In-silico molecular docking for Potential herbal leads from *Withaniasomnifera* L. Dunal for the treatment of Alzheimer's disease

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Abstract. Alzheimer's disease (AD) poses a significant global health challenge, necessitating novel therapeutic interventions. Withaniasomnifera L. Dunal, commonly known as Ashwagandha, has been historically utilized in traditional medicine for its neuroprotective properties. This study employs computational techniques to explore the potential of W. somnifera compounds in targeting key proteins associated with AD. The reported phytoconstituents of W. somnifera were identified and subjected to molecular docking studies against 5NUU (Torpedo californica acetylcholinesterase in complex with a chlorotacrine-tryptophan hybrid inhibitor), as crucial targets. The results revealed several phytoconstituents of W. somnifera exhibiting favorable binding affinities and promising interactions with the target proteins. These findings provide a valuable foundation for further experimental validation and the development of novel therapeutic agents derived from natural sources for the treatment of Alzheimer's.

1 Introduction

Neurological disorders are life-threatening disorders that directly affect the spine and brain of an individual's body, and they also impair the thinking, speaking, walking, and capacity of the person. Neurological and neuropsychiatric disorders also exhibit a notable elevation in mortality and disability rates in comparison with other human health-related disorders (1). There are approximately six hundred neurological disorders reported till now. Alzheimer's disease (AD) is one of the most prevalent neurological disorders, and it is a leading cause of dementia in older individuals, which elevates with age. Among the older population, 95% of elders with AD fall under the late-onset category of the total AD population. According to the data it is expected that at the end of 2050, the cases of AD will reach up to 152 million, out of which 10 million cases are reported every year for dementia(2). AD is clinically characterized by impairment in cognitive functions, behavioral changes, and difficulties in performing day-to-day tasks. Mortality and neuronal dysfunction in AD result from the accumulation of Aβ (amyloid-β) and tau proteins in the middle temporal lobe and neocortical regions of the brain(3). Other pathophysiological challenges associated with AD are imbalances in gultamergic systems and deficiency in the release of neurotransmitters Acetylcholine (Ach).

Regardless of the increase in the incidence of AD cases in recent years, there is still a lack of successful treatment for the diagnosis and halting or reversing the progression of AD, which results in a great impact on the social and economic state. To date, only five drugs have been approved by the US Food and Drug Administration (USFDA) for AD: donepezil, galantamine, rivastigmine, aducanumab, and memantine. Aducanumab is the only one that is used for the clearance of Aβ plaque, while the others are used for symptomatic treatment, i.e., mild-moderate symptoms of AD. Donepezil, galantamine, and rivastigmine are classified as cholinesterase inhibitors, working to enhance acetylcholine levels in the brain. In contrast, Memantine is utilized to elevate chemical glutamate levels and can be administered independently or in combination with cholinesterase inhibitors (4). Other therapies, like hormonal therapies, are also used in the treatment of AD due to their anti-oxidant activities, which help improve the cognitive power of the brain. Prolonged use of NSAIDS (non-steroidal anti-inflammatory drugs) like asprin and ibuprofen is also used to decrease inflammation in AD (5). These present-day conventional medications are not sufficient for treatment; hence they are packed with low efficacy, lots of adverse effects, and side effects that are unavoidable. As the disease progresses, these medications start to deteriorate, which leads to the demand for an alternative therapeutic system with minimal or no side effects (6).

The herbal system of medicine is a better candidate for this, as there are a large number of plants that have been used since ancient times for the management of memory and brain-related neurological disorders. *Withaniasomnifera* L. Dunal, a traditional medicinal plant, is an erect shrub belonging to the family Solanaceae and is used in different marketed formulations for the treatment of neurological disorders. Indian ginseng and winter cherry are synonyms of *W.*somnifera.Conventionally, it is cultivated in Rajasthan, Madhya Pradesh, Punjab, and the hotter regions of India,along with other countries like Pakistan, Nepal, and China. Cultivation starts in the month of June, and harvesting will be completed in the month of March. The roots of *W.somnifera*,which are the medicinally important part, will be harvested in the winter season (7). The roots contain a variety of phytochemical compounds such as alkaloids (Cuseohygrine and Anahygrine), steroidal lactones (withanolides A–Y, withanone, and withaferin-A), phytosterols (sitoindosides VII–X), etc., which are responsible for enormous effects such as neuroprotective activity, anti-anxiety, anti-stress, antioxidant activity, anti-inflammatory, anti-cancer, immunomodulatory, hepatoprotective, and anti-diabetic activity (8). These bioactive compounds are also responsible for the action of scavenging free radicals during the early stages of neurological disorders and show the extension of neuronal axons and dendrites, which helps in the regeneration of neurons during treatment (9). There are various studies also which proves the use of *W.somnifera* in the treatment of Alzheimer's disease but still there is lack of investigations on various phytochemicals that can be used for inhibition of different macromolecular proteins that are responsible for progression of Alzheimer's disease by utilizing in-silico studies(10). By keeping this in consideration, in this study in-silico molecular approaches are utilized for the evaluation of various phytochemicals present in the roots of *W.somnifera*against the acetylcholinestrase inhibitors macromolecule5NUU (Torpedo californica acetylcholinesterase in complex with a chlorotacrine-tryptophan hybrid inhibitor) receptor. The data obtained during this computational research is very encouraging and depicts the ability of W.somnifera as a potential lead for the treatment of AD (11).

2 Material and methods

2.1 In-silico molecular docking

The molecular docking process assesses the intermolecular interaction between small molecules and specific proteins at the atomic level. In this study, intermolecular attractions are studied between the different phytochemicals of W.somnifera i.e., anahygrine, beta-sitosterol, cuscohygrine 1, bufotenine, 27-Deoxy-14-hydroxywithaferin A, D-Glucose, galactitol, hexadecanoylhexopyranoside, nicotine, pelletierine, sitoindoside IX, tropine, withaferine A, withanone, withanolide J, withasomidienone, withanolide A, withanolide K, withanolide L, withanolide M, withanolide Q, withanolide R, withanolide N, withanolide P, withanolide S, withanolide C, withanolide D, withanolide E, withanolide G, withanolide H. AutoDockTools-1.5.7 is used to form these interactions, which were later compared with standards like donepezil, gelantamine, and revastigmine. These ligand interactions were then used again for the receptor 5NUU (Torpedo californica acetylcholinesterase in complex with a chlorotacrine-tryptophan hybrid inhibitor), and the docking score was analyzed using the command prompt of AutoDockVina . To find out the promising phytochemicals for the treatment of AD receptor-ligand interaction, a study was carried out using Discovery Studio Visualizer 2021(12).

2.2 Target receptor identification

The target receptor for in-silico molecular docking on Alzheimer's disease was done by downloading the PDB format of the 5NUU (Torpedo californica acetylcholinesterase in complex with a chlorotacrine-tryptophan hybrid inhibitor) receptor from the Protein Data Bank (rcsb.org) as shown in fig.1. Exclusion of all the water molecules and ions was also performed because they might interfere with the binding of ligands at the site. To stabilize the protein/target receptor, the addition of polar hydrogens followed by Kollman charges was done by using AutoDockToools 1.5.7. The resolution of the protein was 2.50 Å and it had 543 amino acids. The PDB format of the receptor should be converted into the PDBQT format using AutoDockTools 1.5.7(13).

2.3 Ligand preparation

Twenty phytochemicals from the roots of *W. somnifera* were collected from the IMPPAT database and from the existing published articles on *W. somnifera*. Two-dimensional structures were drawn by using ChemDraw Ultra 7.0 and saved as a CDX format file. Three-dimensional structures were also prepared, and energy minimization was also done for each and every ligand by using the ChemDraw 3D Ultra software with version 7.0 and saved with the extension PDB format. These PDB formats of ligands then get converted into PDBQT formats with the help of different commands and preceded into AutoDockToools-1.5.7(14).

Fig1 Macromolecule of Acetykcholinesterase 5NUU (Torpedo californica acetylcholinesterase in complex with a chlorotacrine-tryptophan hybrid inhibitor) receptor for Alzheimer's disease

2.4 Molecular docking analysis

The initial step involves importing the 5NUU receptor PDB format in AutoDockTools 1.5.7, followed by the creation of a grid box with coordinates X = 112.849, Y = 128.178, and Z = 184.430 with dimensions X = 48, Y = 24, and Z = 42 Å. Subsequently, a configuration file was generated with the addition of the pdbqt format of the 5NUU target receptor and each ligand file sequentially and runned in the command prompt. As a result, nine out-put ligand files along with a log file were created with a docking score, which represents the binding affinity values in kcal/mol for each ligand file separately. The ligand-receptor complexes with the lowest binding energies (most negative values) showed the highest binding energies. The ligand-receptor complexes were then visualized in Discovery Studio Visualizer 2021 for checking the complexes with most covalent hydrogen bonds, carbon-hydrogen bonds and van der Waals forces. The higher the number of covalent hydrogen bonds and carbon hydrogen bonds, the greater the stability of the respective ligand in that targeted receptor, which shows the greater the potential of phytoconstituents in the treatment of AD. To determine the success of the docking process, the all-atom root mean square deviation (RMSD) between the predicted binding location and the actual observed position of the ligand should be less than 2Å (15).

3 Results

Intermolecular interactions were performed between the ligand and the targeted receptor for the prediction of the highest potential phytoconstituents for the management of AD by using the Autodock vina.[16] The docking scores (binding affinity) of standard drugs against the crystal structure of the targeted receptor 5NUU were donepezil -7.4 kcal/mol, revastigmine -7.3 kcal/mol, and gelantamine -6.7 kcal/mol, as shown in table 1.[17] Similarly, , binding affinities of different bioactive phytoconstituents of *W.somnifera* against the 5NUU receptor were determined as 27-Deoxy-14-hydroxywithaferine A -9.1 kcal/mol, Withanolide H -9.1 kcal/mol, Withanolide A -8.8 kcal/mol, Withanolide Q -8.8 kcal/mol, Sitoindoside IX -8.5 kcal/mol, Withaferin A -8.4 kcal/mol, Withanolide J -8.2 kcal/mol, Withanolide G -8.0 kcal/mol, Withanolide D -7.8 kcal/mol, Withanolide M -7.7 kcal/mol, Withanolide P -7.6 kcal/mol, Withanolide C -7.6 kcal/mol, Withanolide E -7.2 kcal/mol, Withanolide R -7.2 kcal/mol, Withanolide L -7.2 kcal/mol, Withanolide K -7.1 kcal/mol, Withanolide N -7.1 kcal/mol, Beta-sitosterol -7.0 kcal/mol, Withanolide S -6.9 kcal/mol kcal/mol, and Withasomidienone -6.7 as shown in table 1.[18-20]

Table 1 Docking score of bioactive ligands against the 5NUU (Torpedo californica acetylcholinesterase in complex with a chlorotacrine-tryptophan hybrid inhibitor) receptor

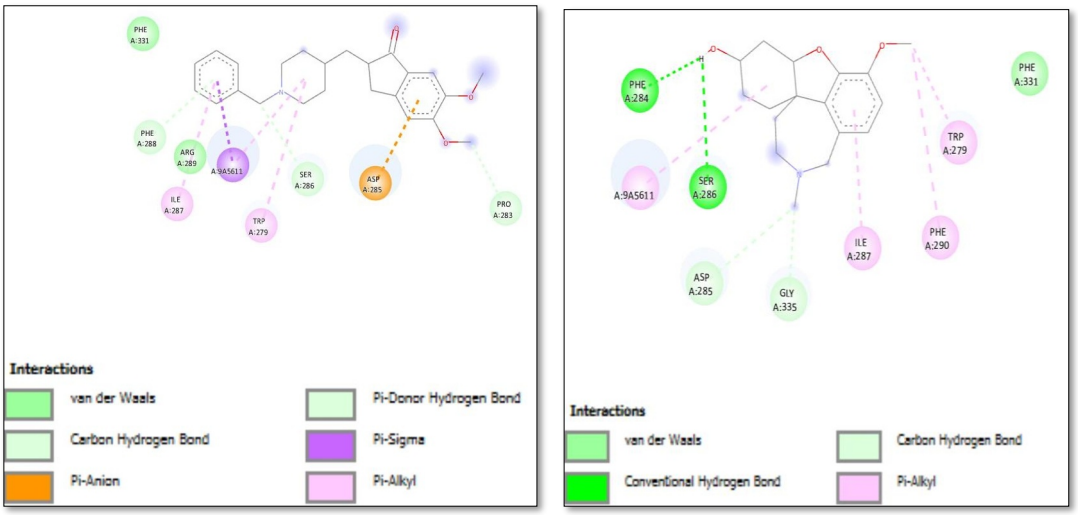
Target	Ligand	Docking score by Autodock vina (kcal/mol)
1.	27-Deoxy-14-hydroxywithaferine A	-9.1
2.	Withanolide H	-9.1
3.	Withanolide A	-8.8
4.	Withanolide Q	-8.8
5.	Sitoindoside IX	-8.5
6.	Withaferin A	-8.4
7.	Withanolide J	-8.2
8.	Withanolide G	-8.0
9.	Withanolide D	-7.8
10.	Withanolide M	-7.7
11.	Withanolide P	-7.6
12.	Withanolide E	-7.2
13.	Withanolide R	-7.2
14.	Withanolide L	-7.2
15.	Withanolide K	-7.1
16.	Withanolide N	-7.1
17.	Beta-sitosterol	-7.0
18.	Withanolide S	-6.9
19.	Withasomidienone	-6.7
20.	Anahygrine	-5.5
21.	Donepezil	-7.4
22.	Revastigmine	-7.3
23.	Gelantamine	-6.7

4 Discussion

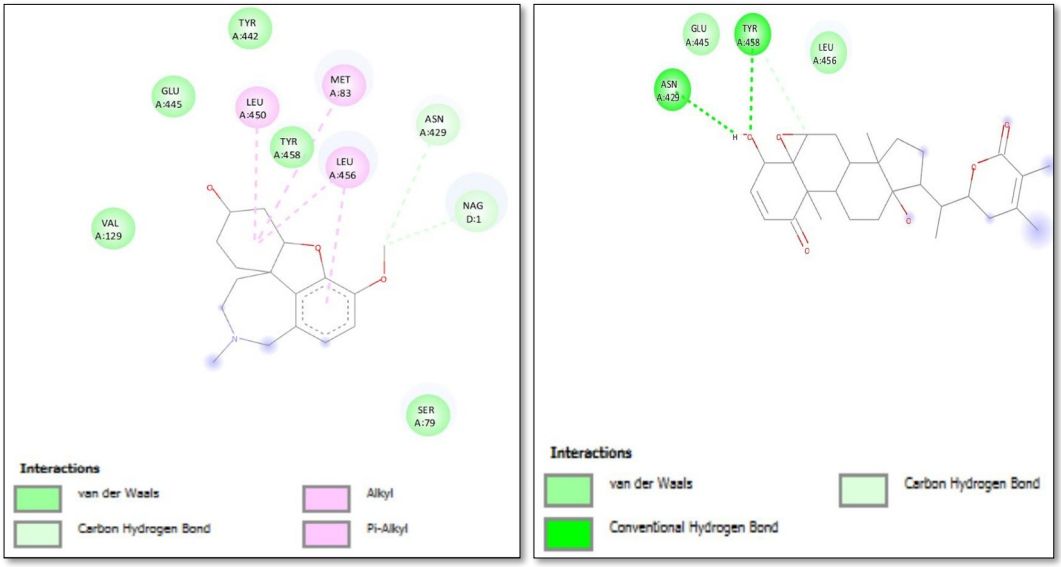
Profile of molecular interaction of USFDAapproved standard drugs; donepezil with the targeted receptor 5NUU contains Carbon H-bond with PRO A:283 with bonding distance of 3.61 Å, two pi-donor hydrogen bonds SER A: 286, PHE A:288, two pi-Alkyl bonds TRP A:279,ILE A:287, pi- Sigma A:9A5611, pi-Anion ASP A: 285 along with two van der waals interactions PHE A:331 and ARG A: 289 as shown in fig. 2(A). The molecular interaction for rivastigmine with 5NUU involves, two Conventional H-bonds PHE A:284 with bonding distance of 1.87 Å, SER A:286 with bond length of 3.01 Å, two Carbon H-bonds ASP A: 285 with bonding length of 3.76 Å, GLY A:335 with bonding distance of 3.36 Å, three pi- Alkyl bonds ILE A:287, PHE A:290 and TRP A:279, with van der wall interactions PHE A:331 as shown in fig.2 (B). Similarly, molecular interaction of Gelantamine with 5NUU was shown as two Carbon H-bonds ASN A:429 with bonding distance of 3.63 Å, NAG D:1 with bonding distance 3.50 Å, two pi-Alkyl bonds LEU A: 450, LEU A: 456, Alkyl bond MET A:83, four van der waal forces were also present TYR A:442, GLU A:445, VAL A: 129 andd SER A:79 as shown in fig.2 (C).

In the same way, after the evaluation of the intermolecular interactions of standard drugs with the target protein 5NUU the interactions for bioactive compounds of *W.somnifera* were also evaluated. Resultantmolecular interaction of 27-Deoxy-14-hydroxywithaferine A ligand with the 5NUU protein showed two Conventional H-bond ASN A: 429 with bonding length of 2.15 Å, TYR A: 458 with bonding distance 2.76 Å, Carbon H-bond TYR A:458 with bonding distance 3.12 Å, with other two van der waals interactions GLU A: 445 and LEU A: 456 as shown in fig.2 (D). The molecular interaction of Withanolide H with 5NUU involves two Conventional H-bond NAG D: 2 with bonding length 2.81 Å, MAN D: 4 of bonding distance 2.83 Å, Carbon H-bond BMA D: 3 with bonding length 3.45 Å, with other van der waal interaction NAG D: 1 as shown in fig.2(E). The molecular interaction of Withanolide A with 5NUU contains three Conventional H-bond GLU A: 445 with bonding distance 2.24 Å, SER A:79 of bonding length 3.38 Å,ASP A: 128 with bond length 2.38 Å, one Carbon H-bond TYR A: 458 with bond distance 2.98 Å, with four van der waalsbonds ASN A: 429, MET A: 83, LEU

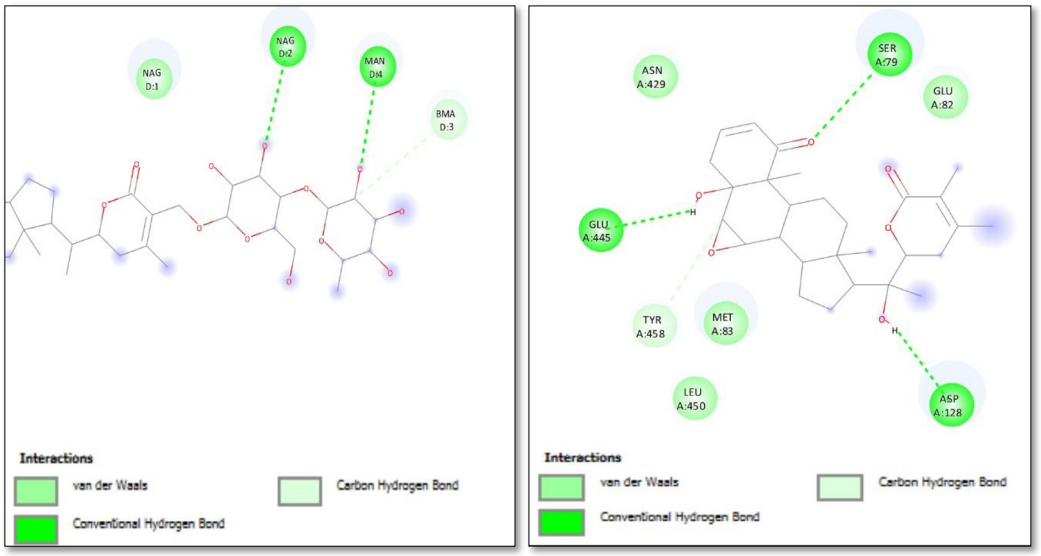
A: 450 and GLU A:82 as shown in fig.2 (F). molecular interaction of Withanolide Q claimed Conventional H-bond GLU A: 445 with bond length 2.26 Å, Carbon H-bond TYR A: 458 with bond distance 3.45 Å, alkyl bond LEU A: 127, two van der waal interactions LEU A: 450, ASN A: 429 and one unfavourableacceptor-acceptor bond ASP A:128 as presented in fig.2 (G). The molecular interaction of Sitoindoside IX with 5NUU showed five Conventional H-bond ASN A: 280 with bonding distance of 2.44 Å, TYR A: 334 with bond distance of 1.97 Å, GLN A: 74 with bond length 3.29, GLY A: 338 with bond distance 3.05 Å, PHE A: 339 with bond distance of 3.10 Å, one van der waal interaction of ALA A:336 as depicted in fig.2 (H). Withaferin A interaction with the targeted protein 5NUU claimed two Conventional H-bonds GLU A:434 with bond length of 3.25 Å, ASN A:457 with bonding distance of 3.11 Å, two Carbon H-bonds LYS A:341 with bond length 3.44 Å, NAG D: 1 with bond distance of 3.65 Å, and with other van der waals ASP A;342, PRO A:433 as shown in fig.2(I). The interactions of Withanolide J with 5NUU contains three Conventional H-bonds SER A: 286 with bond length 2.14 Å, ASP A: 285 with bonding distance 2.78 Å, PHE A: 284 with bond length 2.62, unfavourableacceptor-acceptorand van der waals LEU A: 358 as shown in fig.2 (J). Molecular interaction ofWithanolide G with target protein presented Conventional H-bond TRP A:279 with given bond length of 2.55 Å, Alkyl bond with LEU A: 282, pi-alkyl and with two van der waals VAL A: 281, A: 9A5611 as depicted in fig.2 (K). The interactions of Withanolide D presented two Conventional H-bonds TRP A:279 with bond distance of 2.83 Å, LEU A: 282 with bond distance of 2.73 Å, Carbon H-bond PHE A:284 with given bond size of 3.40 Å, pi-Sigma bond A: 9A5611, and two van der waals TYR A:334, LEU A: 358 as presented in fig.2 (L). The interactions of Withanolide M with the target protein 5NUU contains Conventional H-bond TRP A: 279 with bond length 2.19 Å, two Carbon H-bond SER A: 286 with bond length of 3.62 Å, A: 9A5611 with bon length of 3.57 Å, and van der waals TYR A:334 as shown in fig.2 (M). The Molecular interaction of Withanolide P with target protein 5NUU contains two Conventional H-bonds ASP A: 285 with bond length of 3.24 Å, LEU A: 282 with bond distance 2.05 Å as presented in fig.2 (N).The ligands that were studied for their ligand-receptor affinity are 27-Deoxy-14-hydroxywithaferine A, Withanolide H, Withanolide A, Withanolide Q, Sitoindoside IX, Withaferin A, Withanolide J, Withanolide G, Withanolide D, Withanolide M, and Withanolide P. They have exhibited both conventional H-bonds and carbon H-bond interactions with the amino acid residues, including twenty-four (24) types of conventional H-bonds and nine (9) types of carbon H-bonds. On the contrary, the standard drugs donepezil, revastigmine, and gelantamine contain a total of two (2) conventional H-bonds and five (5) carbon H-bonds. Whereas ligands like Sitoindoside IX, Withanolide M, and Withaferin A contain a greater number of conventional H-bonds and carbon H-bonds, respectively, as compared to standards. The presence of enough van der Waals interactions in the first eleven (11) ligand-receptor complexes was able to predict the solubility in the lipid bilayer. Thus, results show that these 11 phytoconstituents fulfilled all the requirements for anti-Alzheimer's activity and also became more potent as compared to standard drugs (donepezil, revastigmine, and gelantamine).



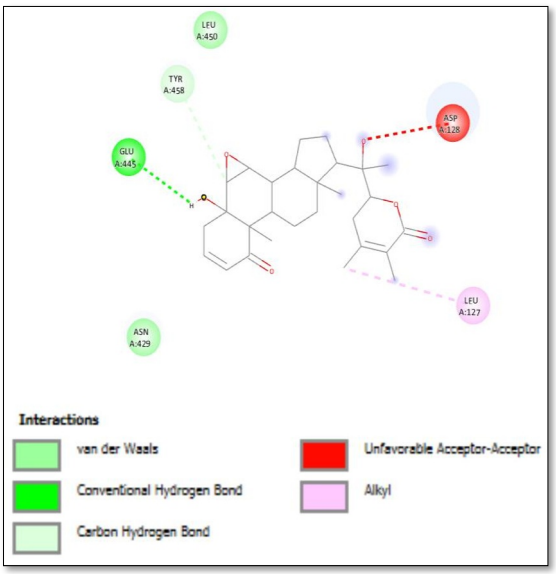
(A) Donepezil(B) Revastigmine

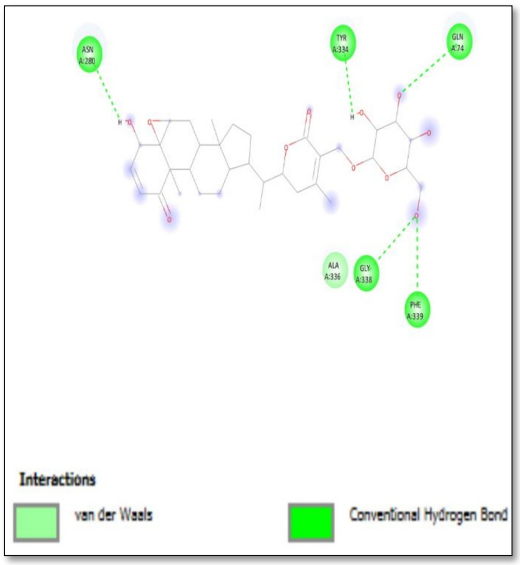


(C) Gelantamine(D) 27-Deoxy-14-hydroxywithaferine A

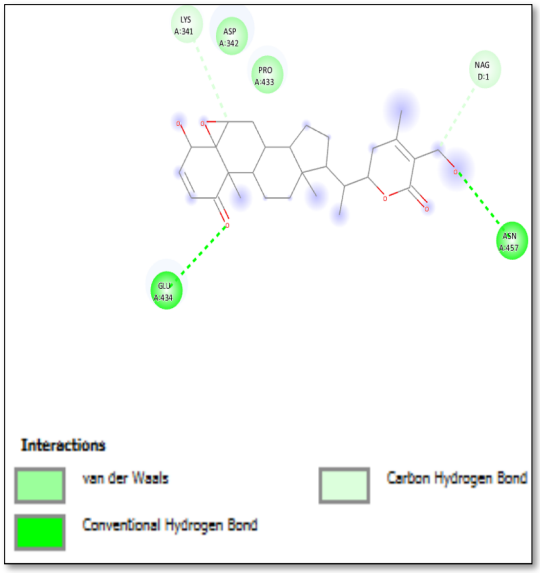


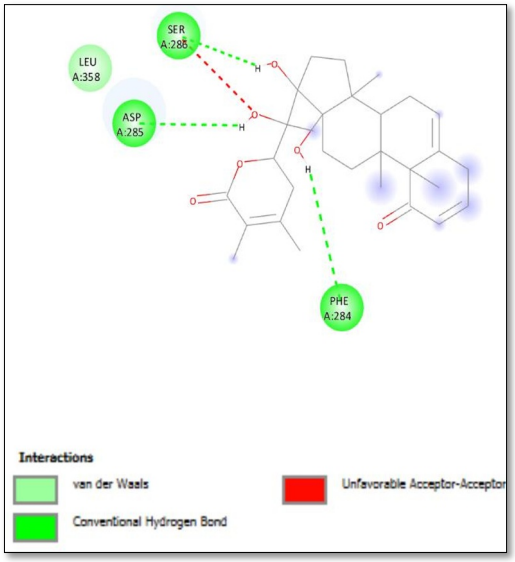
(E) Withanolide H(F) Withanolide A



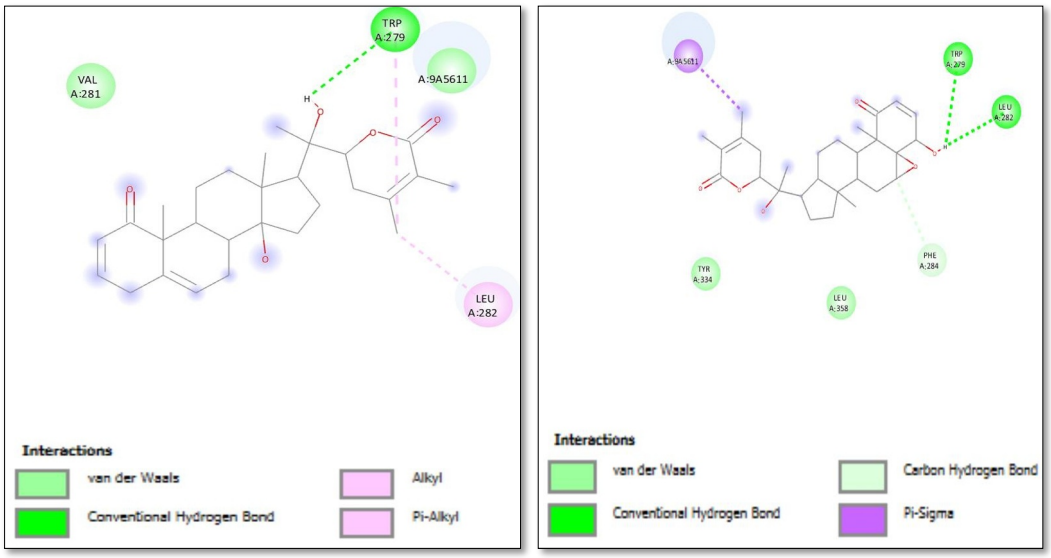


(G) Withanolide Q(H) Sitoindoside IX

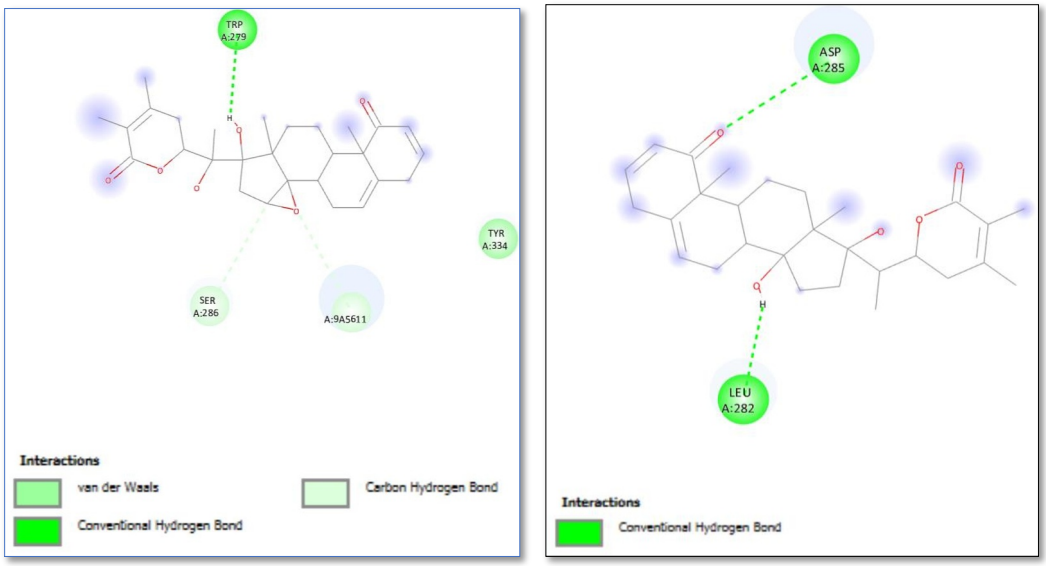




(I) Withaferin A(J) Withanolide J



(K)Withanolide G (L) Withanolide D



(M) Withanolide M(N) Withanolide P

Fig2 Representation of 2-dimensional image of ligands against 5NUU receptor

5 Conclusion

In this in-silico molecular docking study, approaches for the herbal compounds in comparison to US FDA-approved drugs were investigated. The results showed that the phytoconstituents in the roots of *W. somnifera*exhibited more potential. Phytoconstituents like 27-Deoxy-14-hydroxywithaferine A, Withanolide H, Withanolide A, Withanolide Q, Sitoindoside IX, Withaferin A, Withanolide J, Withanolide G, Withanolide D, Withanolide M, and Withanolide P have proved higher binding affinities towards the 5NUU (Torpedo californica acetylcholinesterase in complex with a chlorotacrine-tryptophan hybrid inhibitor) targeted receptor for AD, such as -9.1kcal/mol, -9.1 kcal/mol, -8.8 kcal/mol, -8.8 kcal/mol, -8.5 kcal/mol, -8.4 kcal/mol, -8.2 kcal/mol, -8.0 kcal/mol, -7.8 kcal/mol, -7.7 kcal/mol, and -7.6 kcal/mol, respectively, as compared to the binding affinities of standard prescribed drugs donepezil, revastigmine, and gelantamine. -7.4 kcal/mol, -7.3 kcal/mol, and -6.7 kcal/mol, respectively, for the treatment of AD. Thus, these findings of molecular docking show that *W. somnifera* has the potential to treat AD, and these phytoconstituents will be a good lead for future-based medications for AD.

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