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Exploring the Therapeutic Potential of Grapeseed Phytoconstituent Through Molecular Docking Analysis for Multiple System Atrophy Treatment

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Abstract

Objective: *Alpha-synuclein (α-Syn) aggregates are a common neurodegenerative disorder associated with Parkinson's disease and multiple system atrophy (MSA). As a fruit that is extensively grown, grapes have several pharmacological advantages when it comes to reducing oxidative stress. Research has indicated that grape seed phytoconstituents have a major effect on α-Syn. The objective of this study is to inquire into the pharmacological characteristics and potential therapeutic applications of grape seed derivatives against the targeted protein, α-Syn.* ***Methods:*** *To assess their binding affinity with α-Syn, thirty distinct grape seed components and their phytoconstituents were chosen for this investigation. The PyRx virtual tool was employed for molecular docking processes, utilizing computational analysis based on the molecular structures of both phytocompounds and α-Syn. The protein structure was verified using a collection of tools, such as the PDBsum generator and BIOVIA Discovery studio program. Furthermore, ADMET filters were used to evaluate the ligands pharmacologically.* ***Result:*** *The molecular docking studies indicated that thiamine, the ligand, had a low binding affinity for the protein α-Syn, which was the target.* ***Conclusion:*** *As thiamine has been shown to be a therapeutic agent against α-Syn in Parkinson's disease research, it may be a good choice for MSA and can be utilized to lessen its effects. To validate these results, in vitro studies are still necessary.*

Keywords: Multiple system atrophy, alpha-synuclein, grapeseed, thiamine, ADMET analysis, phytoconstituents, Ramachandran plot, molecular docking

INTRODUCTION

Multiple system atrophy (MSA) is an infrequent yet well-recognized neurological disorder that can be encountered by both neurologists and urologists [1]. This uncommon mobility disorder, which manifests as idiopathic orthostatic hypotension, Parkinsonism, and cerebellar ataxia, is associated with a neurodegenerative disease that is not heritable. Based on previous papers, MSA appears to be primarily sporadic [2]. Three separate conditions are included in MSA: olivopontocerebellar atrophy (OPCA), Shy-Drager syndrome, and striatonigral degeneration (SND) [3]. Ground on the dominant motor phenotype, these disorders present two main variations: the parkinsonian variant (MSA-P) and the cerebellar variant (MSA-C). MSA-P is more common than MSA-C in the western hemisphere [4]. In contrast to Parkinson's disease (PD), which advances more slowly, MSA usually concludes in death nine years following diagnosis [2]. The estimated cumulative incidence of MSA among people over thirty was 9.8 cases per 100,000 as of 2021. Age-adjusted to the U.S. population of 2021, the anticipated cumulative incidence of MSA among individuals 30 years of age or older was 14.2 per 100,000 [5].

Included in the group of neurodegenerative diseases known as α-synucleinopathies [4] is an

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aberrant accumulation of misfolded and hyperphosphorylated alpha-synuclein (α-Syn) [4]. This misfolded α-Syn accumulates throughout neurons and oligodendroglia, affecting many areas of the autonomic, central, and peripheral nervous systems (CNS) [6]. α-Syn, a 140-amino acid protein, has been linked to the etiology of Parkinson's disease [7], [8]. Overexpression of α-Syn results in neuronal loss, axonal degeneration, mitochondrial failure, microgliosis, and ambient oxidative stress [9]. Glial cytoplasmic inclusions (GCIs), intracellular protein aggregates mostly composed of α-Syn that are seen within oligodendrocytes, are the main morphological characteristic of MSA [10]. GCIs, which range in morphology and diameter from 5 to 20 μm, are spherical protein aggregates that are located adjacent to nuclei. Loosely organized α-Syn protein filaments that have been phosphorylated at Ser129 and ubiquitinated make up their major component [11]. Although GCIs are present throughout the brain, they are more common in the cerebellar white matter, pons, substantia nigra, inferior olivary nucleus, and basal ganglia [12]. Although the exact processes underlying the neurodegeneration in MSA are still unknown, our theory suggests that GCIs are a major factor in the neuronal degeneration seen in MSA and that α-Syn inclusions are what cause oligodendrocytes to form [13].

Originating in India and the Indian subcontinent, Ayurvedic medicine is a customized approach to traditional treatment. Its basic therapeutic philosophy is centered on fostering and preserving equilibrium in all facets of a person's life, including the body, mind, and spirit. Some of the well-known Ayurvedic medicinal herbs and formulations that are well-known for improving memory and delaying the aging of the brain include turmeric (*Curcuma longa*), ashwagandha (*Withania somnifera*), gotu kola *(Centella asiatica*), and shankhpushpi (*Convolvulus pluricauli*) [14]. Ayurvedic treatments made from plants are essential to the healing process. Substances derived from plants, animals, or minerals are included in the Ayurvedic pharmacopoeia if their names, identities, characteristics, and medicinal applications are well understood [15].

Fruits stand out as highly valuable sources of nutrients, energy, and health-promoting elements, often regarded as comprehensive foods. Using grapes as an example, their several components – such as the peel, oil from the seeds, and skin – have all been studied for their varied health advantages, which range from strong antioxidant qualities to possible anti-cancer effects [16]. Because of their many uses and nutritional potential, grapes of all kinds have garnered a lot of attention globally [17].

Grape seed *(Vitis vinifera*) is mostly composed of flavonoids, vitamins, terpenoids, tannin, alkane hydrocarbon, long-chain aldehydes, and dicarboxylic acid each playing a major part in oxidative stress and neuroinflammation. Positive findings of the antioxidant activities and free radical scavenging capabilities of the polyphenols and flavonoids found in the grape seed extract (GSE) have sparked considerable attention in them. Studies conducted mostly in vitro have identified the health benefits of grape seed oil, which include its anti-inflammatory, cardioprotective, antibacterial, and anticancer qualities [18]. Grape seed polyphenols have more antioxidant activity when compared to other familiar antioxidants, including vitamin C, vitamin E, and beta-carotene [19]. However, this article gives vitamins more weight because there have been comparatively fewer studies on other antioxidants.

One possible nutraceutical employed in treatment PD is GSE. It has polyphenols, such as resveratrol, gallic acid, anthocyanidin, and proanthocyanidin, which are all neuroprotective against PD, one of the most common neurodegenerative disorders mostly linked to α-Syn aggregation [20, 21].

The body needs thiamine, sometimes referred to as vitamin B1, because it is vital to many biological functions. Its main job is to co-factor with enzymes that are involved in glucose metabolism and energy synthesis [22]. It is essential to get thiamine from food sources because our systems cannot make it on their own. Foods high in thiamine include grains, cereals, and a variety of items made from plants. It is mostly found in plant-based sources in its phosphorylated form, sometimes referred to as thiamine diphosphate ester or thiamine pyrophosphate, which is the vitamin's active form [22]. Several factors connect thiamine to PD [23]. Thiamine deficiency has been linked to the demise of dopaminergic neurons in PD, as thiamine is known for encouraging dopamine release [24]. Conversely, administering

thiamine supplements has demonstrated a capacity to postpone the advancement of PD and the demise of dopaminergic neurons [25]. Studies imply that elevating intracellular thiamine levels may lead to a reduction in α-Syn concentration, potentially mitigating α-Syn aggregation [23]. This suggests that thiamine could have broader applications, not just as a treatment but also in mitigating the effects of multiple system atrophy. The ability of thiamine to impact α-Syn indicates its potential value in therapeutic strategies for addressing MSA.

METHODOLOGY

Retrieval of Ligands

Using data from the medical plant *Vitis vinifera*, potential ligands were found using the IMPPAT (Indian medical plants, phytochemistry and therapeutics) database (https://cb.imsc.res.in/imppat/) [26]. For this experiment, every ligand that was chosen had a standard SMILES notation. SDF formatted copies of the top 30 ligands were received from PubChem (https://pubchem.ncbi.nlm.nih.gov/) [27].

Pharmacological Studies

Switzerland-based SwissADME analysis (http://www.swissadme.ch/index.php) was used for pharmacological evaluations [28]. Five physicochemical characteristics are evaluated in this analysis: Lipinski, TPSA (Topological polar surface area), LogP, GI absorption, and P-glycoprotein (P-gp) substrate qualities.

The Lipinski rules, commonly known as the rule of five (ROF), provide a general framework for assessing drug similarity or assessing if a chemical compound possesses certain properties that could make it a potential oral pharmaceutical for human usage [29].

A useful way to calculate a molecule's polar surface area is to use TPSA [30]. When creating new medications, lipophilicity is a physicochemical factor that must be carefully considered because it has been shown to have a substantial impact on several pharmacokinetic characteristics, including drug absorption, distribution, permeability, and routes of clearance.

GI absorption through the digestive tract is thought to be a complicated process because of several variables that fall mostly into three categories: physicochemical, physiological, and formulation impacts. One of three methods – facilitated diffusion, passive diffusion, or active transport – basically describes the absorption of medications taken orally. These mechanisms rely on the drug's diffusion coefficient, particle size, and other parameters.

P-glycoprotein (P-gp) oversees many toxic substances leaving the cell and into the extracellular space, but it also removes a lot of medications from the cells, which can significantly lower or eliminate their active ingredients [31].

Certain medications will inherently fall outside of the ROF standard parameter cutoffs. The ROF does not apply to vitamins, antibiotics, antifungals, or cardiac glycosides. These substances' structural characteristics enable the medications to function as substrates for naturally occurring transporters [29].

Protein Retrieval and Purification

PDB ID 3Q28, which represents the crystal structure of α-Syn, was acquired from the PDB database at (https://www.rcsb.org/structure/3Q28). The protein's free energy was out of alignment with the crystallographic structure, therefore water molecules had to be removed through a purification process before it could be docked. To avoid any possible interference with the results, all water molecules were removed prior to docking. To simplify the protein structure, just the A-chains remained after any unnecessary chains were eliminated. As seen in Figure 1, the purification procedure also involved the extraction of complexed ligands and prebound heteroatoms from the structure. The BIOVIA DS Discovery Studio was used to carry out this purifying process [32].

Validation of Protein Structure

A technique developed by Sasisekharan during his graduate work on collagen chains in G.N. Ramachandran's lab was applied to validate the protein structure [33]. A polypeptide's amino acid residues can each have a unique set of ϕ and ψ angles; as a result, each residue can be represented as a point on a Ramachandran plot with matching α and β angles. Upon assuming secondary structures, polypeptides twist at distinct torsional angles to generate regular, repetitive structures like α-helix and β-sheet. As a result, when we plot these torsional angles against the Ramachandran plot, we get a very small region on the plot that can be utilised to locate and examine the secondary structure in each polypeptide [34]. To establish how the ligands interact with the proteins, molecular docking requires an understanding of the three-dimensional structures. This technique makes use of torsion angles to describe the structure of proteins and polypeptides. Using an internet server called the PDBsum generator https://www.ebi.ac.uk/thornton-srv/databases/pdbsum/, the purified protein structures were subjected to Ramachandran plot analysis and secondary structure prediction to verify the purified structure of α-Syn [35].

Molecular Docking

The recent deluge of structural and chemical data has made molecular docking an indispensable tool for computational biology and drug development [36]. To facilitate the creation of a stable complex, this computer modeling approach helps anticipate the favorable binding orientation of a ligand to a receptor [37]. Because molecular docking is efficient and affordable, it has become widely used in academic and industrial contexts during the past few decades [36].

In this investigation, the purified protein α-Syn (PDB ID-3Q28) was uploaded as the macromolecule and phytocompounds derived from a plant were loaded into PyRx as ligands [38]. Using OPENBABEL, ligands were translated from the SDF format to the PDB format. Thiamine was separately docked against α-synuclein using the PyRx web server, and energy minimization was carried out. Thiamine was chosen for more research after the docking data were considered. Thiamine's propensity for binding the target protein made it the most promising chemical.

VISUALIZATION

DS BIOVIA Discovery studio was used to envision the docked ligand structures once they were retrieved and saved as.pdb files.

RESULT

Retrieval of Ligands

Grapes of several kinds have attracted a lot of attention from around the world because of their nutritional and functional value. It is mostly made up of vitamins, tannin, alkane hydrocarbon, long-chain aldehydes, terpenoids, flavonoids, and dicarboxylic acid, all of which are important contributors to neuroinflammation and oxidative stress. According to recent studies, PD patients may benefit from using grapeseed as a medication. Thirty phytocompounds were chosen to determine the impact of grapeseed on MSA. These include, thiamine, riboflavin, retinol, heptacosane, astilbin, flavylium, undecane, 2,3-butanediol, octacosanal, hexacosanal, dehydroascorbic acid, zingerone, nonanal, d-tartaric acid, jasmonic acid, choline, ethyl arachidate, roseoside, vomifoliol, ethyl butyrate, 2-phenylethanol, cholesterol, ascorbic acid, damascenone, methyl anthranilate, delphinidin, dehydrovomifoliol, 1-hexanol, ethyl stearate, oxalic acid.

ADMET Analysis

To ensure that medications are produced with the fewest possible negative effects, druglikeness must be verified. To ascertain how beneficial the phytocompounds extracted from *Vitis vinifera* are, pharmacological investigations were conducted on them. A physicochemical screening was performed on the phytoconstituents from *Vitis vinifera* using the optimal parameters given in Table 1. Table 2 demonstrates physiochemical properties of *Vitis vinifera.* Table 3 lists the druglikeness of *Vitis vinifera.*

Table 1. Demonstrates the standards under which the physiochemical screening is conducted.

Properties	Optimal Parameters
Lipinski	0
TPSA	20–150 Å
Lipophilicity (LogP)	–0.4–5.0
GI absorption	High
P-gp	Positive

PHYSIOCHEMICAL PROPERTIES

The phytoconstituent's TPSA is revealed by their physiochemical characteristics.

Table 2. Physiochemical properties of *Vitis vinifera.*

Molecule	Chemical Formula	Molecular Weight	Number of H-Bond Acceptors	Number of H-Bond Donors	TPSA
Thiamine	C12H17N4OS+	265.35	3	2	104.15
Riboflavin	C17H20N4O6	376.36	8	5	161.56
Retinol	C20H30O	286.45	1	1	20.23
Heptacosane	C27H56	380.73	0	0	0
Astilbin	C21H22O11	450.39	11	7	186.37
Flavylium	C15H11O+	207.25	1	0	13.14
Undecane	C11H24	156.31	0	0	0
2,3-Butanediol	C4H10O2	90.12	2	2	40.46
Octacosanal	C28H56O	408.74	1	0	17.07
Hexacosanal	C26H52O	380.69	1	0	17.07
Dehydroascorbic acid	C6H6O6	174.11	6	2	100.9
Zingerone	C11H14O3	194.23	3	1	46.53
Nonanal	C9H18O	142.24	1	0	17.07
d-Tartaric acid	C4H6O6	150.09	6	4	115.06
Jasmonic acid	C12H18O3	210.27	3	1	54.37
Choline	C5H14NO+	104.17	1	1	20.23
Ethyl arachidate	C22H44O2	340.58	2	0	26.3
Roseoside	C19H30O8	386.44	8	5	136.68
Vomifoliol	C13H20O3	224.3	3	2	57.53
Ethyl butyrate	C6H12O2	116.16	2	0	26.3
2-Phenylethanol	C8H10O	122.16	1	1	20.23
Cholesterol	C27H46O	386.65	1	1	20.23
Ascorbic acid	C6H8O6	176.12	6	4	107.22
Damascenone	C13H18O	190.28	1	0	17.07
Methyl anthranilate	C8H9NO2	151.16	2	1	52.32
Delphinidin	C15H11ClO7	338.7	7	6	134.52
Dehydrovomifoliol	C13H18O3	222.28	3	1	54.37
1-Hexanol	C6H14O	102.17	1	1	20.23
Ethyl stearate	C20H40O2	312.53	2	0	26.3
Oxalic acid	C2H2O4	90.03	4	2	74.6

DRUGLIKENESS

The druglikeness is listed in Table 3 and includes four parameters: Lipinski, Ghose, Egan, and Muegge, which screen for phytoconstituents.

Table 3. Lists the druglikeness of *Vitis vinifera.*

Molecule	Lipinski	Ghose	Egan	Muegge
Thiamine	0	0	0	0
Riboflavin	0	1	1	1
Retinol	0	1	1	1
Heptacosane	1	3	1	1
Astilbin	2	0	1	1
Flavylium	0	0	0	0
Undecane	1	1	0	0
2,3-Butanediol	0	3	0	0
Octacosanal	1	3	1	1
Hexacosanal	1	2	1	1
Dehydroascorbic acid	0	3	0	0
Zingerone	0	0	0	0
Nonanal	0	1	0	0
d-Tartaric acid	0	4	0	0
Jasmonic acid	0	0	0	0
Choline	0	2	0	0
Ethyl arachidate	1	1	1	1
Roseoside	0	1	0	1
Vomifoliol	0	0	0	0
Ethyl butyrate	0	2	0	0
2-Phenylethanol	0	3	0	0
Cholesterol	1	2	0	1
Ascorbic acid	0	2	0	0
Damascenone	0	0	0	0
Methyl anthranilate	0	1	0	0
Delphinidin	1	0	0	1
Dehydrovomifoliol	0	0	0	0
1-Hexanol	0	2	0	0
Ethyl stearate	1	1	1	1
Oxalic acid	0	4	0	0

PHARMACOKINETICS

Table 4 shows three parameters: GI absorption, P-gp substrate, Lipophilicity which further categorises the selected phytoconstituents.

Thiamine is a vitamin B that has been identified as the perfect phytochemical based on the previously mentioned optimal characteristics. Molecular docking and the Ramachandran plot will be carried out as follows.

Secondary Structure and Ramachandran Plots

PROCHECK was used to create the secondary structure and Ramachandran plots of A-Syn, which are shown in Figure 1. The target protein does not lie in the forbidden zone, as shown by the fact that, of the 309 residues examined, 93.1% are in the most desired areas, 6.9% in further allowed regions, and none in generously allowed or barred regions.

The projected secondary structure of protein A-Syn is shown in Figure 2 and is based on the PDBsum data. It includes 1 sheet, 2 beta hairpins, 1 psi loop, 3 beta bulges, 15 strands, 20 helices, 16 helix-helix contacts, 26 beta turns, and 4 gamma turns.

Molecular Docking Analysis

According to molecular docking studies, thiamine had the lowest binding affinity and the highest interconnection with the target protein, α-Syn.

Table 4. Shows the pharmacokinetic properties of *vitis vinifera*.

Molecule	GI absorption	P-Gp Substrate	Lipophilicity
Thiamine	High	Yes	–1.6
Riboflavin	Low	No	1.63
Retinol	Low	No	1.63
Heptacosane	Low	Yes	7.32
Astilbin	Low	Yes	2.02
Flavylium	High	Yes	–0.76
Undecane	Low	No	3.59
2,3-Butanediol	High	No	1.26
Octacosanal	Low	Yes	6.9
Hexacosanal	Low	No	6.48
Dehydroascorbic acid	Low	No	–0.56
Zingerone	High	No	2.09
Nonanal	High	No	2.44
d-Tartaric acid	Low	No	–0.82
Jasmonic acid	High	No	1.9
Choline	Low	No	–2.14
Ethyl arachidate	Low	No	5.59
Roseoside	Low	Yes	1.29
Vomifoliol	High	No	2.23
Ethyl butyrate	High	No	1.9
2-Phenylethanol	High	No	1.7
Cholesterol	Low	No	4.96
Ascorbic acid	High	No	–0.31
Damascenone	High	No	2.74
Methyl anthranilate	High	No	1.78
Delphinidin	High	Yes	–5.53
Dehydrovomifoliol	High	No	1.91
1-Hexanol	High	No	2.03
Ethyl stearate	Low	No	5.47
Oxalic acid	High	No	–0.35

Visualization

In Biovia Discovery Studio, the docked complex between thiamine and α-Syn, which has a binding energy of -6, was displayed for visualization reasons. The ligand binds to the amino groups in the protein's A chain, including MET 331, ASP 66, ARG 67, TRP 341, ARG 345, PRO 155, GLU 154, and TYR 156, TRP 63, LEU 263, GLU 112, ASN 13, ALA 64, and LYS 16, according to an analysis of the 2D interaction diagrams (Figure 3).

In this instance, ARG and the target protein's o-chain are joined via a hydrogen bond. Along with having pi-stigma and pi-pi stacking bonds attached to the protein, the pi-sulfur bond binds TRP to the protein's sulphur group (Figure 4). The target protein and LYS are bound together via a pi-cation link. Alkyl and pi-alkyl bonds bind LEU and ALA to the target protein.

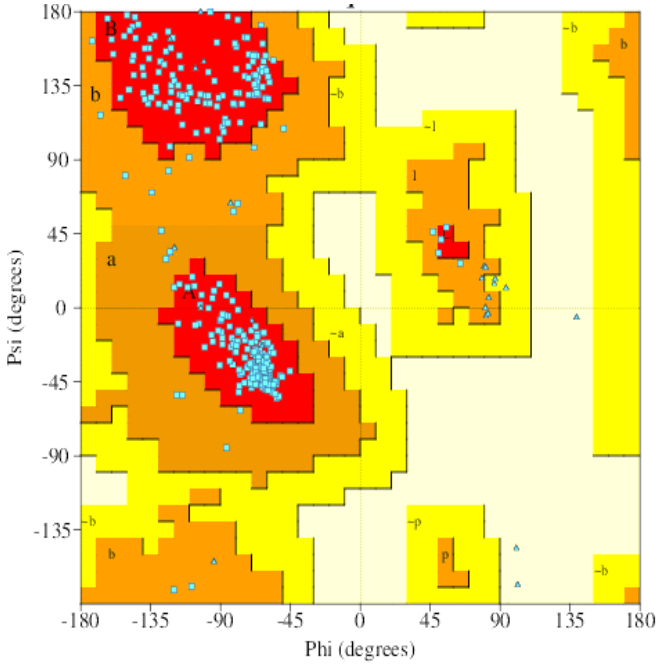

Figure 1. Ramachandran plot of α-Syn protein using PDBsum.

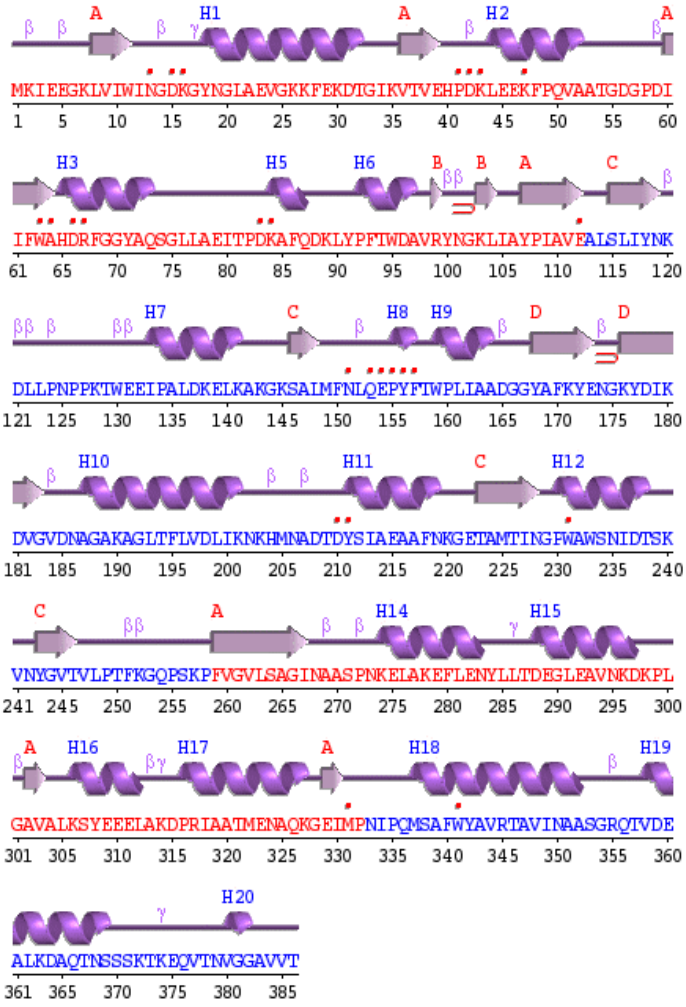

Figure 2. Secondary structure of protein A-Syn using PDBsum.

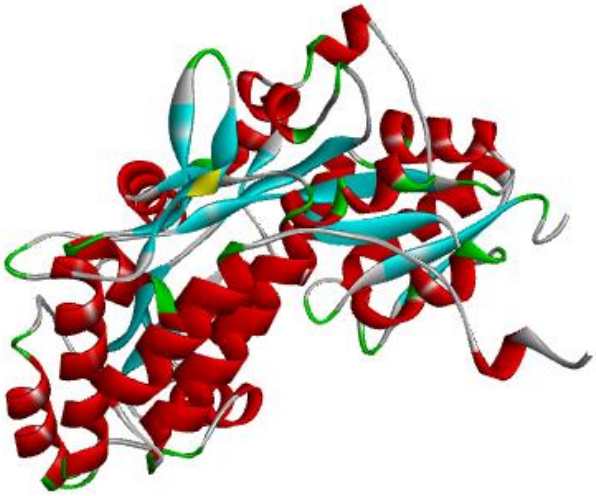

Figure 3. α-Syn protein structure.

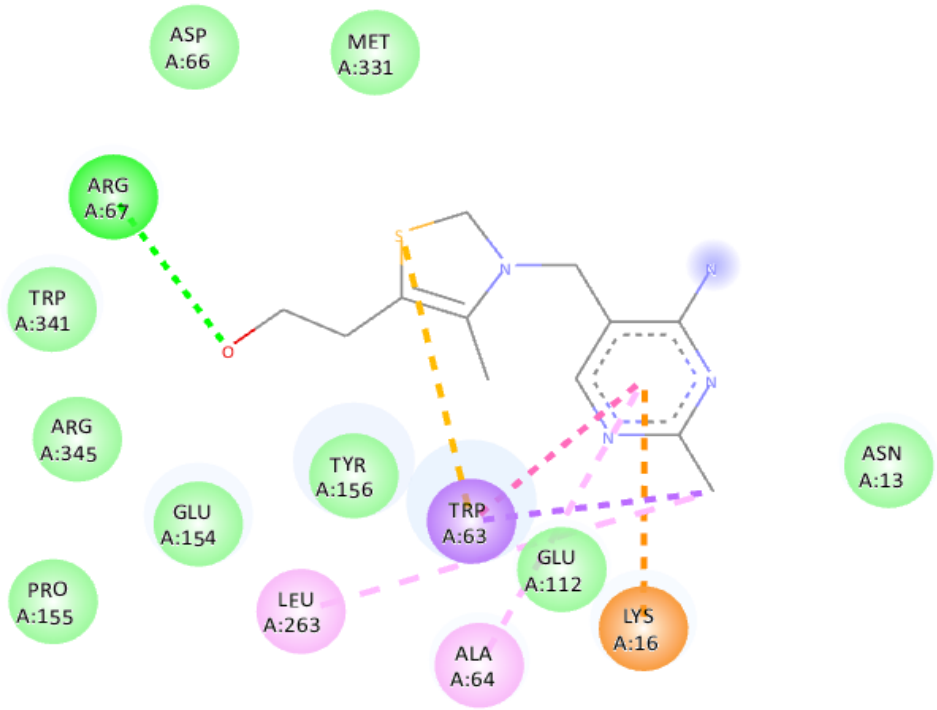

Figure 4. Visualization of 2D structure of target protein and ligand interaction.

DISCUSSION

Clinical signs of MSA, a neurodegenerative disease that progresses over time, include parkinsonism, problems with the cerebellum, and autonomic dysfunction [39]. Extrapyramidal, pyramidal, cerebellar, and autonomic presentations are the different subtypes of these symptoms. Postural instability and stiffness are examples of extrapyramidal symptoms that are like PD symptoms. Autonomic dysfunction is also prevalent, encompassing issues related to digestion and cardiovascular functioning. Furthermore, nonmotor symptoms, such as dyspnea, emotional dysregulation, insomnia, and cognitive deterioration may appear gradually [11].

The human brain normally expresses α-Syn, a protein with 140 amino acids and a weight of 14 kDa [39]. It is essential for controlling dopamine reuptake, release, and presynaptic structure. Although α-Syn is mostly present in presynaptic areas, oligodendrocytes and their progenitors absorb it when neurons release it into the extracellular environment. Argodendrocytes mostly exhibit argyrophilic filamentous GCIs, which have been identified as a significant neuropathological hallmark for MSA. Neuronal degeneration, brain atrophy, demyelination, and nerve cell mutations are associated with the accumulation of α-Syn in oligodendrocytes in patients with MSA [11].

Flavonoids, including anthocyanins, flavones, and flavanols, phenolics, and complex vitamins E and B, are the main constituents of grapes [17]. The phenolic components found in *Vitis vinífera* are organic substances that serve as both a defence against immune system attacks and a shield against reactive oxygen species. They can sequester free radicals due to the presence of one or more aromatic rings in their structure; the quantity and location of these hydroxyl groups determine the antioxidant activity of the compound [1].

As thiamine is involved in many biological activities, it is often referred to as vitamin B1. Thiamine is an essential vitamin for the body. Thiamine shortage causes these enzymes to function less efficiently, reduces pyruvate oxidation, and causes lactate to build up in the blood and brain. According to earlier research, raising intracellular thiamine levels may cause α-Syn concentration to drop, which may lessen α-Syn aggregation [23]. Due to its well-known ability to facilitate dopamine release, thiamine is a key component of PD treatment [24].

Because of their established pharmacological advantages, 30 grapeseed fruit derivatives were selected for this study. Thiamine was chosen for additional examination because it showed the lowest binding affinity (-6) of any of them with the target protein α-Syn. Dassault Systems BIOVIA Discovery Studio was used to visualize these interactions. Thiamine may influence α-Syn, which implies that it may be useful in treating MSA, as it has already been studied against PD. Research possibilities can be expanded by pursuing in vitro experiments to further explore this possibility.

CONCLUSIONS

Thiamine, a water-soluble vitamin essential for various biological functions, has been implicated in certain inherited and degenerative nervous system disorders. Recent findings suggest that deficiencies in thiamine, either due to impaired intracellular transport or structural enzymatic abnormalities, may contribute to the pathogenesis of these conditions. Treatment with thiamine has shown promising results in alleviating symptoms associated with conditions like PD, indicating its potential therapeutic value in managing related disorders, such as MSA. Further exploration into thiamine's impact on alpha-synuclein, a protein associated with neurodegenerative diseases, is warranted, including in vitro analyses of its interactions with the target protein. Additionally, investigating thiamine's effects on the SNCA gene could provide valuable insights into its mechanisms of action in the central nervous system.

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Abbreviations

Multiple system atrophy	MSA
Striatonigral degeneration	SND
olivopontocerebellar atrophy	OPCA
Alpha-synuclein	α-Syn
Parkinson's disease	PD

Central nervous systems	CNS
Glial cytoplasmic inclusions	GCI
Grape seed extract	GSE
Topological polar surface area	TPSA
Gastrointestinal	GI
Substrate of P-glycoprotein	P-gp
Rule of Five	ROF

REFERENCES

1. Sakakibara R. Multiple System Atrophy. In: Liao L, Madersbacher H, editors. Neurourology. Dordrecht: Springer; 2019. 549–562. doi:10.1007/978-94-017-7509-0_65.
2. Herrera-Vaquero M, Heras-Garvin A, Krismer F, Deleanu R, Boesch S, Wenning GK, et al. Signs of early cellular dysfunction in multiple system atrophy. Neuropathol Appl Neurobiol. 2021;47(2):268–282. doi:10.1111/nan.12661.
3. Dickson DW, Liu WK, Hardy J, Farrer M, Mehta N, Uitti R, et al. Widespread alterations of α-synuclein in multiple system atrophy. Am J Pathol. 1999;155(4):1241–1251. doi:10.1016/S0002-9440(10)65226-1.
4. Campese N, Fanciulli A, Stefanova N, Haybaeck JS, Kiechl, Wenning GK. Neuropathology of multiple system atrophy: Kurt Jellinger`s legacy. J Neural Transm. 2021;128(10):1481–1494. doi:10.1007/s00702-021-02383-3.
5. Kaplan S, Xie H, Wang J. Estimating the prevalence and incidence of multiple system atrophy in the USA: Insights from a national claims database. Parkinsonism Relat Disord. 2023;117:105920. doi:10.1016/j.parkreldis.2023.105920.
6. Jellinger KA. Multiple system atrophy - a clinicopathological update. Free Neuropathol. 2020;1:1–17. doi:10.17879/freeneuropathology-2020-2813.
7. Fitzgerald E, Murphy S, Martinson HA. Alpha-synuclein pathology and the role of the microbiota in Parkinson's disease. Front Neurosci. 2019;13. doi:10.3389/fnins.2019.00369.
8. Srinivasan E, Chandrasekhar G, Chandrasekar P, Anbarasu K, Vickram AS, Karunakaran R, et al. Alpha-synuclein aggregation in Parkinson's disease. Front Med. 2021;8:736978. doi:10.3389/fmed.2021.736978.
9. Stefanova N, Bücke P, Duerr S, Wenning GK. Multiple system atrophy: an update. Lancet Neurol. 2009;8(12):1172–1178. doi:10.1016/S1474-4422(09)70288-1.
10. Compagnoni GM, Fonzo AD. Understanding the pathogenesis of multiple system atrophy: state of the art and future perspectives. Acta Neuropathol Commun. 2019;7(1):113. doi:10.1186/s40478-019-0730-6.01
11. Lee HJ, Ricarte D, Ortiz D, Lee SJ. Models of multiple system atrophy. Exp Mol Med. 2019;51(11):1–10. doi:10.1038/s12276-019-0346-8.
12. Koga S, Dickson DW. Recent advances in neuropathology, biomarkers and therapeutic approach of multiple system atrophy. J Neurol Neurosurg Psychiatry. 2018;89(2):175–184. doi:10.1136/jnnp-2017-315813
13. Yazawa I, Giasson BI, Sasaki R, Zhang B, Joyce S, Uryu K, et al. Mouse model of multiple system atrophy α-synuclein expression in oligodendrocytes causes glial and neuronal degeneration. Neuron. 2005;4596):847–859. doi:10.1016/j.neuron.2005.01.032.
14. Farooqui A, Farooqui T, Madan A, Ong JHJ, Ong WY. Ayurvedic medicine for the treatment of dementia: mechanistic aspects. Evid Based Complement Alternat Med. 2018. doi:10.1155/2018/2481076.
15. Kumar S, Dobos GJ, Rampp T. The significance of Ayurvedic medicinal plants. J Evid Based Complement Alternat Med. 2017;22(3):494–501. doi:10.1177/2156587216671392.
16. Chavan SS, Kesari M. Trust-(Copyright-2022) [Online]. 2022;1. Maharatta. 2022. Available from: www.mahratta.org.

17. Caetano SS, de Moura M, Sobreira AC, Barroso AB, Pinheiro-Sant'Ana HM, Della Lucia CM, et al. Characterization and bioactive compounds of organic Bordeaux grape seed oil and flours (Vitis labrusca L.). Res Soc Dev. 2022;11(14):e55111435888. doi:10.33448/rsd-v11i14.35888.
18. Garavaglia J, Markoski MM, Oliveira A, Marcadenti A. Grape seed oil compounds: Biological and chemical actions for health. Nutr Metab Insights. 2016;9:NMI-S32910. doi:10.4137/NMI.S32910.
19. Gupta M, Dey S, Marbaniang D, Pal P, Ray S, Mazumder B. Grape seed extract: having a potential health benefits. J Food Sci Technol. 2020;57(4):1205–1215. doi:10.1007/s13197-019-04113-w.
20. Hey G, Nair N, Klann E, Gurrala A, Safarpour D, Mai V, et al. Therapies for Parkinson's disease and the gut microbiome: evidence for bidirectional connection. Front Aging Neurosci. 2023;15:1151850. doi:10.3389/fnagi.2023.1151850.
21. Fandy SJ. Grape seed extract's neuroprotective effect and parkinson's disease: A systematic review. Malang Neurol J. 2023;9(1):44–51. doi:10.21776/ub.mnj.2023.009.01.9.
22. Polegato BF, Pereira AG, Azevedo PS, Costa NA, Zornoff LA, Paiva SA, et al. Role of thiamin in health and disease. Nutr Clin Pract. 2019;34(4):558–564. doi:10.1002/ncp.10234.
23. Costantini A, Pala MI, Grossi E, Mondonico S, Cardelli LE, Jenner C, et al. Long-term treatment with high-dose thiamine in Parkinson disease: An open-label pilot study. J Altern Complement Med. 2015;21(12):740–747. doi:10.1089/acm.2014.0353.
24. Luong KVQ, Nguyễn LTH. The beneficial role of thiamine in Parkinson disease. CNS Neurosci Ther. 2013;19(7):461–468. doi:10.1111/cns.12078.
25. Rai SN, Singh P, Steinbusch HW, Vamanu E, Ashraf G, Singh MP. The role of vitamins in neurodegenerative disease: An update. Biomed. 2021;9(10):1284. doi:10.3390/biomedicines9101284.
26. Mohanraj K, Karthikeyan BS, Vivek-Ananth RP, Chand RB, Aparna SR, Mangalapandi P, et al. IMPPAT: A curated database of Indian medicinal plants, phytochemistry and therapeutics. Sci Rep. 2018;8(1):4329. doi:10.1038/s41598-018-22631-z.
27. Kim S, Thiessen PA, Bolton EE, Chen J, Fu G, Gindulyte A, et al. PubChem substance and compound databases. Nucleic Acids Res. 2016;44(D1):D1202–D1213. doi:10.1093/nar/gkv951.
28. Tripathi P, Ghosh S, Talapatra SN. Bioavailability prediction of phytochemicals present in Calotropis procera (Aiton) R. Br. by using Swiss-ADME tool. World Sci News. 2019;131:147–163.
29. Ivanović V, Rančić M, Arsić B, Pavlović A. Lipinski's rule of five, famous extensions and famous exceptions. Chemia Naissensis. 2020;3(1):171–177.
30. Prasanna S, Doerksen RJ. Topological polar surface area: A useful descriptor in 2D-QSAR. Curr Med Chem. 2008;16(1):21–41. doi:10.2174/092986709787002817.
31. Chandrasekaran B, Abed SN, Al-Attraqchi O, Kuche K, Tekade RK. Computer-Aided Prediction of Pharmacokinetic (ADMET) Properties. In: Tekade RK, editor. Dosage Form Design Parameters. 1st edition. Amsterdam: Elsevier; 2018. 731–755. doi:10.1016/B978-0-12-814421-3.00021-X.
32. Rani N, Khare N, Jha AK. Molecular docking study of dihydrohelenalin against DNMT1 to treat oral cancer. Int J Res Anal Rev. 2020;7(3):427–437.
33. Hollingsworth SA, Karplus PA. A fresh look at the Ramachandran plot and the occurrence of standard structures in proteins. Biomol Concept. 2010;1(3–4):271–283. doi:10.1515/bmc.2010.022.
34. Kumar P, Arya A. Ramachandran plot-A simplified approach [Online]. Available from: esearchgate.net/profile/Pranav-Kumar36/publication/330158666_Ramachandran_plot_A_simplified_approach/links/5c304d76458515a4c70d377b/Ramachandran-plot-A-simplified-approach.pdf.
35. Laskowski RA. Enhancing the functional annotation of PDB structures in PDBsum using key figures extracted from the literature. Bioinform. 20074;23(14):1824–1827. doi:10.1093/bioinformatics/btm085.
36. Pawar RP, Rohane SH. Role of autodock vina in PyRx molecular docking. Asian J. Res Chem. 2021;14(2):132–134. doi:10.5958/0974-4150.2021.00024.9.
37. Agarwal S, Mehrotra R. An overview of molecular docking. JSM Chem. 2016;49(2):1024.

38. Tahir M, Baharuddin M, Najib A. In silico screening of brotowali (Tinospora crispa L.) chemical compounds as α-glucosidase inhibitor using the pyrx program. AIP Conf Proc. 2023;2595:050009. doi:10.1063/5.0123693.
39. Valdinocci D, Radford RAW, Goulding M, Hayashi J, Chung RS, Pountney DL. Extracellular interactions of Alpha-synuclein in multiple system atrophy. Int J Mol Sci. 2018;19(12):4129. doi:10.3390/ijms19124129.

