that contribute considerably to the progression of the disease include mitochondrial dysfunction, neuroinflammation, excitotoxicity and oxidative damage. [1,2]

Neurodegenerative disorders are becoming a more common problem in the world because of the advancement of age, environment, metabolic disorders and genetic predisposition. The present allopathic medicines are used primarily for symptomatic relief; these draw significant drawbacks like poor bioavailability, low penetration of blood brain barrier, toxicity, drug interactions and adverse effects during long term therapy. Furthermore, most synthetic drugs only affect a single pathological pathway when in fact these disorders are multifactorial. [3,4]

Ayurvedic medicinal plants and phytoconstituents have attracted the interest owing to their neuroprotective and multi-target therapeutic effects. The antioxidant, anti-inflammatory, anti-cholinesterase, anti-amyloidogenic and neuroregenerative properties of bioactive compounds like curcumin, bacoside A, withanolides and ginkgolides have been reported.

Such natural bioactive compounds can decrease oxidative stress, protein aggregation, restore the balance of neurotransmitters, and support the survival of neurons, without the high toxicity effects of certain synthetic ones. They have a number of poor pharmacokinetic properties, though, such as low aqueous solubility, high metabolic turnover, low gastrointestinal absorption, and insufficient permeability to the blood–brain barrier, which is known as the “bioavailability barrier” [5–9]

Advances in computational biology and computer-aided drug discovery has made it possible to quickly screen the huge pool of therapeutic molecules by molecular docking and in-silico ADMET properties. The binding affinity and interaction of the compounds with the specific neurodegenerative targets such as acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), MAO-B, β -secretase and α -synuclein are evaluated through molecular docking. ADMET studies involve assessing the different pharmacokinetic and toxicity properties of the compound including absorption, metabolism, blood-brain barrier permeability and hepatotoxicity. [10,11]

This present work compares the selected ayurvedic phytoconstituents with allopathic drugs for the neurodegenerative targets by molecular docking studies and in-silico ADMET studies. The goal of the study is to determine compounds with high binding affinity, favorable PK and good safety profile and the use of computational pharmacology to integrate the traditional Ayurvedic knowledge for the development of safer and effective Neuroprotective drugs.

MATERIALS AND METHODS

Selection of Compounds

All the phytoconstituents found in Ayurvedic medicine mentioned to have a neuroprotective



effect were selected along with some common allopathic drugs for comparison. The SDF files of the ligands were retrieved from the PubChem database. [12,13]

Protein and Ligand Preparation.

The structure of acetylcholinesterase (AChE) and dopamine D2 receptor (D2R) were retrieved from the Protein Data Bank (PDB). PyMOL and Discovery Studio Visualizer were used to prepare the protein, which involved removing the water molecules and minimizing the energy. Optimization of ligands and preparation in an appropriate docking format. [14–16]

Molecular Docking

The ability to bind the protein and interaction between the protein and the ligand molecule was studied by molecular docking software named AutoDock Vina. Discovery Studio Visualizer and PyMOL were used to analyze the binding energy, hydrogen bonding, hydrophobic interactions, and interacting residues. [17,18]

In-Silico ADMET Analysis

SwissADME was used to perform ADMET properties such as absorption, distribution, metabolism, excretion, blood brain barrier permeability, cytochrome P450 interactions, toxicity and drug-likeness. Oral bioavailability was estimated using Lipinski's and Veber's rules. [19,20]

Comparative Evaluation

The docking scores and ADMET properties of the phytoconstituents were compared with the standard drugs to find the compounds with good docking score, safety, and pharmacokinetic properties.

RESULTS AND DISCUSSION

Allopathic drugs have been selected and the Ayurvedic phytoconstituents were docked to acetylcholinesterase (AChE, PDB ID: 4EY7) and dopamine D2 receptor (D2R, PDB ID: 6CM4) with the help of AutoDock Vina. The more negative the docking score the greater the binding affinity was. [21]

Bisnorcymserine (AChE) and Bromocriptine (D2R) exhibited the highest binding affinities with AChE (−7.6 kcal/mol) and D2R (−7.9 kcal/mol), respectively, among allopathic drugs. Regarding phytoconstituents, the one that had the highest affinity with AChE was Ginkgolide B (−8.7 kcal/mol) and the very good interaction with D2R was Withaferin A (−7.4 kcal/mol). Berberine, Piperine, Resveratrol, Curcumin and Huperzine A also had good interaction, indicating that they might have neuroprotective properties. [22–25]

SwissADME was used to carry out seven key ADMET properties assessment, namely gastrointestinal absorption, blood–brain barrier permeability, solubility, metabolism, and drug-likeness. Most allopathic drugs presented favorable pharmacokinetic parameters, while some phytoconstituents had drawbacks, such as the low solubility and BBB permeability. But Huperzine A, Berberine, Piperine, Resveratrol and 6-Gingerol had the desired ADMET property. Piperine also showed bioavailability enhancement properties. [27]

The comparative analysis revealed several phytoconstituents from Ayurveda to show docking affinities similar to or better than the typical allopathic drugs. But their only problem was in the poor pharmacokinetic optimization instead of lack of biological activity. Based on the results, phytochemicals like Ginkgolide B, Withaferin A, Huperzine A, Berberine, Piperine and Resveratrol can be used as potential lead compounds for further development of drugs to treat



neurodegenerative disorders following optimization of their formulations. [23–27]

Table 1: Physicochemical and ADME Properties of Selected Allopathic Drugs

Drug Name	Mol. Weight	H-bond Donors	H-Bond Acceptors	Consensus Log P	Molar Refractivity	TPSA(A ²)	Solubility Class	GI Absorption	BBB Permeant
Donepezil	379.49	0	4	4.00	115.31	38.77	Moderately Soluble	High	Yes
Galantamine	287.35	1	4	1.92	84.05	41.93	Soluble	High	Yes
Rivastigmine	250.34	0	3	2.34	73.12	32.78	Soluble	High	Yes
Tacrine	198.26	1	1	2.59	63.58	38.91	Soluble	High	Yes
Phenserine	337.42	1	3	2.87	106.15	44.81	Moderately Soluble	High	Yes
Ladostigil	272.34	1	3	2.42	78.15	41.57	Moderately Soluble	High	Yes
Cymserine	379.50	1	3	3.79	120.73	44.81	Moderately Soluble	High	Yes
Bisnorcymserine	351.44	3	3	3.59	110.93	62.39	Moderately Soluble	High	Yes
Bromocriptine	654.59	3	6	3.12	177.59	118.21	Poorly Soluble	High	No
Cabergoline	451.60	2	4	3.05	136.63	71.68	Moderately Soluble	High	Yes
Apomorphine	267.32	2	3	2.47	83.02	43.70	Soluble	High	Yes
Ropinirole	260.37	1	2	2.85	83.25	32.34	Soluble	High	Yes

Table 2: Physicochemical and ADME Properties of Selected Ayurvedic Phytoconstituents

Drug Name	Mol. Weight	H-bond Donors	H-Bond Acceptors	Consensus Log P	Molar Refractivity	TPSA(A²)	Solubility Class	GI Absorption	BBB Permeant
Ginkgolide B	424.40	3	10	-0.38	93.29	148.82	Soluble	Low	No
Curcumin	368.38	2	6	3.20	102.8	93.06	Poorly Soluble	High	No
Huperzine A	242.32	2	2	1.84	72.87	58.88	Soluble	High	Yes
Catechin	290.27	5	6	0.36	74.33	110.38	Very Soluble	High	No
Resveratrol	228.24	3	3	3.13	67.88	60.69	Moderately Soluble	High	Yes
6-Gingerol	294.39	2	4	2.76	84.55	66.76	Moderately Soluble	High	Yes
Withaferin A	470.60	2	6	3.83	127.49	96.36	Moderately Soluble	High	No
Bacosine	456.70	2	3	8.39	136.91	57.53	Poorly Soluble	Low	No
Berberine	336.36	0	4	3.62	94.87	40.80	Soluble	High	Yes
Reserpine	608.68	1	10	4.04	165.52	117.78	Poorly Soluble	High	No
Piperine	285.34	0	3	3.46	85.47	38.77	Moderately Soluble	High	Yes
L-DOPA	197.19	4	5	-2.74	49.55	103.78	Very Soluble	High	No

Table 10: Docking of Allopathic drugs with 4EY7(AChE)

Drug	Docking score (Kcal/mol)	Distance (Å)	Amino acid residue	Group involved	Type of interaction
Donepezil	-7.3	3.65496	A:ASN533:OD1	Carbon Hydrogen Bond	Hydrogen Bond
		3.27773	A:GLN413:OE1	Carbon Hydrogen Bond	Hydrogen Bond
		5.1515	A:PRO235	Alkyl	Hydrophobic
		3.92445	A:PRO410	Alkyl	Hydrophobic
		4.27499	A:PRO537	Alkyl	Hydrophobic
		5.24083	A:HIS405	Pi-Alkyl	Hydrophobic
		5.15306	A:PRO537	Pi-Alkyl	Hydrophobic
Galantamine	-6.5	2.72357	A:ASN233:O	Conventional Hydrogen Bond	Hydrogen Bond
		2.74237	A:GLU313:OE1	Conventional Hydrogen Bond	Hydrogen Bond
		2.55999	:UNK0:O	Conventional Hydrogen Bond	Hydrogen Bond
		4.77058	A:PRO235	Alkyl	Hydrophobic
		4.7524	A:PRO235	Pi-Alkyl	Hydrophobic
Rivastigmine	-5.5	2.46962	A:ARG296:HH21	Conventional Hydrogen Bond	Hydrogen Bond
		2.81904	A:HIS405:HE2	Conventional Hydrogen Bond	Hydrogen Bond
		3.33746	A:PRO235:O	Carbon Hydrogen Bond	Hydrogen Bond
		3.49601	A:ASN533:OD1	Carbon Hydrogen Bond	Hydrogen Bond
		4.73344	A:HIS405:NE2	Pi-Cation	Electrostatic
		4.70943	A:HIS405	Pi-Pi T-shaped	Hydrophobic

		5.13486	A:PRO235	Pi-Alkyl	Hydrophobic
Drug	Docking score (Kcal/mol)	Distance (Å)	Amino acid residue	Group involved	Type of interaction
Tacrine	-6.6	3.99398	A:GLU313:OE1	Pi-Anion	Electrostatic
		4.55091	A:LEU536	Alkyl	Hydrophobic
		4.70703	A:PRO537	Alkyl	Hydrophobic
		4.92357	A:LEU540	Alkyl	Hydrophobic
		5.2494	A:PRO537	Pi-Alkyl	Hydrophobic
		4.9966	A:PRO410	Pi-Alkyl	Hydrophobic
Phenserine	-7.2	2.79774	A:THR238:O	Conventional Hydrogen Bond	Hydrogen Bond
		3.5465	A:PRO235:CA	Carbon Hydrogen Bond	Hydrogen Bond
		3.72793	A:GLN413:OE1	Carbon Hydrogen Bond	Hydrogen Bond
		3.45811	A:TRP532:O	Carbon Hydrogen Bond	Hydrogen Bond
		3.64527	A:ASN533:OD1	Carbon Hydrogen Bond	Hydrogen Bond
		3.77399	A:GLU313:OE1:B	Carbon Hydrogen Bond	Hydrogen Bond
		3.22001	A:GLU313:OE1	Pi-Anion	Electrostatic
		3.92757	A:VAL239:CG2	Pi-Sigma	Hydrophobic
		5.44087	A:PRO235	Pi-Alkyl	Hydrophobic
Drug	Docking score (Kcal/mol)	Distance (Å)	Amino acid residue	Group involved	Type of interaction
Lados tigit	-5.8	3.48059	A:TRP532:O	Carbon Hydrogen Bond	Hydrogen Bond

		5.33629	A:PRO235	Alkyl	Hydrophobic
		4.42578	A:VAL239	Alkyl	Hydrophobic
		4.78224	A:PRO235	Pi-Alkyl	Hydrophobic
Cymserine	-7.3	2.57386	A:ARG296:HE	Conventional Hydrogen Bond	Hydrogen Bond
		3.03669	A:HIS405:HE2	Conventional Hydrogen Bond	Hydrogen Bond
		3.60859	A:GLU313:OE1	Carbon Hydrogen Bond	Hydrogen Bond
		4.40318	A:HIS405:NE2	Pi-Cation	Electrostatic
		3.60641	A:HIS405:CE1	Pi-Sigma	Hydrophobic
		4.73887	A:HIS405	Pi-Pi T-shaped	Hydrophobic
		5.17688	A:PRO235	Pi-Alkyl	Hydrophobic
Bisnocymserine	-7.6	2.54528	A:TRP532:O	Conventional Hydrogen Bond	Hydrogen Bond
		4.28896	A:ARG296:NH2	Pi-Cation	Electrostatic
		5.33615	A:HIS405	Pi-Pi T-shaped	Hydrophobic
		5.46515	A:VAL239	Alkyl	Hydrophobic
		5.40028	A:LEU536	Pi-Alkyl	Hydrophobic

Table 11: Docking of Allopathic drugs with 6CM4(DRD2)

Drug	Docking score (Kcal/mol)	Distance (Å)	Amino acid residue	Group involved	Type of interaction
Bromocriptine	-7.9	4.22459	A:PHE50	Pi-Pi Stacked	Hydrophobic
		4.70067	A:PHE50	Pi-Pi Stacked	Hydrophobic
		5.37926	A:ILE424	Alkyl	Hydrophobic
		3.96877	A:LEU438	Alkyl	Hydrophobic
		4.79629	A:LEU441	Alkyl	Hydrophobic

		5.04712	A:ALA46	Pi-Alkyl	Hydrophobic
		5.43131	A:VAL47	Pi-Alkyl	Hydrophobic
Cabergoline	-5.9	3.69189	A:LEU40:O	Carbon Hydrogen Bond	Hydrogen Bond
		3.59904	A:ALA410:O	Carbon Hydrogen Bond	Hydrogen Bond
		4.14199	A:LEU40	Alkyl	Hydrophobic
		4.64798	A:TYR37	Pi-Alkyl	Hydrophobic
		5.23116	A:TRP413	Pi-Alkyl	Hydrophobic
		4.07988	A:TRP413	Pi-Alkyl	Hydrophobic
		4.55696	A:LEU414	Pi-Alkyl	Hydrophobic
		4.88659	A:VAL417	Pi-Alkyl	Hydrophobic
		5.44706	A:LEU414	Pi-Alkyl	Hydrophobic
		4.50234	A:VAL417	Pi-Alkyl	Hydrophobic
Ropinirole	-5.4	3.57505	A:LEU40:O	Carbon Hydrogen	Hydrogen Bond
		4.47857	A:LEU40	Alkyl	Hydrophobic
		4.35793	A:LEU44	Alkyl	Hydrophobic
		4.31383	A:VAL47	Alkyl	Hydrophobic
		4.98463	A:LEU40	Pi-Alkyl	Hydrophobic
Drug	Docking score (Kcal/mol)	Distance (Å)	Amino acid residue	Group involved	Type of interaction
Apomorphine	-6.5	3.39507	A:GLY1156:O	Carbon Hydrogen Bond	Hydrogen Bond
		3.29142	A:ASP1092:OD1	Pi-Anion	Electrostatic
		2.97435	A:GLN373:HE22	Pi-Donor Hydrogen Bond	Hydrogen Bond
		5.02709	A:VAL1094	Pi-Alkyl	Hydrophobic
		3.99173	A:LYS369	Pi-Alkyl	Hydrophobic
Pergolide	-6.1	3.58876	A:LEU40:O	Carbon Hydrogen Bond	Hydrogen Bond
		3.65875	A:ALA410:O	Carbon Hydrogen Bond	Hydrogen Bond
		3.99344	A:VAL417:CG2	Pi-Sigma	Hydrophobic

		4.97267	A:LEU43	Alkyl	Hydrophobic
		3.72424	A:LEU43	Alkyl	Hydrophobic
		4.71471	A:LEU40	Alkyl	Hydrophobic
		4.63039	A:LEU44	Alkyl	Hydrophobic
		4.52298	A:LEU40	Alkyl	Hydrophobic
		4.50956	A:LEU41	Alkyl	Hydrophobic
		4.60807	A:VAL47	Alkyl	Hydrophobic
		4.77246	A:TRP413	Pi-Alkyl	Hydrophobic
		4.10223	A:TRP413	Pi-Alkyl	Hydrophobic
		4.62158	A:LEU414	Pi-Alkyl	Hydrophobic
		4.93142	A:VAL417	Pi-Alkyl	Hydrophobic
		5.35178	A:LEU414	Pi-Alkyl	Hydrophobic

Table 12: Docking of Ayurvedic Phytoconstituents with 4EY7(AChE)

Drug	Docking score (Kcal/mol)	Distance (Å)	Amino acid residue	Group involved	Type of interaction
Ginkgolide B	-8.7	2.30798	A:ASN233:HD21	Conventional Hydrogen Bond	Hydrogen Bond
		2.92813	A:ASN233:O	Conventional Hydrogen Bond	Hydrogen Bond
		2.20446	A:GLU313:OE1	Conventional Hydrogen Bond	Hydrogen Bond
		2.28261	A:TRP532:O	Conventional Hydrogen Bond	Hydrogen Bond
		5.17926	A:LEU540	Alkyl	Hydrophobic
Curcumin	-6.9	2.38349	A:ARG247:HH21	Conventional Hydrogen Bond	Hydrogen Bond
		2.25622	A:ARG296:HE	Conventional Hydrogen Bond	Hydrogen Bond
		2.28468	A:ARG296:HH21	Conventional Hydrogen Bond	Hydrogen Bond

		3.99501	A:VAL239:CG2	Pi-Sigma	Hydrophobic
		4.57752	A:PRO235	Pi-Alkyl	Hydrophobic
Huperzine A	-6.9	2.32347	A:ASN233:HD21	Conventional Hydrogen Bond	Hydrogen Bond
		2.90532	A:ASN233:O	Conventional Hydrogen Bond	Hydrogen Bond
		1.86633	A:GLU313:OE1	Conventional Hydrogen Bond	Hydrogen Bond
		4.3123	A:PRO235	Alkyl	Hydrophobic
		4.45982	A:PRO537	Alkyl	Hydrophobic
		4.75419	A:LEU540	Alkyl	Hydrophobic
		4.59972	A:HIS405	Pi-Alkyl	Hydrophobic
Drug	Docking score (Kcal/mol)	Distance (Å)	Amino acid residue	Group involved	Type of interaction
Catechin	-6.8	2.30883	A:ARG296:HH21	Conventional Hydrogen Bond	Hydrogen Bond
		2.37684	A:ASN533:OD1	Conventional Hydrogen Bond	Hydrogen Bond
		2.3074	A:ASN533:OD1	Conventional Hydrogen Bond	Hydrogen Bond
		2.65419	A:PRO368:O	Conventional Hydrogen Bond	Hydrogen Bond
		3.57304	A:HIS405:CE1	Conventional Hydrogen Bond	Hydrogen Bond
		4.51207	A:GLU313:OE1	Pi-Anion	Electrostatic
		5.01103	A:PRO235	Pi-Alkyl	Hydrophobic
Resveratrol	-6.3	2.46679	A:TRP532:O	Conventional Hydrogen Bond	Hydrogen Bond
		2.22516	A:ASN533:OD1	Conventional Hydrogen Bond	Hydrogen Bond
		5.10044	A:VAL370	Pi-Alkyl	Hydrophobic
		5.13832	A:PRO235	Pi-Alkyl	Hydrophobic

6-Gingerol	-5.5	2.15494	A:ASN233:HD21	Conventional Hydrogen Bond	Hydrogen Bond
		2.34952	A:ASN233:O	Conventional Hydrogen Bond	Hydrogen Bond
		2.51597	A:GLU313:OE1	Conventional Hydrogen Bond	Hydrogen Bond
		3.59252	A:PRO537:O	Carbon Hydrogen Bond	Hydrogen Bond
		3.38444	A:GLU313:OE1:B	Pi-Anion	Electrostatic
		4.23003	A:PRO235	Alkyl	Hydrophobic
		4.80396	A:PRO537	Alkyl	Hydrophobic
		4.56592	A:LEU540	Alkyl	Hydrophobic
		4.97129	A:HIS405	Pi-Alkyl	Hydrophobic
		5.25324	A:PRO537	Pi-Alkyl	Hydrophobic

Table 13: Docking of Ayurvedic Phytoconstituents with 6CM4(DRD2)

Drug	Docking score (Kcal/mol)	Distance (Å)	Amino acid residue	Group involved	Type of interaction
Withaferin A	-7.4	2.54187	:UNK0:H	Conventional Hydrogen Bond	Hydrogen Bond
		4.88625	A:ALA410	Alkyl	Hydrophobic
Bacosine	-7.2	5.27439	A:LEU40	Alkyl	Hydrophobic
		4.57475	A:LEU44	Alkyl	Hydrophobic
		5.00562	A:VAL417	Alkyl	Hydrophobic
Berberine	-6.4	3.50047	A:LEU40:O	Carbon Hydrogen Bond	Hydrogen Bond
		3.51316	A:VAL417:CG1	Pi-Sigma	Hydrophobic
		3.72149	A:VAL47	Alkyl	Hydrophobic
		4.77167	A:VAL421	Alkyl	Hydrophobic
		4.84516	A:ILE424	Alkyl	Hydrophobic
		4.92641	A:LEU40	Pi-Alkyl	Hydrophobic

Reserpine	-6.4	2.25259	A:THR428:HG1	Conventional Hydrogen Bond	Hydrogen Bond
		3.79078	A:THR427:O	Carbon Hydrogen Bond	Hydrogen Bond
		3.79659	A:THR428:O	Carbon Hydrogen Bond	Hydrogen Bond
		3.62821	A:THR427:O	Carbon Hydrogen Bond	Hydrogen Bond
		3.63064	A:THR427:CG2	Pi-Sigma	Hydrophobic
		3.95487	A:ARG434:CB	Pi-Sigma	Hydrophobic
		4.7782	A:PRO423:C,O;ILE424:N	Amide-Pi Stacked	Hydrophobic
		3.87273	A:ILE431	Alkyl	Hydrophobic
		3.93211	A:LYS435	Alkyl	Hydrophobic
		4.69037	A:VAL47	Alkyl	Hydrophobic
		4.88215	A:ILE424	Alkyl	Hydrophobic
		5.40837	A:ILE424	Pi-Alkyl	Hydrophobic
Piperine	-6.1	3.68754	A:ALA420:O	Carbon Hydrogen Bond	Hydrogen Bond
		3.5534	A:LEU44:CD1	Pi-Sigma	Hydrophobic
		4.91103	A:VAL47	Pi-Alkyl	Hydrophobic
		4.81497	A:VAL417	Pi-Alkyl	Hydrophobic
		4.86676	A:ALA420	Pi-Alkyl	Hydrophobic
L-DOPA	-4.7	2.14155	A:ARG220:HH21	Conventional Hydrogen Bond	Hydrogen Bond
		2.75554	A:LYS369:HN	Conventional Hydrogen Bond	Hydrogen Bond
		2.02169	A:LYS370:HN	Conventional Hydrogen Bond	Hydrogen Bond
		5.34085	A:VAL1094	Pi-Alkyl	Hydrophobic
		3.61267	A:LYS369	Pi-Alkyl	Hydrophobic

CONCLUSION

In the present in-silico study, molecular docking interactions and ADMET properties of selected allopathic drugs and Ayurvedic phytoconstituents were studied and compared with the important targets of neurodegenerative diseases such as Acetylcholinesterase (AChE) and Dopamine D2 receptor. The docking analysis results showed that both types of compounds have strong binding potential to the chosen protein targets, suggesting their application in the management of neurodegenerative diseases.

The compounds studied revealed that some of the phytochemicals present in Ayurvedic products like Ginkgolide B, Withaferin A were found to have docking scores similar to or better than some of the marketed allopathic drugs. The results indicated that natural phytoconstituents have a significant intrinsic neuroprotective activity that could be used to develop novel drug molecules.

The optimized pharmacokinetic properties such as gastrointestinal absorption, permeability through blood–brain barrier, solubility and oral bioavailability observed in the case of majority of allopathic drugs through the ADMET analysis properties enhance their current clinical effectiveness. Conversely, some phytoconstituents had some restrictions that were related to poor bioavailability and poor BBB penetration despite the strong receptor binding interactions.

Considering all these factors, the study suggests that the use of allopathic drugs is most effective for treating neurodegenerative diseases, as they have an optimum efficacy and pharmacokinetic profile. When Ayurvedic phytoconstituents were tested for the neuroprotective potential, they appeared to be promising therapeutic candidates to be used as support or potential alternate therapeutic agents after further pharmacokinetic optimization, formulation development and experimental validation.

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