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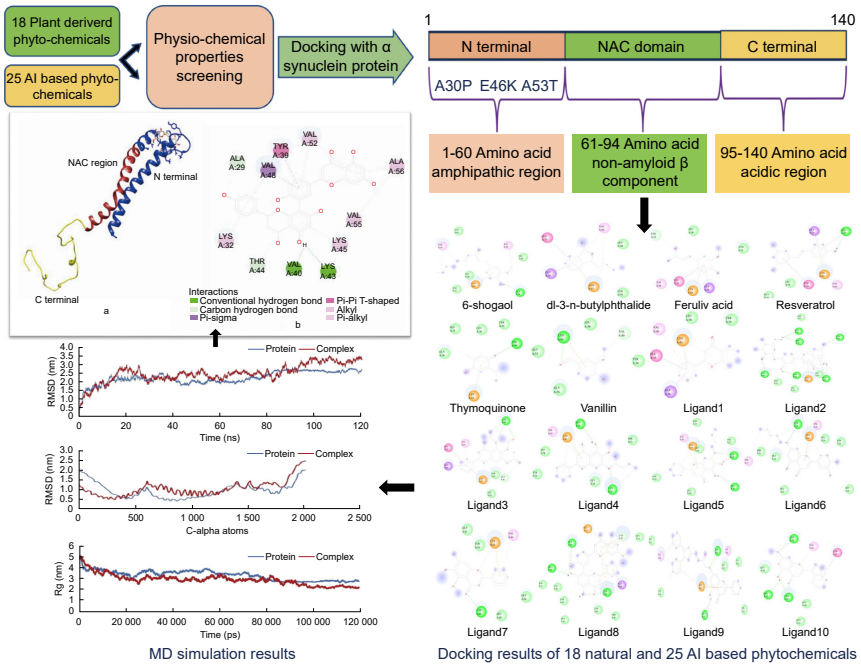
Diseases & Research

In Silico Therapeutic Approaches Based on Natural Phytochemicals Against Alpha Synuclein Protein Involved in Parkinson's Disease

Graphical abstract



MD simulation results

Docking results of 18 natural and 25 AI based phytochemicals

Authors

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In Silico Therapeutic Approaches Based on Natural Phytochemicals Against Alpha Synuclein Protein Involved in Parkinson's Disease

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Backgrounds: Finding novel therapies that stop a-synuclein oligomerisation and, consequently, the progression of Parkinson's disease (PD) may result from the identification of putative neuroprotective substances that bind to a-synuclein.Thus, in silico methods play a critical role in cutting down on the time and expenses related to testing drugs with negligible or no neuroprotective effect in experiments.
Methods: Prior research has examined novel compounds for naturally occurring antioxidant phytochemicals, chosen AI-based compounds, and docked these compounds with the protein α-synuclein (1XQ8) The molecule with the highest binding affinity is used in MD simulation to ensure structural stability.
Results: We investigate the regulatory functions of the alpha synuclein protein using computational molecular docking and MD simulations. MD simulations revealed that the primary amino acid residues Lys32, Leu38, Val40, Glu35, Gly36, Lys43, Thr44, Lys45, Glu46, Gly47, and Val48 bind to certain amino acid residues of alpha synuclein, especially the basic residues located in amino acid residues 1–61. These results validate previous experimental studies. This analysis using MD modeling revealed the N-terminal residues. Eight natural and ten artificial intelligence-based ligands were docked with the alpha synuclein protein. Our investigation revealed that the ligand4 would assist to suppress the disease condition of Parkinson's disease, based on prior research on the potential regulatory role of various natural phytochemicals that are significant for Parkinson's disease.
Conclusion: Therefore, it is thought that these phytochemicals could be employed as potential bioenhancers in the therapy of Parkinson's disease. The current investigation could be expanded for future experimental validation and would provide light on the identification of natural phytochemicals and AI-based compounds against SNCA as an alternative treatment of Parkinson's disease.
Keywords: Alpha synuclein; Molecular docking; Molecular dynamics simulation; Neuroprotective; Parkinson's disease; Phytochemicals.

Introduction

Age-related neurodegenerative disease's second most prevalent form is PD. Moreover, alpha (α)-synuclein seems to be involved in the genesis of PD and has been linked with familial as well as sporadic ways of the condition[1]. In order to protect the antioxidant defence system against a range of pathogenic diseases and stress-related disorders, plants contain physiologically active phytochemicals that may be employed therapeutically as primary and secondary metabolites[2]. Cells can be shielded from oxidative damage by products of plant as well as their bioactive phytochemicals, which effectively enhance cellular antioxidant as well as scavenge oxygen free radicals defence system and associated compounds. Therefore, therapy options aiming at lowering neuroinflammation, oxidative stress, α-synuclein accumulation, as well as mitochondrial dysfunction might be exceedingly promising for treating PD[3]. The loss of nigrostriatal dopaminergic innervation is the pathological hallmark of Parkinson's disease (PD), though neurodegeneration affects cells in other parts of the neural network in addition to nigral dopaminergic neurons. PD is a highly heterogeneous condition due to its broad pathology, and there is currently no appropriate diagnostic test. Nowadays, a diagnosis is made based on clinical symptoms, and two of the following clinical characteristics must be present in order to be diagnosed: resting tremor, bradykinesia, stiffness, and/or postural instability[4]. However, clinical criteria can only result in a diagnosis of probable Parkinson's disease (PD); a conclusive diagnosis necessitates a histological evaluation that identifies Lewy bodies (LBs) or Lewy neurites that contain α- synuclein.

Although the precise causes of Parkinson's disease (PD) are still unknown, research indicates that a mix of environmental and genetic variables may play a role in its development. These elements cause oxidative damage, endoplasmic reticulum (ER) stress, mitochondrial malfunction, and persistent neuroinflammation—all of which contribute to Parkinson's disease (PD) pathogenesis. Therefore, a complicated interaction between hereditary and environmental factors plays a role in the etiology of Parkinson's disease. These pathogenic alterations lead to oxidative stress, microglial activation, and mitochondrial dysfunction, which in turn causes SNpc degeneration and the beginning of Parkinson's disease symptoms[5].

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One important factor in the degeneration of dopaminergic neurones as well as advancement of PD is misfolding of α-synuclein. The α-synuclein protein is composed of three sections: N-terminal (1–60), middle (61–95), as well as C-terminal (96–140) (Fig. 1). A53T, A30P, E46K, and G51D are among the symptomatic mutations present in autopsies of patients having PD who had several brain synucleinopathies[6]. First area is known to bind to membrane phospholipids. Its function in the aggregation and hydrophobicity define the core area. Lastly, strong thermal stability is a result of the C-terminal region's high acidity. Interestingly, experimental results revealed that neuroprotective chemicals bind with N- as well as C-terminal, but compounds that are neurotoxic prefer the N-terminal[7]. Furthermore, the central area is known to have a role in α-synuclein aggregation. Natural polyphenolic compounds and black tea extracts were exhibited dose dependant inhibitory effect on α-synuclein aggregation using structure activity analysis[8]. While drugs that produce very compact structure likely to be neurotoxic, which bind with α-synuclein as well as generate structure that is loop among N- as well as C-terminus that is supposed to be neuroprotective[9]. There is no surprise that a number of medications have the ability to attach N- as well as C-terminus, strengthening this collaboration as well as preventing α-synuclein from misfolding. These medications could be neuroprotective. On the other hand, medications like amphetamines that exclusively bind with N-terminus might promote α-synuclein misfolding by blocking the contact among N- as well as C-terminus. These medications might be neurotoxin. A more comprehensive understanding of α-Synuclein's basic function as well as its neurodegenerative part illnesses has resulted from its independent discovery through several research methodologies[10]. Its presynaptic function was initially demonstrated when it was discovered utilizing antibodies that were specific to isolated cholinergic vesicles from Torpedo electric organ. Furthermore, name "synuclein" was coined due to its observation near the nuclear envelope[11]. Phytochemicals are physiologically active substances that often correlate to secondary metabolites found in plants, such as terpenoids, flavonoids, and alkaloids. Natural compounds like curcumin, myricetin, and baicalein have been shown in recent studies to decrease α-synuclein aggregation, lower oxidative stress, and maybe prevent neurodegeneration[12]. The capacity of green tea's epigallocatechin gallate (EGCG) for rerouting α-synuclein fibrillation into benign aggregates is another example of the therapeutic promise of natural chemicals in Parkinson's disease treatment[13].

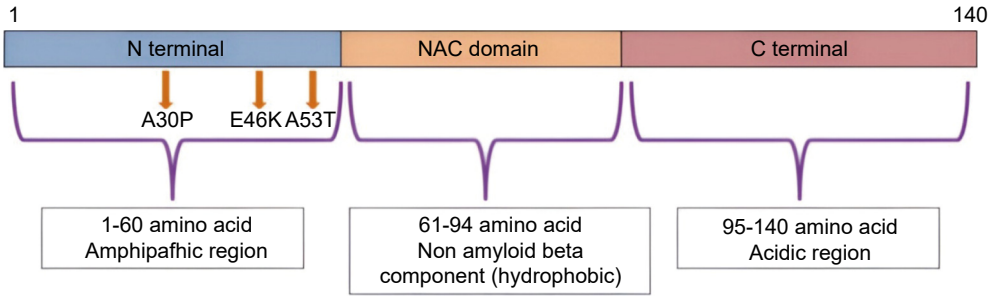

Fig. 1. The α-synuclein (140-residue polypeptide) protein schematically.

Nutritional problems and vitamin deficiencies, such as folate, vitamin B6, and vitamin B12, are common in PD patients. Long-term L-dopa therapy is also associated with deficiencies in folate, vitamin B6, and vitamin B12. These conditions increase the amount of homocysteine in the blood, leading to hyper homocysteinemia, which may be related to the pathophysiology of Parkinson's disease (PD)[14]. Additionally, astrocytes' anti-inflammatory and antioxidant characteristics are affected by genetic alterations in Parkinson's disease. Astrocytes' functional role is severely altered in Parkinson's disease. Restoring astrocytes' anti-inflammatory and antioxidant properties could therefore be a different therapeutic approach for the treatment of Parkinson's disease. Metformin, an anti-diabetic medication, has been demonstrated to enhance astrocytes' anti-inflammatory and antioxidant properties in a variety of neurodegenerative conditions, including Parkinson's disease[15].

Therefore, this study focusses on qualities that are neuroprotective as well as plant extracts action mechanism, formulations that are extract-based as well as phytochemicals obtained from plants which target toxicity, aggregation, fibrillation, as well as α-synuclein oligomerisation in several animal models of PD[16]. But since current drugs do not target the suppression of α-synuclein oligomerisation, treatments that stop these bodies from forming by blocking α-synuclein oligomerisation could be useful in the battle against this and other synucleinopathies[17,18]. In order to identify possible naturally occurring neuroprotective compounds, we employed cheminformatics methods as well as molecular docking and MD simulations to examine compounds which are tested experimentally as well as bound to α-synuclein, resulting in either neuroprotective or neurotoxic action. We discovered ten putative naturally occurring neuroprotective compounds that have large α-synuclein H-bonds and a chemical structure comparable to neuroprotective chemicals. We anticipate that these compounds might contribute for developing novel, efficacious therapeutics for PD. Positive neuroprotective role of phytochemicals effects must be assessed using biochemical, biophysical, and neurochemical methods, as well as their applicability to possible PD treatment patients.

Material and methods

Preparation of ligand

Eighteen naturally occurring phytochemicals are chosen as ligands. The SMILE format of ligands had been selected through PubChem database (https://pubchem.ncbi.nlm.nih.gov), then look up these SMILEs in the Swiss ADME[19] database (Supplementary table 1) to analyse their physiochemical properties. Finally,

we download all of these ligands in SDF format from database (PubChem). Then, artificial intelligence (AI) based searching done in the Coconut dB (COlleCtion of Open Natural prodUcTs dataBase) for additional compounds associated with these 18 recognised phytochemicals using PrinS3 software (PRinS3. V.2.3.0.; Link: https://prescience.in/prins3/). Next, we selected 25 compounds, based on their physiochemical properties, and developed a ligand library for docking. Out of these 18 naturals (Fig. 2) and 25 phytochemicals (Fig. 3), we have selected only 7 natural and 10 AI based phytochemicals using PrinS3 software which are capable of penetrating blood-brain barrier.

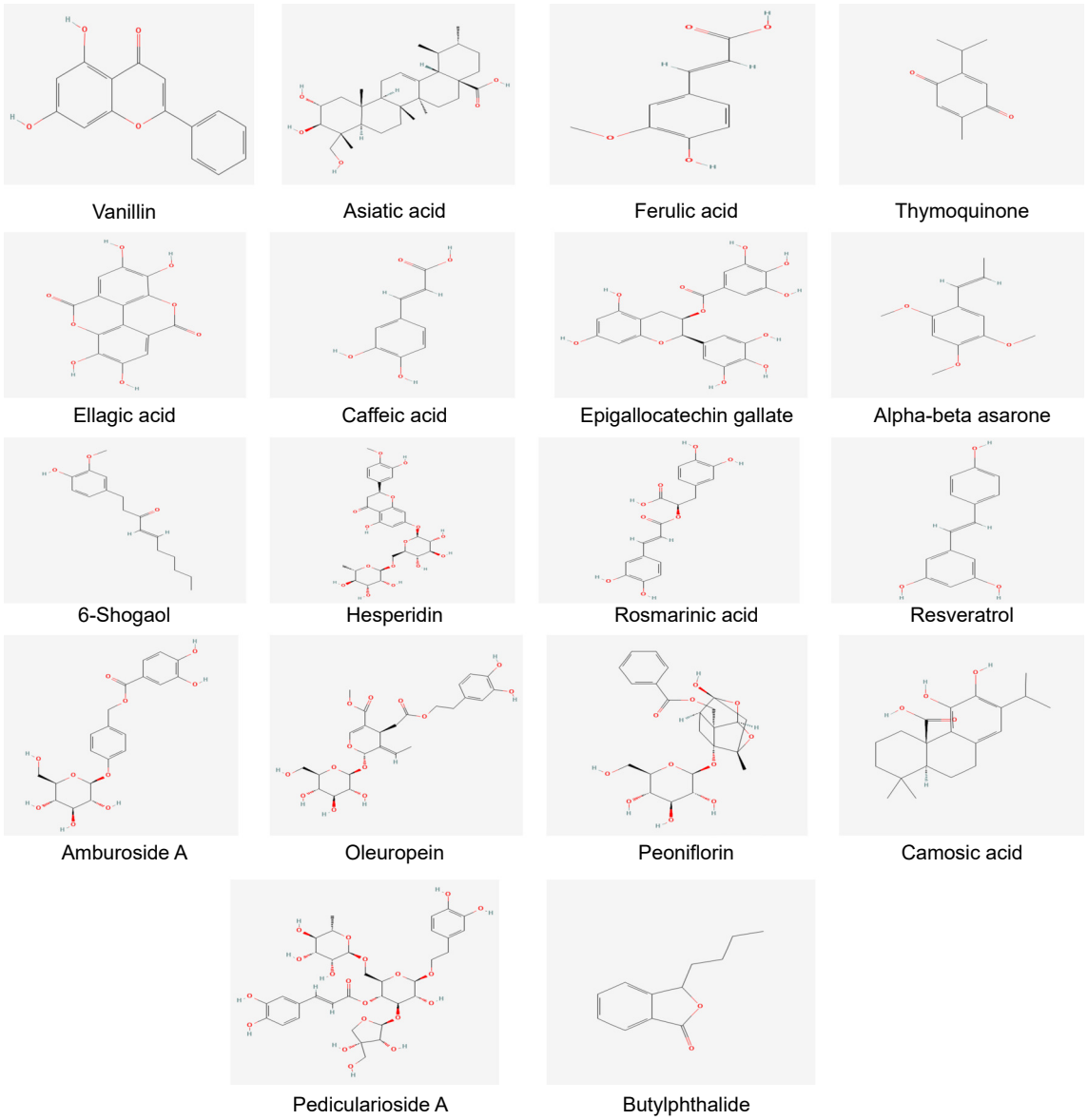

Fig. 2. Chemical structures of the selected phytochemical compounds.

Protein structure preparation

Alpha-synuclein, PDB accession number (1XQ8), was used as a target protein and its 3D crystal structure was acquired through Protein Data Bank. Before storing them in PDB format, they are improved by adding hydrogen atoms, deleting unnecessary water molecules from the target protein structures, and preparing the protein for docking studies using Biovia Discovery Studio Visualiser[20]. The PyRx program is used to convert these processed protein and ligands structures to the PDBQT file[21]. Additionally, the other setup options were left at their default settings. The amino acids of active sites of protein targets were added. For docking experiments, the grid area that could be the ligand binding domain was identified[22].

Molecular docking study of α-synuclein

The chemicals may bind to either or both of the α-synuclein's N- and C-termini, and their binding mechanism may influence their neuroprotective or neurotoxic effects. In this study, molecular docking was performed using PyRx, an open-source virtual

screening tool, for studying binding interactions among various compounds as well as target protein α-synuclein (PDB ID: 1XQ8). The docking protocol employed the AutoDock Vina algorithm with an exhaustiveness of 8 to ensure thorough exploration of binding poses. AutoDock Vina, a new program for molecular docking and virtual screening, has been presented. Vina uses a sophisticated gradient optimization method in its local optimization procedure. Molecular docking is a computational procedure that attempts to predict noncovalent binding of macromolecules or, more frequently, of a macromolecule (receptor) and a small molecule (ligand) efficiently, starting with their unbound structures, structures obtained from MD simulations, or homology modelling, etc. The goal is to predict the bound conformations and the binding affinity[23]. The prediction of binding of small molecules to proteins is of particular practical importance because it is used to screen virtual libraries of drug-like molecules in order to obtain leads for further drug development.

The grid box was placed at the binding region, which contains the amino acid residues Lys32, Val49, Lys45, Glu46, Gly47, Val48, Glu35, Gly36, Leu38, Val40, Lys43, Thr44, as well as His50 and is encircled by hydrogen bonding and hydrophobic interactions around the active site. Based on the selected amino acids, construct a grid box around the receptor protein using the grid box tool. The grid box's dimensions of 43.39 × 61.77 × 25.0 Å, with a centre at (242.99, 70.15, -15.15), were optimised to include the protein's active site. The docked ligand-receptor complex was evaluated using the lowest binding affinity (kcal/mol) data. For the best docked postures, Discovery Studio was used to analyse the docking stances. For comparing interaction of amino acids included in docking studies, distance between a receptor's amino acid and phytocompounds was measured and the findings were verified[24,25]. Docking score of ligands against the binding target was compared to determine the interaction analysis. The docking results revealed significant hydrophobic interactions and H-bonds between the ligands and specific amino acid residues in the N-terminal region of α-synuclein, which were categorized as

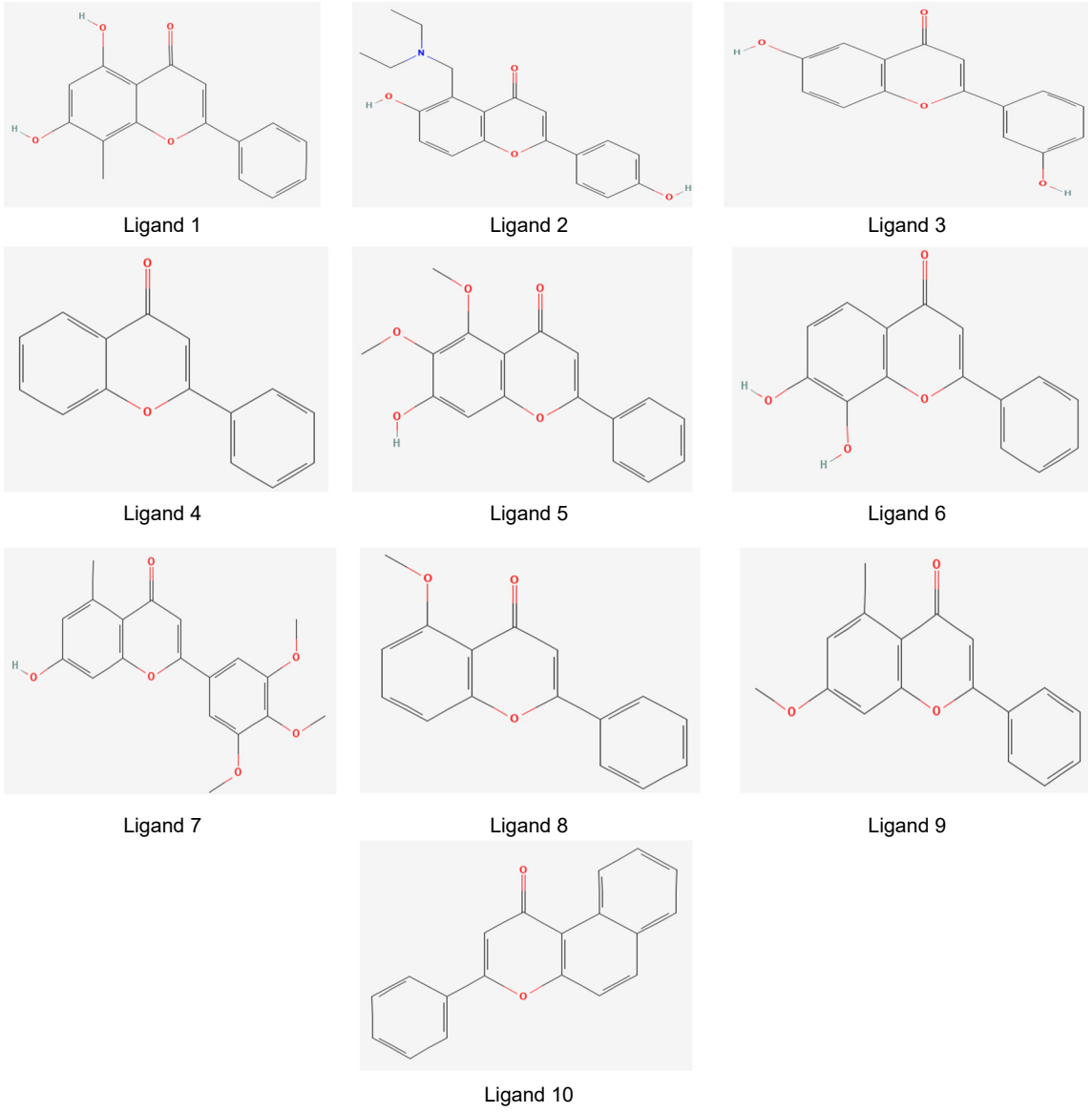

Fig. 3. Chemical structures of the selected natural compounds.

neuroprotective interactions. This systematic docking approach provided valuable insights into the potential neuroprotective results of selected compounds and their implications in mitigating neurodegenerative processes[26].

Molecular dynamics simulation

MD simulations on the alpha synuclein protein docking complex with ligand in order to investigate the macromolecular interactions on a computer platform that replicates the biological conditions. All MD simulation files were created using an HP Z8 workstation using GROMACS (Groningen machine for chemical simulations) software, version 5.1.5. All molecules, unless otherwise noted, were solvated using the extended simple point charge (SPC/E) water model in a triclinic box at least 10 from the box's edges after being exposed to the all-atom CHARMM 27 force field. To maintain the system's neutrality at the default pH of 7.0, sufficient counter ions (87 Cl^- and 96 Na^+) were supplied to the solvent. LINCS approaches were used to limit all of the bond lengths[27]. Long-range electrostatic interactions had been determined with the use of smooth particle mesh Ewald (PME) way. To get rid of the steric conflicts and the improper geometry, we carried out the steepest descent minimisations. The isochoric-isothermal (NVT) Berendsen thermostat approach was used to equilibrate all of the systems at 310 K for 100 ps. Then, for 100 ps at the same temperature as well as constant pressure (1 atm), the isothermal-isobaric (NPT) Parrinello-Rahman ensemble approach was used[28]. Each MD simulation took 80 nanoseconds to complete. To confirm the stability and compactness of the systems after simulation, the "gmx rms" as well as "gmx gyrate" tools of GROMACS had been used to calculate radius of gyration and the root mean square deviations of backbone atoms, respectively[29]. Using "gmx rmsf" tool, atomic fluctuations of Cα-residues has been determined. With the use of certain RMSD threshold, the most stable conformation was chosen out of the simulated trajectories in the 50–80 ns range. The Prodigy server calculated the free energy for the docking complexes[30].

Results

Molecular docking studies

Based on the *in-silico* screening data from earlier investigations, 18 natural phytocompounds were selected against the alpha-synuclein protein. Moreover, molecular docking as well as MD simulation investigations had been performed on phytocompounds to know the possible inhibitors. For this, AutoDock Vina, which has a built-in docking algorithm in PyRx software, was utilised. The phytocompounds' interaction with the target alpha-synuclein protein receptor's active site residues and the docking complexes' binding energy values were determined. after all complexes have been docked (Table 1). Chrysin has the highest binding affinity from the studied natural photochemical and ligand 4 showed best binding affinity of -7.2 Kcal/mol amongst 10 ligands. All phytocompounds and their binding interface residues with 1XQ8 targets were visualized using the Discovery Studio (Fig. 4). To find possible hit phytocompounds with the lowest binding energy values in comparison to the clinically authorised reference medications, comparative docking studies were carried out. The N- as well as C-terminus and might result in AS forming a loop by folding back on itself. We previously hypothesised that loop creation stops AS from aggregating because the central NAC area is unable to generate the linear structure needed to participate in the synthesis of β-sheets. Long-term studies into the action mechanisms these compounds have might cause powerful drugs development to treat PD. The binding interface among ligand as well as protein would be composed of the charged amino acid residues Lys32, Gly47, Glu35, Gly36, Leu38, Val40, Lys43, Thr44, Lys45, Glu46, and Val48 from the alpha-synuclein protein. It's seen that forming a stable alpha synuclein protein complex involves a variety of non-bonded electrostatic interactions, H-bonds, as well as van der Waals contacts. Even though the majority of ligands attach themselves to the protein, all 17 of these ligands share the residues Tyr39, Glu35, Lys43, and Val40.

Table 1. DOCKING results of 7 natural phytochemicals and AI based natural 10 compounds.

Molecule Name	Binding Affinity
6-shogaol	-4.2
Chrysin	-6
Ferulic acid	-4.7
Resveratrol	-5.2
Thymoquinone	-4.2
Vanillin	-3.7
dl-3-n-buta	-4.7
Ligand 1	-5.7
Ligand 2	-6.6
Ligand 3	-5.6
Ligand 4	-7.2
Ligand 5	-5.8
Ligand 6	-6.1
Ligand 7	-6.2
Ligand 8	-6.2
Ligand 9	-6.4
Ligand 10	-6.3

MD simulation analysis

Plotting the change in the RMSD of the backbone atoms against time scale allowed for the determination of the MD simulation run's progress (Fig. 5A). After 30 ns of simulation running, the alpha-synuclein complex protein was found to be stabilised (RMSD ~ 2.5 nm), whereas the control protein was shown to be destabilised in comparison to the complex protein (RMSD ~ 2 nm). Whereas, protein folding is measured by radius of gyration (Rg) and it shows that after binding with the ligand 4, the protein becomes more compact as Rg reduced from 4 nm to 3 nm (Fig. 5B). Moreover, additionally, we computed the alpha-synuclein protein's Cα atoms' root-mean-square fluctuations (RMSFs) during MD simulation (Fig. 5C). The alpha-synuclein complex protein was fluctuating around binding interface regions (RMSF ~ 1.5 nm), whereas the control protein was found to be stabilized as compared to complex protein (RMSF ~ 0.5–0.8 nm).

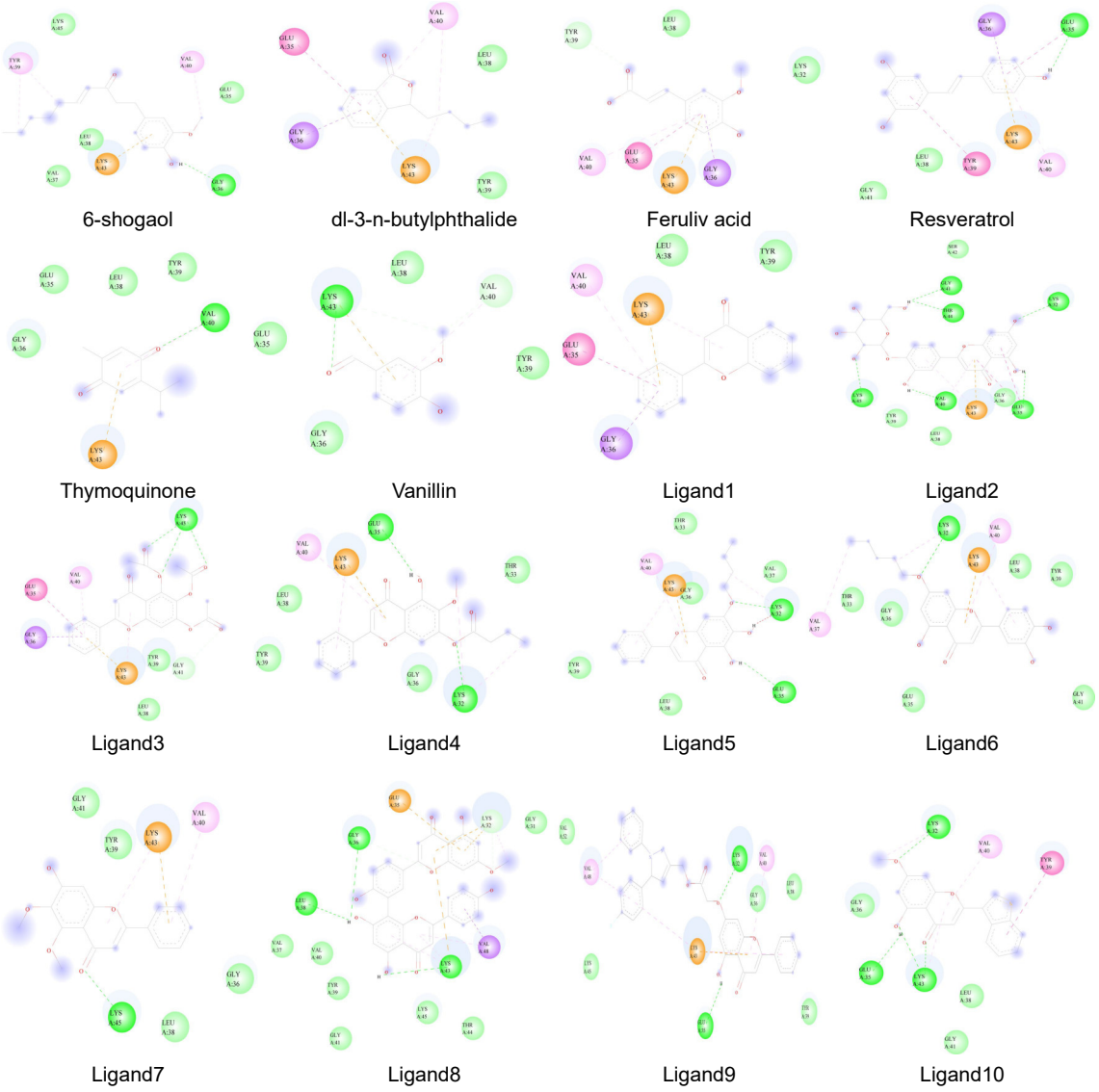

Fig. 4. Binding interfaces of 7 natural phytochemicals and AI based natural 10 compounds.

After simulation the stable most conformation was retrieved from 50–80 ns simulation time frame (Fig. 6A). Then PRODIGY server had been used to forecast protein-protein complex binding energy of the of ligand 4and found that -10.27 kcal/mol. According to MD studies on ligand 4 with protein complexes, the amino acid residues Lys32, Val40, Tyr39, Glu35, and Lys43 were most involved in forming the alpha synuclein protein complex (Fig. 6B). The conventional hydrogen bonds showed between the amino acid Val40 and Lys43.

Discussion

The aetiology of familial PD and the observation that almost all patients exhibit synuclein aggregation point to a major part in protein α-synuclein in sporadic illness. Millions of individuals worldwide suffer with PD, a neurological disorder[31]. Using *in vivo* animal models, rodent species, including as rats and mice, continue to be the predominant approach for researching PD-related pathophysiology. Neurotoxins such as rotenone, MPTP, and 6-OHDA enable researchers to create animal models of Parkinson's disease (PD) that deplete dopamine. In addition to 6-OHDA, neurotoxins like rotenone and MPTP can cause Parkinson's disease (PD)-like symptoms such motor dysfunction and damage to dopaminergic neurons, which can be used as a testing ground for therapeutic treatments like herbal extracts[32]. These *in vivo* models have been used in several research to examine the neuroprotective properties of various herbal plants, offering insights into possible medicinal applications. Both *in vitro* and *in vivo* models are useful for understanding the pathophysiology of Parkinson's disease and assessing treatment options. The analysis of experimental results depends heavily from the choices made regarding animal models and neurotoxins and assessment methodologies. Dopaminergic neurodegeneration with the MPTP model offers effective outcomes when creating neurotoxicity but does not fully mirror the full range of PD pathology which present in human patient's *in vivo* models offer systemic insights and behavioural results, while *in vitro* models provide mechanistic

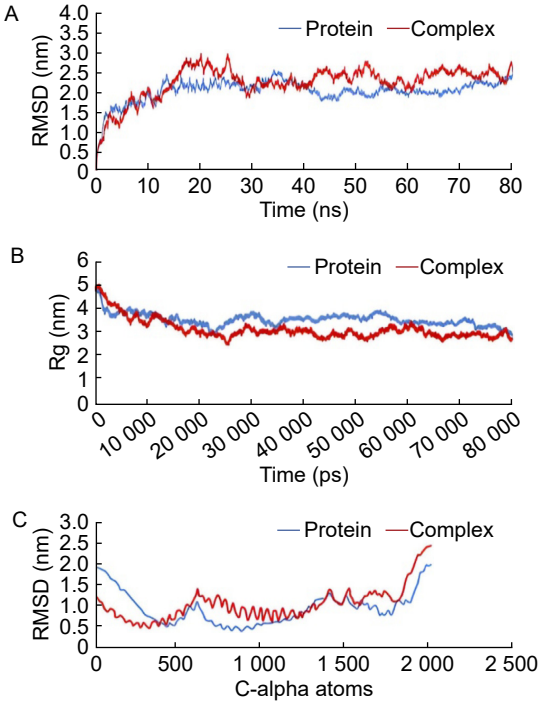

Fig. 5. Progress of molecular dynamics (MD) simulation runs of the protein unbound and ligand bound conditions.
A. The extent of fluctuations of the complex protein was greater than that of the normal protein.
B. Variation in Rg value of the different systems with the progress of the MD run.
C. Variations in root mean square fluctuation (RMSF) values of the different systems throughout the MD simulation runs.

information at the cellular level[33]. Lewy bodies, which has been mostly formed of the protein α-synuclein, as well as the gradual loss of neurones in the substantia nigra are hallmarks of PD. According to recent research, oxidative stress increases neuronal susceptibility and promotes α-synuclein aggregation, which exacerbates neurodegeneration in PD patients. SNCA is the gene which encodes this 140-amino acid protein. According to several studies, this protein's neurotoxic oligomers and amyloid fibrils may have a role in the onset of PD and Lewy pathology. The first treatment option for PD is medication that mimics or replaces dopamine functions. The aim of this medication is to alleviate the symptoms of the disease by treating dopamine deficiency[34]. Although there isn't any clinical data to completely support health advantages of phytochemicals, naturally occurring lipophilic phytochemicals have a high affinity for receptors, a quicker metabolism, and greater bioavailability. Additionally, they have little trouble entering the brain via the blood-brain barrier. PD, which depends upon individual course of main indications, currently has no conventional treatment. Natural items are used to treat PD, particularly naturally occurring phytochemicals obtained from food that have antioxidant capacity and might be a trustworthy source of medication[35]. For instance, in preclinical research, curcumin, resveratrol, and catechins have demonstrated encouraging outcomes in lowering α-synuclein aggregation and oxidative stress[36]. According to a previous study, neuroprotective molecules that have particular differences that might be correlated with activity which they show while linking to α-synuclein[37]. To improve the ability to reverse the deterioration in neurone function and disease resistance, it is essential to regularly provide these naturally occurring phytochemicals. The results included in the earlier study have collectively shown the antiparkinsonian benefits of antioxidant phytochemicals. The progression of PD gets significantly influenced by stress that is oxidative and neuroinflammation. Therefore, our research shows that antioxidant phytochemicals' anti-inflammatory properties provide a safe way to guard against brain injury by lowering oxidative stress and preventing lipid per oxidation activity[38]. With the use of *in-silico* techniques, like molecular docking as well as molecular dynamics simulations, 875 naturally occurring phytochemicals were assessed for their capacity to prevent α-synuclein aggregation[39]. A number of molecules specially Alpinetin exhibited -3.2 Kcal/mol binding energy, indicating their potential as PD treatment agents. Natural products' anti-inflammatory and antioxidative qualities are also highlighted, as is their contribution to improving autophagy and mitochondrial homeostasis[40]. Additionally, some natural substances may prevent α-synuclein from aggregating abnormally, which would lay the groundwork for the creation of innovative treatment approaches that target the protein's aggregation

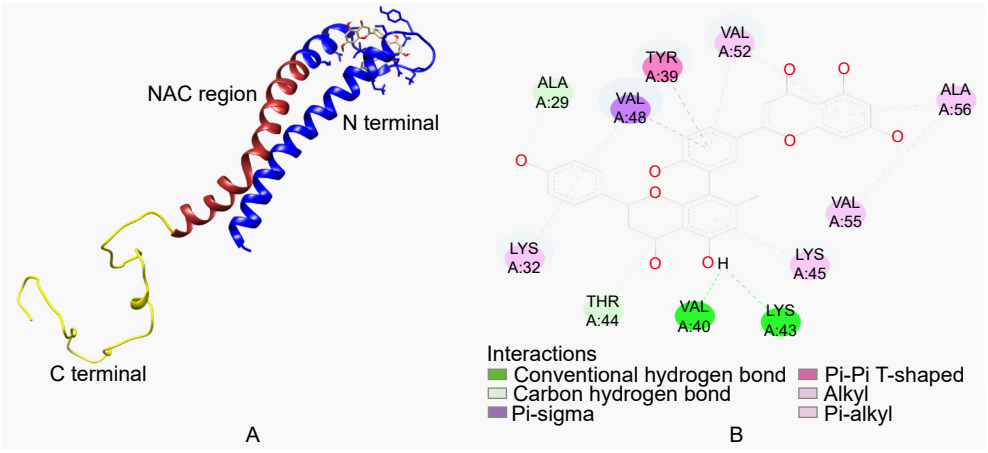

Fig. 6. The 3D and 2D conformation of stable most structure of protein ligand 4 complex.
A. The three-dimensional structure of protein ligand 4 complex where red colour shows N terminal region of α-synuclein, yellow colour shows the NAC region and blue colour shows the C terminal region of α-synuclein protein.
B. The 2D image of binding interface residues and interaction pattern of ligand 4 and alpha synuclein protein.

pathways[41]. The natural neuroprotective drugs like Epigallocatechin gallate (-6.098 Kcal/mol), Scutellarein (-5.886), Myricetin (-5.780), Nortriptyline (-5.780), Curcumin (-5.258), Nordihydroguaiaretic acid (-4.786), Caffeine (-3.738), and Metformin (-2.800 Kcal/mol) have all been seen to link both N- as well as C-terminus of α-synuclein[42]. Their respective mean binding affinities are mentioned in bracket. Additionally, they have little trouble entering the brain via the blood-brain barrier. PD, which depends on the individual course of main symptoms, currently has no conventional treatment. Natural items have also been used to treat PD. Chrysin is a flavonoid with cytoprotective, anti-inflammatory, and antioxidant qualities that is mostly found in propolis, honey, and passion fruit. Chrysin, sometimes referred to as chrysinic acid, is a member of the flavone class. The plants *Yerba santa*, *Pelargonium crispum*, *Passiflora incarnate*, marsh skullcap, and *Oroxylem indicum* are the principal sources of honey, propolis, fruits, and vegetables. Its pharmacological characteristics include anti-inflammatory, anti-tumor, anti-asthmatic, antihyperlipidemic, cardioprotective, neuroprotective, and renoprotective effects (Fig. 7). Chrysin has been shown to have neuroprotective effects via a variety of pathways, such as GABA mimetic qualities, MAO inhibition, anti-oxidant, anti-inflammatory, and anti-apoptotic actions[43]. Tyrosine hydroxylase, dopamine, and apoptotic proteins (cleaved caspase-3 and Bax) are among the clinical markers associated with Parkinson's disease (PD) that are considerably protected by resveratrol treatment. The pathophysiology of the disease includes markedly reduced levels of dopamine transporter, synaptophysin, and postsynaptic density protein 95 (PSD-95), as well as increased levels of vesicular monoamine transporter and dramatically altered dendritic arborization. Treatment with resveratrol greatly repaired such impaired neural transmission. Depleted glutathione (GSH), mitochondrial complex-I activity with concurrently elevated lipid peroxidation, nitrite level, and calcium levels are examples of biochemical changes that were also markedly decreased by resveratrol administration[44]. Tyrosine hydroxylase, dopamine, and apoptotic proteins (cleaved caspase-3 and Bax) are among the clinical markers associated with Parkinson's disease (PD) that are considerably protected by resveratrol treatment (Fig. 8). The pathophysiology of the disease includes markedly reduced levels of dopamine transporter, synaptophysin, and postsynaptic density protein 95 (PSD-95), as well as increased levels of vesicular monoamine transporter and dramatically altered dendritic arborization. Treatment with resveratrol greatly repaired such impaired neural transmission. Endoplasmic reticulum (ER) stress-related signalling and phosphorylated nuclear factor erythroid 2-related factor 2 (Nrf2) are induced by altered calcium levels, and the level of phosphorylated Nrf2 was further elevated with resveratrol therapy. When resveratrol was administered, the concurrently reduced level of proteasome activity was lessened[45]. Ferulic acid, a member of the hydroxycinnamic acid family, is a significant part of many therapeutic herbs. FA in its pure form is a yellowish powder that shares structural similarities with curcumin, a well-researched natural compound with strong neuroprotective properties. FA alleviated behavioural impairments and reduced neuroinflammation in the MPTP mice model of Parkinson's disease. MPTP is mostly utilized to create models of Parkinson's disease in mice and nonhuman primates. However, rats are resistant to MPTP for unexplained reasons, while mice, particularly the C57BL/6 strain, are extremely sensitive (Fig. 9). These MPTP dosages administered over a brief period of time are regarded as an acute model of Parkinson's disease. Additionally, the MPTP model exhibits motor deficits, a nonprogressive manner of cell death, and no intracytoplasmic inclusion of α-synuclein[46].

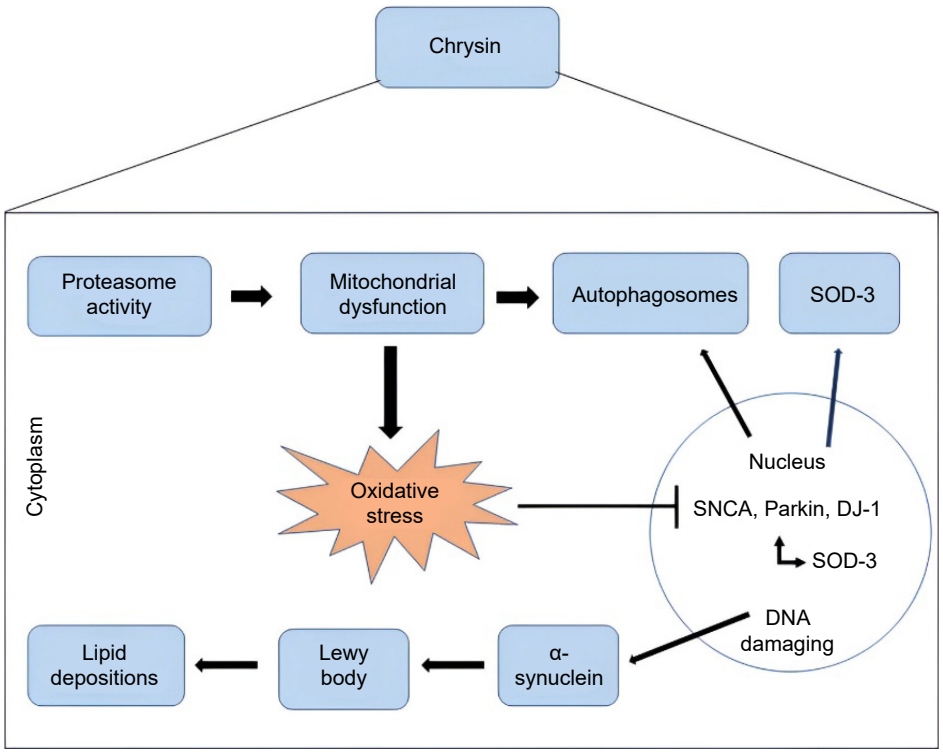

Fig. 7. Mechanism of actions in Chrysin in neuronal cell.

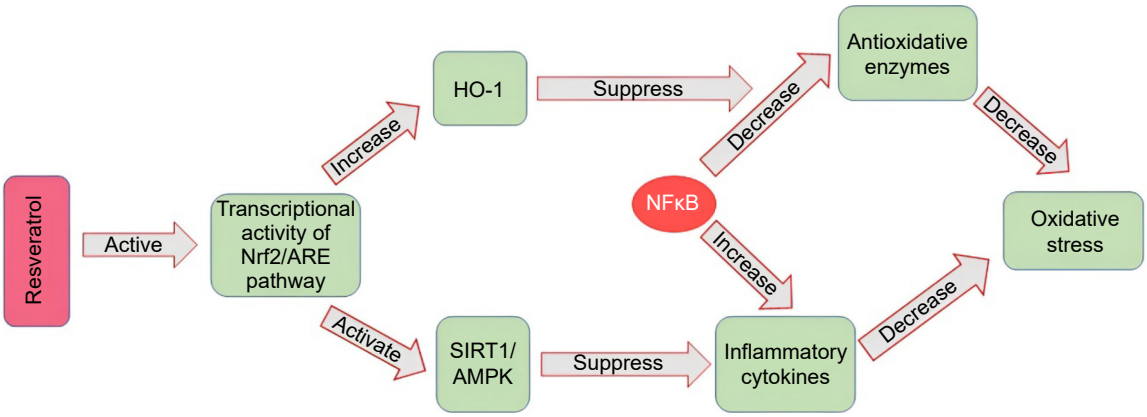

Fig. 8. Mechanism of actions in Resveratrol in neuronal cell.

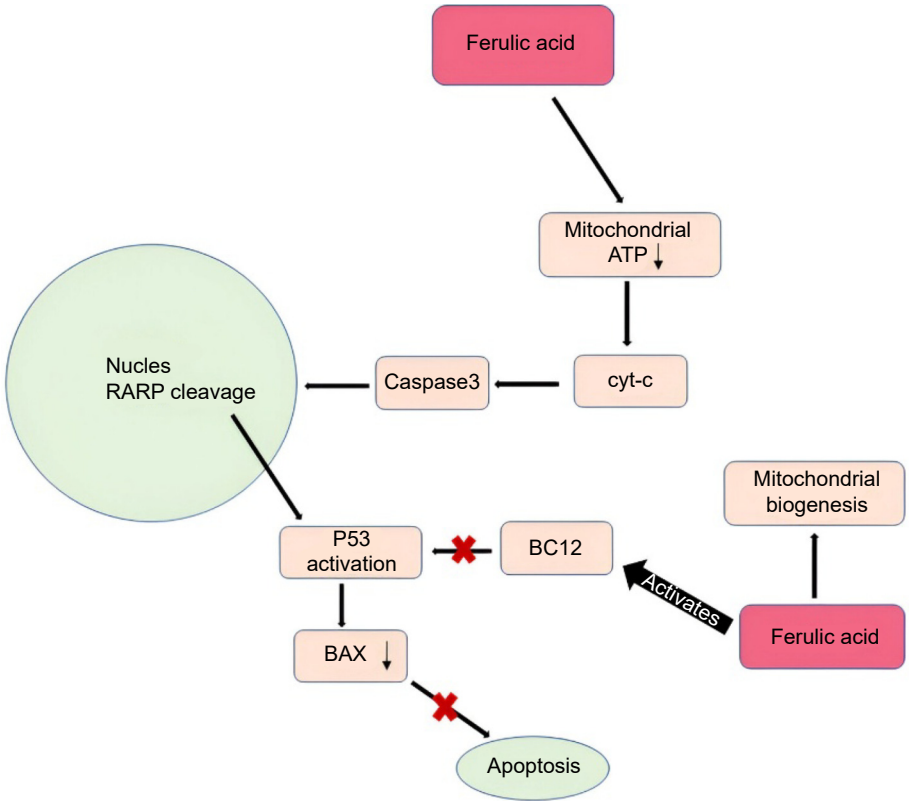

Fig. 9. Mechanism of actions in Ferulic Acid in neuronal cell.

Our research of α-synuclein targeting used a parallel methodology using AutoDock via PyRx to anticipate high-affinity interactions. In our study, the natural phytochemicals 6-shogaol, Chrysin, Ferulic acid, Resveratrol, Thymoquinone, Vanilin, and dl-3-n-buta were shown to have binding affinities in the range of -3.7 to -6.0 Kcal/mol, according to docking score. Chrysin had the highest binding affinity among these natural phytochemicals, while Ligand 4 had the highest binding affinity (-7.2 Kcal/mol) among the ten AI-based phytochemicals. To improve the ability to reverse the decline in neurone function and disease resistance, we formed 2 groups of molecules with the help of results found in the literature as well as conducted in silico analysis of them. According to earlier findings, the preference for residues and the number of H bonds with α-synuclein in 50 binding positions. Glu126, Val40, Lys32, as well as Lys45 could be useful in locating possible neuroprotective compounds that prevent α-synuclein oligomerisation. To lower the number of experimental failures, BBB permeability and drug likeness study of molecules should also be performed prior to experimental testing. Based on their theoretical interaction with α-synuclein and structural resemblance to known neuroprotective chemicals, we identified six natural compounds in this work that may have neuroprotective properties.

In-silico screening results from earlier research indicate that 18 natural phytocompounds target alpha-synuclein proteins. To assess possible inhibitors, phytocompounds were also put through

molecular docking experiments and MD simulation. This was done using AutoDock Vina, which has a docking technique included into PyRx software. Following a physiochemical screening of 10 compounds, molecular docking was done with alpha-synuclein. All 18 of these ligands share the residues Val40, Lys43, Tyr39, and Glu35, even though the bulk of them attach to the protein. The alpha synuclein protein complex was mostly formed by the amino acid residues Lys32, Val40, Tyr39, Glu35, and Lys43 as well as the binding interfaces Lys32, Lys43, Val40, and Glu35 from Ligand 4. Following the docking examination, we selected ligand 4, which, for more molecular dynamic simulation research, has the greatest affinity for binding. Based on the estimated H-bonding as well as free binding energy, docking analysis assigned ligand 4 and alpha synuclein a significant binding posture. The main amino acid residues identified by MD studies are Lys32, Glu46, Gly47, Thr44, Lys45, Glu35, Gly36, Leu38, Val40, Lys43, and Val48. Through its interaction with important residues in the binding interface, ligand 4 modulates α-synuclein aggregation, as demonstrated by our study, that makes it a good candidate for development that is therapeutic. Although *in vivo* as well as *in vitro* investigations required for further validation of the therapeutic molecules.

Conclusion

Alpha synuclein protein and natural phytochemical complexes were examined in depth from a molecular perspective. In the current study, we attempted to use MD simulations as well as computational molecular docking to examine regulatory functions of the alpha synuclein protein. Alpha synuclein's particular amino acid residues, particularly the basic amino acid residues found in amino acid residues 1–61, bind to the major amino acid residues Lys32, Leu38, Val40, Glu35, Gly36, Lys43, Thr44, Lys45, Glu46, Gly47, and Val48 were identified by MD simulations. These findings corroborate earlier experimental investigations. The N-terminal residues were discovered by this MD simulation investigation. By docking eight natural and ten AI-based ligands with the alpha synuclein protein. Our investigation revealed that the ligand 4 would assist to suppress the disease condition of Parkinson's disease, based on prior research on the potential regulatory role of various natural phytochemicals that are significant for Parkinson's disease. Thus, it is hypothesized that these phytochemicals may be used as putative bioenhancer in PD treatment. The present study would throw lights on discovery of natural phytochemicals and AI based compounds against SNCA as an alternative treatment of PD and may be further extended for experimental validation in the future. There are some drawbacks of molecular docking is the uncertainty around the accuracy of binding energies provided by scoring algorithms. This is because certain intermolecular interaction factors, such the solvation effect and entropy change, are difficult to estimate with accuracy. The study of Parkinson's disease (PD) can benefit greatly from the use of rodents and nonhuman primates; however, it is vital to consider the limits of these models when interpreting findings.

Abbreviations

BBB, Blood-brain barrier; CHARMM, Chemistry at HARvard Macromolecular Mechanics; EGCG, Epigallocatechin gallate; GROMACS, Groningen machine for chemical simulations; MD, Molecular dynamics; NVT, Constant number of particles (N), volume (V), and temperature (T); PD, Parkinson's disease; PDB, Protein Data Bank; PDBQT, Protein Data Bank, Partial Charge (Q), & Atom Type (T); PME, Particle Mesh Ewald; RMSD, Root Mean Square Deviation; RMSFs, Root-mean-square fluctuations; SDF format, Structure Data Format; SMILE format, Simplified Molecular Input Line Entry System; SNCA, Synuclein Alpha; Swiss ADME, Swiss Institute of Bioinformatics, Absorption, Distribution, Metabolism and Excretion.

Ethics approval and consent to participate

Not required as no human samples involved in this study.

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Conflicts of interest

The authors declare no conflicts of interest.

Authors' contributions

AS: Wrote the manuscript and prepared all figures and tables, DB: analyzed molecular docking data, SB: analyzed molecular dynamics run, SG: critically reviewed the manuscript and supervised the project. AB: funding support for instrumentation of MD run and approved the final version of the manuscript.

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