Acta Neurophysiologica

Academic Strive
Researcher's perception is our reality

Research Article *Volume 4 Issue 4*

Herbal Bioactive Compounds in Enhancing Bioavailability of Neurodegenerative Drugs-A Molecular Docking Study

Roy C and Ghosh P*

Department of Physiology, West Bengal State University, India

***Corresponding author:** Pratiti Ghosh, Department of Physiology, West Bengal State University, Kolkata-700126, India, Phone no: 07980358881; Email: pratitig@wbsu.ac.in

Received Date: April 24, 2023; **Published Date:** June 26, 2023

Abstract

Introduction: The treatment of neurodegenerative diseases may face challenge due to an efflux transporter, p-glycoprotein residing at the blood brain barrier which normally curtails bioavailability of xenobiotics and chemotherapeutic drugs.

Objective: This study is aimed at performing molecular docking to identify potential herbal inhibitors of p-glycoprotein which would enhance drug bioavailability inside the target cell.

Methods: Druggability and pharmacokinetic attributes of the bioactive compounds were evaluated and their binding interactions were assessed against p-glycoprotein (6C0V) utilizing molecular docking with CDOCKER program of Discovery Studio.

Results: The herbal inhibitors viz., palmatine from Tinospora cordifolia, withanolide D and somniferine from Withania somnifera, hemidescine from Hemidesmus indicus have been ranked as the top interacting molecules against p-glycoprotein based on their binding efficacy.

Conclusion: These medicinal herbs if used in conjunction with drugs, are expected to enhance their bioavailability and may simultaneously alleviate the neurodegenerative diseases. The lead compounds maybe considered for in vivo experiments and clinical trials to augment the medical treatment.

Keywords: Bioactive Compounds; Docking; Herb; Inhibitor; Neurodegenerative Disease; P-Glycoprotein

Abbreviations: BBB: Blood-Brain Barrier; MDR: Multidrug Resistance; AD: Alzheimer's Disease; ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicity; MD: Molecular Dynamics; PD: Parkinson's Disease.

Introduction

Neurodegenerative diseases encompass a wide range of disorders that result from progressive and irreversible neuronal degeneration leading to the deterioration of cognitive and motor functions. It is estimated that millions of people worldwide suffer from these debilitating diseases which remains ambiguous until the disease has advanced afflicting large portion of aging population. The etiology of neurodegenerative disease is multifactorial and involve a combination of genetic, environmental and lifestyle factors, associated with molecular mechanisms including oxidative stress, protein misfolding, mitochondrial defects, synaptic dysfunction, cell cycle dysregulation, and neuro-inflammation [1].

Drug efflux transporters such as p-glycoprotein residing at the blood-brain barrier (BBB) and blood-spinal cord barrier serve as defence mechanism against xenobiotics but pose

major obstacle to drug delivery to central nervous system and is responsible for multidrug resistance (MDR) [2]. Thus, extensive work has been carried out in identification of p-glycoprotein inhibitors which when co-administered with such drugs, would enhance their bioavailability inside the target cell.

Medicinal herbs and their active metabolites have played significant role in treatment of neurodegenerative diseases since antiquity. Withania somnifera has been shown to improve cognitive function and reduce oxidative stress in animal studies [3]. The promising role of natural bioactive compounds in alleviating Alzheimer's disease (AD) is attributed to their anti-cholinesterase, anti-inflammatory and anti-apoptotic effect [4]. These secondary metabolites have functional scaffolds to revert p-glycoprotein mediated MDR [5]. Most neurodegenerative drugs viz., levodopa, pergolide, pramipexole [6]; donepezil [7]; riluzole [8] are substrates of p-glycoprotein and are thus effluxed by the cell. Here, nine plants with neuroprotective proficiency viz., Withania somnifera [9]; Tinospora cordifolia [10]; Hemidesmus indicus [11]; Saraca indica [12]; Nardostachys jatamansi [13]; Aloe barbadensis [14]; Nelumbo nucifera [15]; Swertia chirata [16]; Mucuna pruriens [17] have been selected to screen their inhibitory potential against the efflux transporter by molecular docking. The objective of the study is to identify neuroprotective herbal constituents as p-glycoprotein inhibitors which would help retention of allopathic drugs inside the target cell.

Materials and Methods

Protein preparation: The structure of p-glycoprotein (PDB code: 6C0V) [18] was downloaded from RCSB protein data bank (http://www.rcsb.org). The protein preparation module of Discovery Studio was used for structure optimization and energy minimization. Dogsitescorer server was utilized for the detection of potential binding pockets of p-glycoprotein (https://proteins.plus/#dogsite).

Ligand Preparation

Canonical smiles of 154 bioactive compounds from nine medicinal herbs and control drug doxycycline was obtained from Pubchem, ChemSpider and Chembl databases. The canonical smiles were then translated into spatial data file format using online SMILE translator. The molecules were optimized using filter ligands module available in the Discovery Studio platform for assigning proper bond orders and generation of accessible tautomers, stereoisomers, and ionization states.

Drug Likeness and ADMET Analysis

Molinspiration tool was employed for calculation of drug-likeness attributes of small molecules. Different molecular descriptors such as molecular weight, number of hydrogen bond accepters, number of hydrogen bond donors and lipophilicity were calculated utilizing Lipinski's rule of five. pkCSM server was utilized for evaluation of ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) property of the components.

Molecular Docking Analysis

In a search for a potential inhibitor against p-glycoprotein, molecular docking was performed using CDOCKER program of Discovery Studio. CDOCKER is a grid-based molecular docking method that employs a molecular dynamics (MD) simulated-annealing-based algorithm to dock ligands into a receptor's active site. The protein is kept rigid while the ligands are allowed to flex followed by a final minimization step to refine the docked poses. After docking, the top ranked poses for each component were analyzed based on lowest binding free energy, hydrogen bonds and hydrophobic interactions.

Results

Drug Likeness and ADMET Analysis

154 components of nine neuroprotective herbs were initially screened based on druggability and ADMET properties. 131 compounds displayed acceptable drug-likeness properties which indicated that these compounds may easily be transported, diffused, and absorbed by the body. The drug-likeness attributes of 10 components (inhibitors) have been enlisted in Table 1.

S.no.	Compounds	MW	LogP	nOHNH	nON	nViola tions
1	Palmatine	352.41	3.38	0	4	0
2	Withanolide D	470.61	4.15	2	6	0
3	Somniferine	608.69	2.69	2	9	1
4	Hemidescine	650.85	4.33	3	10	1
5	Syringaresinol	418.44	2.62	2	8	0
6	Heminine	608.81	3.63	4	9	1

7	12-deoxywithastromon olide	470.6	3.2	2	6	0
8	16-Dehydropregnenolo ne	314.47	3.81	1	2	0
9	Withaferin A	470.61	3.86	2	6	0
10	Tembetarine	344.43	-1.6	2	5	0

Table 1: Drug-Likeness attributes of ten p-glycoprotein inhibitors.
MW-Molecular weight, LogP-Log of octanol/water partition coefficient, nON-No. of hydrogen bond acceptors, nOHNH -No. of hydrogen bond donors, nViolations- No. of rule of five violations.

The result of pharmacokinetic study of 10 components have been summarized in Table 2. 26 components from a pool of 154 components were found to be p-glycoprotein inhibitors and their ADMET values were within an acceptable range. All the compounds showed good intestinal absorption with moderate BBB penetration.

S.no.	Compounds	Water solubility (log mol/L)	CYP P450 2D6 inhibition	Intestinal absorption (% absorbed)	BBB permeability (log BB)	Fraction unbound (Fu)
1	Palmatine	-4.194	Yes	97.084	-0.112	0.245
2	Withanolide D	-5.127	No	99.2	-0.315	0.093
3	Somniferine	-3.12	No	94.052	-0.548	0.262
4	Hemidescine	-5.441	No	84.224	-1.333	0.186
5	Syringaresinol	-3.92	No	78.823	-0.771	0
6	Heminine	-5.392	No	73.96	-1.186	0.213
7	12- deoxywithastromonolide	-4.893	No	84.79	0.023	0.088
8	16-Dehydropregnenolone	-4.735	No	96.151	0.148	0.123
9	Withaferin A	-5.063	No	85.345	-0.03	0.105
10	Tembetarine	-3.684	No	94.491	-0.474	0.102

Table 2: ADMET properties of ten p-glycoprotein inhibitors.

Molecular Docking Analysis

The bioactive compounds were screened against the efflux transporter, p-glycoprotein by performing molecular docking using the computational program CDOCKER. The inhibitors of the efflux carrier protein were ranked based on their magnitude of negative binding free energy along with hydrogen bond and hydrophobic interactions, all of which play significant role in stabilizing appropriate conformation of ligand at the active site of the receptor.

The docking results demonstrated that out of 154 natural compounds used in the present study, four bioactive components viz., palmatine, withanolide D, somniferine and hemidescine have a higher binding energy of −117.85, −96.66, −92.28, and −88.77 kcal/mol, respectively, than the control drug doxycycline whose binding energy was determined to be -79.09 Kcal/mol. These four natural compounds were identified as the best compounds interacting with p-glycoprotein based on their binding potential. The details of binding interactions of inhibitory components are displayed in Table 3.

S.no	Inhibitory components	No of H bond	Binding site (H bond)	No of Hydro phobic interaction	Binding site (Hydrophobic interaction)	Binding energy (kcal/mol)
1	Palmatine	1	THR76	1	ILE736	-117.85
2	Withanolide D	3	GLU972,SER979,GLY737	6	PHE79, PHE336, ILE736, LEU332, LEU975, PHE732	-96.66

3	Somniferine	3	PHE79, THR76, THR740	6	PHE79, LEU332, LEU975, ILE736, ILE328, ALA80	-92.28
4	Hemidescine	0	-	11	PHE79, PHE336, PHE732, PHE72, ILE328, ALA80, LEU332, LEU976, LEU975, ILE736, ALA729	-88.77
5	Syringaresinol	4	LEU332, ALA729, SER979, GLU972	5	PHE72, PHE79, LEU332, LEU975, ILE736	-79.8
6	Heminine	4	SER979, GLU972, ALA729, GLY737	6	PHE79, PHE72, LEU332, ILE736, ALA729, LEU976	-78.51
7	12-deoxywithastromonolide	0	-	8	PHE72, PHE732, PHE79, LEU332, LEU976, LEU975, ILE736, ALA729	-74.91
8	16-Dehydropregnenolone	0	-	7	PHE732, PHE72, PHE336, LEU976, LEU975, LEU332, ILE736	-71.24
9	Withaferin A	2	PHE79, PHE336	9	PHE72, PHE336, ILE736, PHE732, PHE983, LEU332, LEU975, LEU976, ALA729	-69.94
10	Tembetarine	2	PHE336, SER979	3	PHE336, PHE732, ILE736	-67.39
11	Doxycycline	1	LEU976	3	PHE732, ILE736, LEU332	-79.09

Table 3: Binding interactions of inhibitory components and control drug doxycycline against pglycoprotein.

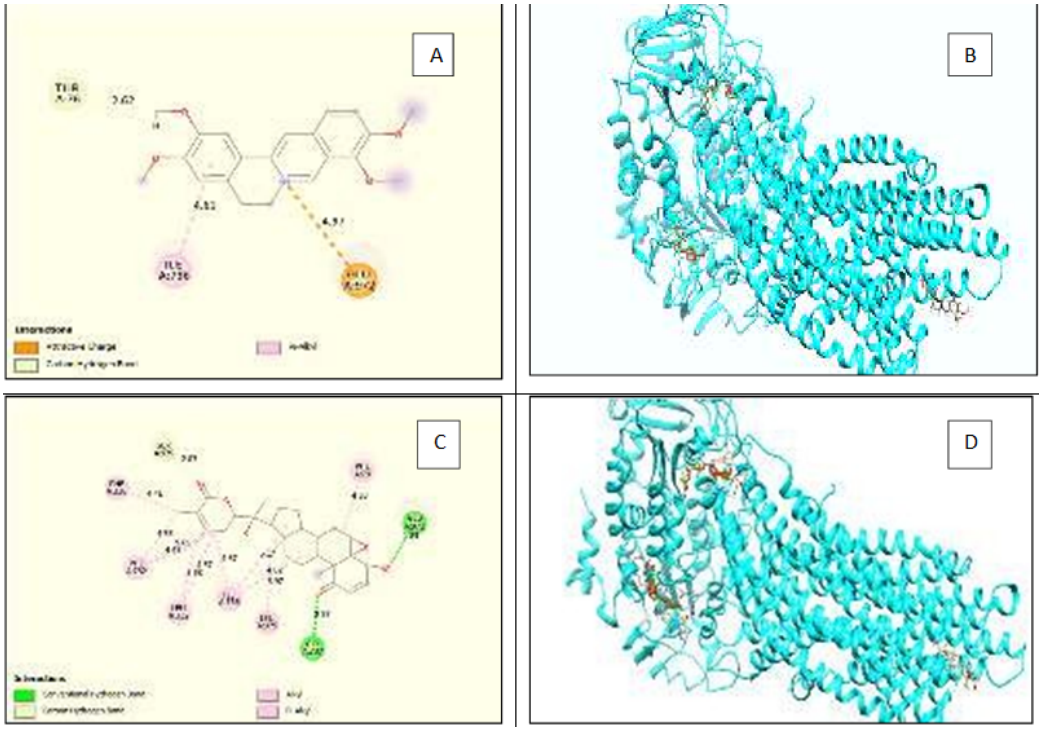

Figure 1: Docking interactions of human p-glycoprotein with herbal compounds: (A-B) Palmatine and (CD) Withanolide D: Graphics generated by Discovery Studio (left) and Chimera (right).

From the 2D interaction plot (Figure 1), it was observed that palmatine formed one hydrogen bond with amino acid residue THR76 (2.62 Å), and one hydrophobic interaction (pi-alkyl) with ILE736 (4.61 Å). In case of withanolide D, three residues, viz., GLU972 (1.84 Å), SER979 (2.83 Å), and GLY737 (2.87 Å), formed the hydrogen bonds and six hydrophobic (alkyl and pi-alkyl) interactions were observed with amino acid residues PHE79, PHE336, ILE736, LEU332, LEU975, PHE732 at distance of 4.30 Å, 4.41 Å, 4.57 Å, 4.57 Å, 4.62 Å and 4.55 A° respectively. Somniferine exhibited hydrogen bond with three residues, viz., PHE79 (2.44 Å), THR76 (3.07 Å), and THR740 (2.29 Å), and six hydrophobic (alkyl and pi-alkyl) interactions with amino acid residues PHE79, LEU332, LEU975, ILE736, ILE328, ALA80 at distance of 4.94 Å, 4.54 Å, 5.06 Å, 5.14 Å, 5.39 Å and 4.39 A° respectively.

Discussion

Overexpression of p-glycoprotein is responsible for MDR that severely limits the effectiveness of neurodegenerative drugs. Overcoming p-glycoprotein mediated drug efflux is an important approach to enhance the bioavailability of its substrate drugs.

Herbal bioactive compounds exert synergism with neurodegenerative drugs and overcome resistance via modulation of p-glycoprotein transport function. Inhibition of p-glycoprotein in adriamycinresistant human breast cancer cell line MCF-7/ADR by syringaresinol [19] (Swertia chirata); reversion of MDR in NCI/ADR-RES cells by β-Sitosterol [20] (Aloe barbadensis); modulation of MDR1 efflux function through stimulation of ATPase enzymes by palmatine [21] (Tinospora cordifolia) signify the efficacy of neuroprotective components in modulation of p-glycoprotein mediated drug efflux.

Herbal extracts and their active metabolites have been reported to improve cognitive function and slow down progression of neurodegenerative diseases [22]. Neferine (Nelumbo nucifera) exerted neuroprotection against 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine-induced Parkinson's disease (PD) in mice through its anti-inflammatory effect, downregulation of pro-inflammatory cytokines as well as upregulation of dopamine levels [23]. Similar neuroprotective effect was observed on administration of A B C D kaempferol (Saraca indica) in ovariectomized rat models of sporadic AD via elevation of neuroinflammation markers and improvement of cognitive impairment [24]. Nardosinone from Nardostachys jatamansi decreased motor and cognitive symptoms in PD mice model by regulating dopamine receptor D2 expression [25]. Therefore, these medicinal herbs if used in conjunction with neurodegenerative drugs, are expected to enhance their bioavailability and simultaneously impart additional neuroprotection.

Our finding suggests that palmatine, an isoquinoline alkaloid from Tinospora cordifolia with its better binding affinity and stronger interactions than doxycycline maybe considered as the lead compound in circumvention of p-glycoprotein mediated drug efflux. Additionally, palmatine has been reported to manage oxidative stress-mediated neurological diseases [26], reduce formation of amyloid plaques, prevent tau protein aggregation and improve learning and memory in AD mice model [27].

Conclusion

The neuroprotective natural p-glycoprotein inhibitors showed compliance with the Lipinski's rule of five and met essential conditions for ADMET properties. Their binding affinity promises increased bioavailability of the neurodegenerative drugs, thereby making them potential lead molecules for coadministration. The current study manifested that palmatine, withanolide D, somniferine and hemidescine might play crucial role in circumvention of drug efflux and serve as potential candidates for amelioration of neurodegeneration. Further in vitro and in vivo experiments are needed to corroborate the results of the present study.

Acknowledgement

We would like to express our sincere gratitude to West Bengal State University for providing the infrastructural facilities to pursue our studies.

Conflict of Interest

The authors declare that there are no conflicts of interest.

References

1. Sirin S, Dolanbay SN, Aslim B (2023) Role of plant derived alkaloids as antioxidant agents for neurodegenerative diseases. Health Sciences Review 6: 100071.

2. Roy C, Ghosh P (2023) Co-administration of herbal inhibitors of p-glycoprotein with renal drugs enhance their bioavailability–in silico approach. J Herbmed Pharmacol 12(2): 241-249.

3. Mikulska P, Malinowska M, Ignacyk M, Szustowski P, Nowak J, et al. (2023) Ashwagandha (Withania somnifera)-Current research on the health-promoting activities: a narrative review. Pharmaceutics 15(4): 1057.

4. Rao RV, Descamps O, John V, Bredesen DE (2012) Ayurvedic medicinal plants for Alzheimer's disease: a review. Alzheimers Res Ther 4(3): 22.

5. Ganesan M, Kanimozhi G, Pradhapsingh B, Khan HA, Alhomida AS, et al. (2021) Phytochemicals reverse p-glycoprotein mediated multidrug resistance via signal transduction pathways. Biomed Pharmacother 139: 111632-111641.

6. Vautier S, Milane A, Fernandez C, Buyse M, Chacun H, et al. (2008) Interactions between antiparkinsonian drugs and ABCB1/p-glycoprotein at the blood-brain barrier in a rat brain endothelial cell model. Neurosci Lett 442(1): 19-23.

7. Takeuchi R, Shinozaki K, Nakanishi T, Tamai I (2016) Local drug-drug interaction of donepezil with cilostazol at breast cancer resistance protein (ABCG2) increases drug accumulation in heart. Drug Metab Dispos 44(1): 68-74.

8. Chan GN, Evans RA, Banks DB, Mesev EV, Miller DS, et al. (2017) Selective induction of P-glycoprotein at the CNS barriers during symptomatic stage of an ALS animal model. Neurosci Lett 639: 103-113.

9. Dar NJ, Muzamil A (2020) Neurodegenerative diseases and Withania somnifera (L.): an update. J Ethnopharmacol 256: 112769.

10. Birla H, Rai SN, Singh SS, Zahra W, Rawat A, et al. (2019) Tinospora cordifolia suppresses neuroinflammation in Parkinsonian mouse model. Neuromolecular Med 21(1): 42-53.

11. Shete RV, Bodhankar SL (2010) Hemidesmus indicus: Evaluation of its nootropic effect in mice. Int J Pharma Bio Sci 1(3): PS55.

12. Cheruku SP, Chamallamudi MR, Ramalingayya GV, Biswas S, Gourishetti K, et al. (2019) Neuroprotective potential of methanolic extract of Saraca asoca bark against doxorubicin-induced neurotoxicity. Phcog Mag 15(61): 309-316.

13. Ahmad M, Yousuf S, Khan MB, Hoda MN, Ahmad AS, et al. (2006) Attenuation by Nardostachys jatamansi of 6-hydroxydopamine-induced Parkinsonism in rats: Behavioral, neurochemical, and immunohistochemical studies. Pharmacol Biochem Behav 83: 150-60.

14. Bagewadi H, Khan A (2015) Investigation of antiparkinsonian effect of aloe vera on haloperidol induced experimental animal model. Indian J Pharm Biol Res 3(1): 108-113.

15. Yin S, Ran Q, Yang J, Zhao Y, Li C (2020) Nootropic effect of neferine on aluminium chloride-induced Alzheimer's disease in experimental models. J Biochem Mol Toxicol 34(2): e22429.

16. Sharma M, Malim FM, Goswami A, Sharma N, Juvvalapalli SS, et al. (2023) Neuroprotective effect of swertiamarin in a rotenone model of Parkinson's disease: role of neuroinflammation and alphasynuclein accumulation. ACS Pharmacol Transl Sci 6(1): 40-51.

17. Yadav SK, Rai SN, Singh SP (2017) Mucuna pruriens reduces inducible nitric oxide synthase expression in Parkinsonian mice model. J Chem Neuroanat 80: 1-10.

18. Kim Y, Chen J (2018) Molecular structure of human P-glycoprotein in the ATP-bound, outwardfacing conformation. Science 359(6378): 915-919.

19. Hee JY, Yeon CS, Ah-Reum H, Kyung SM (2007) P-glycoprotein inhibitory activity of two phenolic compounds, (−)-syringaresinol and tricin from Sasa borealis. Chem Biodivers 4(1): 12-16.

20. Rubis B, Polrolniczak A, Knula H, Potapinska O, Kaczmarek M, et al. (2010) Phytosterols in physiological concentrations target multidrug resistant cancer cells. Med Chem 6(4): 184-190.

21. Selase A, Cynthia AD, Newman O, Williams A, Michael O (2021) Palmatine sensitizes chemoresistant triple negative breast cancer cells via efflux inhibition of multidrug resistant protein 1. Sci Afr 14: e01022.

22. Ruvanthika PN, Manikandan S (2019) A review on the neuroprotective effect of Nelumbo nucifera seed pod. Int J Res Pharm Sci 10: 2307-2310.

23. Jing S, Wang Z, Zhang J, Li X, Huang R (2021) Neuroprotective effect of neferine, an alkaloid against the 1- methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine induced Parkinson's disease mouse model. Pharmacog Mag 17(73): 186-192.

24. Kouhestani S, Jafari A, Babaei P (2018) Kaempferol attenuates cognitive deficit via regulating oxidative stress and neuroinflammation in an ovariectomized rat model of sporadic dementia. Neural Regen Res 13(10): 1827-1832.

25. Bian LH, Yao ZW, Zhao CB, Li QY, Shi JL, et al. (2021) Nardosinone alleviates Parkinson's Disease symptoms in mice by regulating dopamine D2 receptor. Evid Based Complement Alternat Med 2021: 6686965.

26. Chaves SKM, Afzal MI, Islam MT, Hameed A, Da Mata

AMOF, et al. (2020) Palmatine antioxidant and anti-acetylcholinesterase activities: A pre-clinical assessment. Cell Mol Biol 66(4): 54-59.

27. Kiris I, Kukula KW, Karayel BM, Gurel B, Coskun J, et al. (2023) Proteomic alterations in the cerebellum and hippocampus in an Alzheimer's disease mouse model: alleviating effect of palmatine. Biomed Pharmacother 158: 114111.