

Virtual Screening of Compounds from *Valeriana Jatamansi* with α -Synuclein

Preenon Bagchi

Research Scholar, Dept. of Bioinformatics, School of
Bioengineering, SRM University, Kattankulathur,
Tamil Nadu, India
e.mail: prithish.bagchi@gmail.com

Waheeta Hopper

Professor & Head, Dept. of Bioinformatics, School of
Bioengineering, SRM University, Kattankulathur,
Tamil Nadu, India
e.mail: waheetahop@gmail.com

Abstract—Aggregation of α -synuclein causes Lewy Body Dementia (LBD). *Homo sapiens* α synuclein gi|49456267 from NCBI database was taken. 3D structure of SNCA protein was modelled using Homology Modelling. *Valeriana jatamansi*, an Indian herb, is most frequently used in mental disorders. The structures of *Valeriana jatamansi*'s eleven compounds were sketched using Chemsketch and converted to 3D. These compounds were virtually screened with the receptor SNCA protein using Maestro9.1. SNCA protein showed good interaction with jatamanin11 from *Valeriana jatamansi*

Keywords- lewy body; α -synuclein; homology modeling; virtual screening

I. INTRODUCTION

Alpha-synuclein (α -synuclein) also known as SNCA, a protein in humans encoded by the SNCA gene. Aggregated alpha-synuclein proteins in brain lesions are hallmarks of some neurodegenerative diseases (synucleinopathies) [1]. The gene for α -synuclein, SNCA, is located on chromosome 4q21. There are numerous findings suggesting a seminal role for α -synuclein in several neurodegenerative diseases. α -synuclein is a component of Lewy bodies [1, 2]. Lewy Body Dementia (LBD) is one of the most common types of progressive dementia. Lewy body dementia was first described by Dr. Levi in 1912. The main cause of LBD is the presence of some small inclusions called 'Lewy body' which consists of the protein α -synuclein [3, 4].

Valeriana jatamansi is a small herbaceous species of family Valerianaceae. It is a perennial, dwarf, hairy, rhizomatous herb forming a group of thick roots covered with fibres. The plant mostly grows randomly in steep areas, moist, rocky, undisturbed grassy slopes or on stones with coarse sandy loam soil. The herb grows in Alpine Himalayas at an altitude of 3000-5000 metres. Reports suggest that the species is becoming extinct due to over-exploitation of rhizomes for its medicinal value, habitat degradation and other biotic interferences in its distribution ranges [5, 6, 7, 8].

Eleven jatamanins including a new lignan, (+)-9'-isovaleroylariciresinol are extracted from whole plants of *V. jatamansi* (Fig. 1) [9].

II. METHODOLOGY

Homo sapiens alpha synuclein gi|49456267 was retrieved from the National Center for Biotechnology Information

(NCBI). Homology modeling was done using the following template:

- 2KKW A: Chain A, Slas-Micelle Bound Alpha-Synuclein [e-value - 2e-73]

Using BLAST search engine against Protein Data Bank (PDB) the above template was selected and its crystal structure was downloaded from PDB. 3D structure (*.pdb) of SNCA protein was modelled by using the software *Modeller9v8*. Five models of SNCA protein were generated. The best model was selected by using *Rampage Ramachandran Plot server*.

The chemical structures of eleven jatamanins were drawn using *ACD/Chemsketch* software. These were converted to 3d and saved as *.mol file.

The protein SNCA was prepared by using Protein Preparation Wizard of Maestro9.1 software, optimized and minimized. The receptor grid was set up and active site residues for the proteins were assigned by using the Receptor Grid Generation panel.

The grid region assigned for SNCA protein was 19, 30, 31, 40, 56, 102, 125, 129, 130, 136, 140 [10, 11].

The ligands (active compounds of the plant) were converted to a single file. Using LigPrep, energy minimization was done.

The Virtual Screening was carried out using the SNCA protein and the ligands prepared above.

III. RESULTS & DISCUSSION

The SNCA protein models were generated by *Modeller9v8*. Using *Rampage Ramachandran Plot server* the values of SNCA protein obtained in favoured, allowed and outlier region was noted (Table 1, Fig. 2).

As per the Ramachandran Plot, Model 2 was selected as the best protein since it is having least residues in the outlier region (Fig. 3).

The eleven jatamanins were then virtually screened with the SNCA protein using Maestro software.

Of the eleven compounds screened, jatamanin11 showed good interaction with SNCA protein. Jatamanin11 showed interaction with SNCA's ASP121, ASN122, GLU126 and TYR125 (Fig. 4). The glide score was -7.33.

IV. CONCLUSION

SNCA protein showed good interaction with jatamanin11 from *Valeriana jatamansi*.

Among the eleven compounds selected, jatamanin11 showed good interaction with α -synuclein protein; hence this compound could be checked for *in-vitro* & *in-vivo* trials to establish its effectiveness in curing Lewy body dementia.

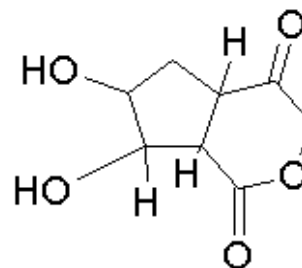
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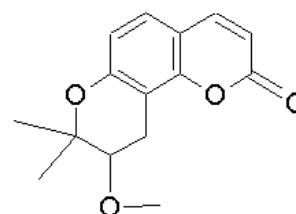
TABLE I. VALUES OF SNCA PROTEIN OBTAINED IN FAVOURED, ALLOWED AND OUTLIER REGION USING RAMPAGE RAMACHANDRAN PLOT SERVER.

| | Number of residues in favoured region (~98.0% expected) | Number of residues in allowed region (~2.0% expected) | Number of residues in outlier region | Selected |
|---------|---|---|--------------------------------------|----------|
| Model 1 | 135 (97.8%) | 0 (0.0%) | 3 (2.2%) | |
| Model 2 | 136 (98.6%) | 1 (0.7%) | 1 (0.7%) | selected |
| Model 3 | 135 (97.8%) | 1 (0.7%) | 2 (1.4%) | |
| Model 4 | 132 (95.7%) | 4 (2.9%) | 2 (1.4%) | |

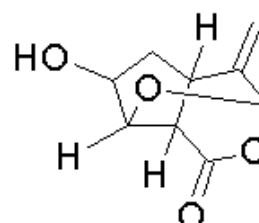
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|---------|-------------|----------|----------|--|
| Model 5 | 136 (98.6%) | 0 (0.0%) | 2 (1.4%) | |
|---------|-------------|----------|----------|--|



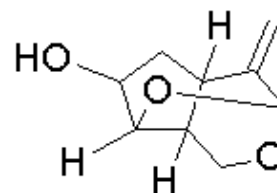
Jatamanin 1



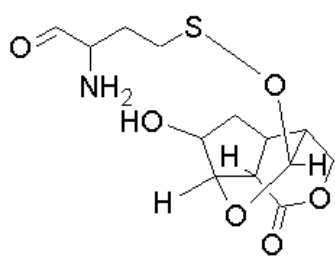
Jatamanin 2



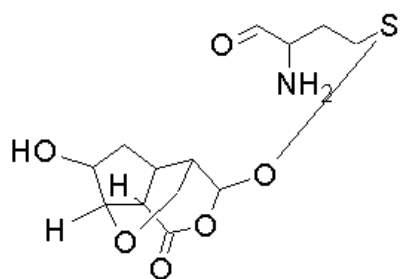
Jatamanin 3



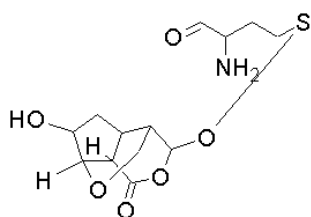
Jatamanin 4



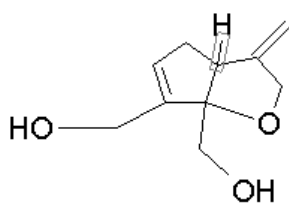
Jatamanin 5



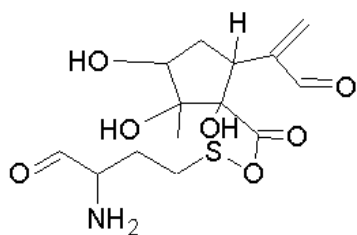
Jatamanin 6



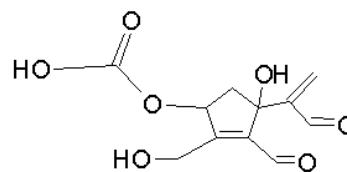
Jatamanin 7



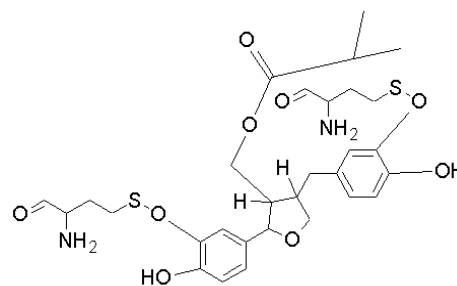
Jatamanin 8



Jatamanin 9



Jatamanin 10



Jatamanin 11

Figure 1. Chemical structure of eleven jatamanins (1-11) from *V. jatamansi*

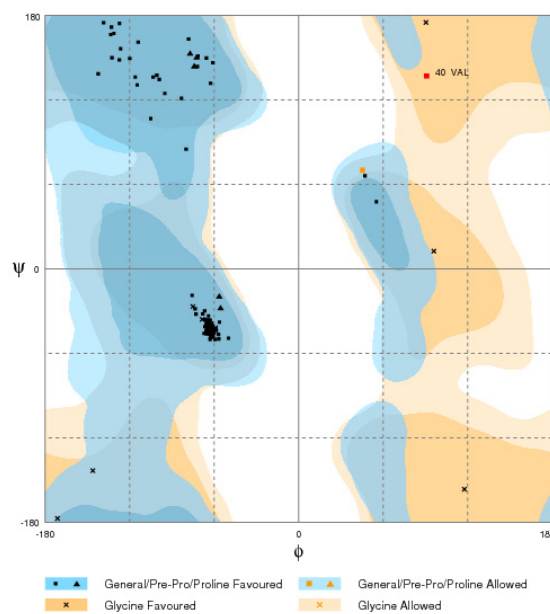


Figure 2. Ramachandran Plot of model 2 of SNCA protein.

Title: SNCA.B99990002

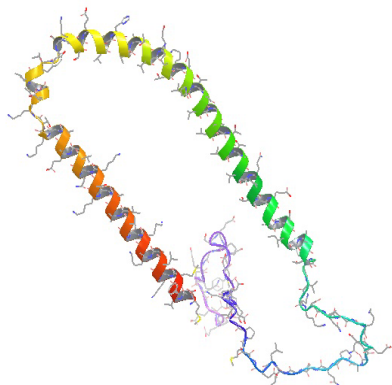


Figure 3. Visualization of SNCA best stable protein (model 2 generated by modeller9v8)

Title: xp_rcp1_frag_SNCA.B99990002_42698

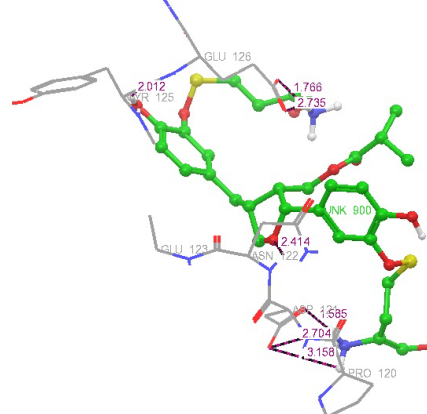


Figure 4. Interaction of SNCA protein with jatamanin11 from *Valeriana jatamansi*