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Multi-Target Molecular Docking of Anantmul (*Hemidesmus indicus*) Compounds for Tay-Sachs Disease Treatment

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Abstract

This research aimed to study the effects of the plant Anantmul (Hemidesmus indicus) in the treatment of Tay-Sachs disease using molecular docking studies. Tay-Sachs disease is a neurodegenerative autosomal recessive disorder caused due to accumulation of the molecule GM2 ganglioside which is caused due to lack of enzyme Beta Hexosaminidase which breaks down GM2 Ganglioside. Anantmul (Hemidesmus indicus) is a an ayurvedic plant used in the Indian subcontinent that has many medicinal uses, such as anti-cancer, anti-diabetic, anti-inflammatory, etc. using IMPATT software about 110 phytochemicals were discovered in Anantmul, then using SWISS Absorption, Distribution, Metabolism, and Excretion about 45 compounds were screened based on the Lipinski's rule. Then they were further screened based on toxicity using ProTox software down to 11 compounds. These 11 compounds were selected for molecular docking analysis on the protein Hexosaminidase to study their interaction and binding energy. Out of these, the top 6 compounds with the highest binding energy were taken for visualization. The compound with the highest binding energy was found to be Abieta-7,13-dien-18-oic acid with a binding energy of –7.4.

Keywords: Tay-Sachs disease, molecular docking, beta-hexosaminidase, GM2 ganglioside, Lipinski's rule

INTRODUCTION

Tay-Sachs disease is an autosomal recessive lysosome storage metabolic disorder. Tay-Sachs disease is characterized by acute neurodegeneration. Microglial expansion and inflammation. In most cases, this disease occurs during the infancy stage, in the juvenile form of the disease it occurs during adolescence, and in rare cases the onset of the symptoms occurs during adulthood. The typical symptoms of the disease are muscle weakness, ataxia, speech, and mental disorders.

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This disease is caused due to deficiency of the protein beta Hexosaminidase A (HEX A) due to various mutations in the alpha subunit of this gene. HEX A is an enzyme that is responsible for breaking down the molecule GM2 Ganglioside. Because of the lack of HEX, an enzyme there will be an accumulation of GM2 Ganglioside in the lysosomes of nerve cells which will lead to neurodegeneration. According to research 1 in every 32,000 people born in the United States has Tay-Sachs disease. This disease is most common among Ashkenazi Jewish descendants. And 1 in 250 people are carriers of this disease in the United States [1].

Some of the treatments used in this disease are gene therapy, and substrate reduction therapy using bone marrow transplant.

Anantmul or *Hemidesus Indicus* is a prostrate or semi-erect shrub found throughout India. It is an Ayurvedic medicinal plant. It is mainly used as a tonic, demulcent, diaphoretic, and blood purifier. It is mainly used in the treatment of syphilis, bronchitis, and various skin diseases. This plant contains various amounts of phytochemicals which help in the treatment of various diseases. It contains a significant amount of Rutin in its leaves. It contains many sterols like phytosterols, *Hemidesmus* and saponins. It contains coumarins, terpenoids, starch, and tannic acid are also present. Because of this Anantmul can be used in the treatment of various diseases.it can be used as an anti-bacterial, antioxidant, neuroprotective, and anti-carcinogenic. This research aimed to find alternative and cheap treatments for Tay-Sachs diseases by molecular docking of various screened Anantmul compounds with HEX A protein to increase its expression [2].

MATERIALS AND METHODS

Retrieval of Ligand

The secondary phytochemicals or secondary metabolites of the plant Anantmul (*Hemidesmus indicus*) were retrieved from the database IMPPAT (Indian Medicinal plants, phytochemistry and Therapeutics) (https://cb.imsc.res.in/imppat/home).

From this, a total of 110 phytocompounds were found and retrieved and then their canonical smiles and 2D SDF (Standard Data Files) were retrieved from PUB chem. (https://pubchem.ncbi.nlm.nih.gov/) [3].

- *Retrieval of Protein:* Tay-Sachs disease is caused due to deficiency of HEX A protein because of this the molecular target that was used in this research was HEX A. The three-dimensional structure of this protein was downloaded from the RCSB protein databank (https://www.rcsb.org/). Its PDB (Protein Database) ID is: 2GJX. This was resolved through X-ray crystallography at a resolution of 2.80 A [4].
- *Purification of Protein:* The protein that was selected was then sent to purification using the software Biovia Discovery studio. First, the water molecules were removed, then the hetero atoms were removed, then all the chains were removed except the A chain for analysis and then finally polar hydrogen atoms were added purifying the protein [5].
- *Protein Structure Validation:* To perform the molecular docking the 3S structure and the quality of the protein had to be determined since molecular docking predicts how ligands interact with the target protein hence the purified protein was validated using Ramachandran plot analysis using the software SAVESv6.0 (https://saves.mbi.ucla.edu/) [6–8].

Molecular Docking

Docking is the study of the interaction between ligand molecules and target proteins. The Docking software used in this research was PyRx to perform the docking of purified HEX A protein with phytochemicals of *H. indicus*. From the 110 phytochemicals about 11 compounds were screened for the docking. First, the ligands were downloaded at 2D SDF files then the purified protein was loaded, then the ligands were loaded using open babel then they were subjected to energy minimization then they converted to PDBqt format then the grid parameters were set and the docking began. For each ligand, we got about 9 binding affinities and the ones with zero RMSD (Root Mean Square Deviation) were selected and from that the ones with the high binding affinities were taken [9–11].

Molecular Visualization

The ligands with the high binding affinities were taken for visualization using the software Biovia Discovery Studio. Here, their binding energies and binding regions were studied and analyzed.

Pharmacological Properties of Ligands

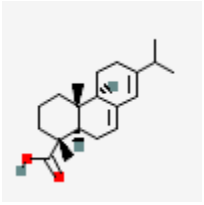
Drug discovery and development can be made more quicker and more affordable by understanding the pharmacological and ADMET (Absorption, Distribution, Metabolism, and Excretion) properties of

all the phytocompounds through Insilco studies. We can easily find the drug with the highest possibility of success using Insilco studies hence decreasing the possibility of drug failure. The physiochemical and ADMET properties of the phytocompounds of *H. indicus* were evaluated and analyzed using the SWISS ADMET tool (http://www.swissadme.ch/) [12].

Results

Retrieval of Ligands

Anantmul (*H. indicus*) is an Ayurvedic medicinal plant with various medicinal properties. It has various phytocompounds, such as terpenoids, flavonoids, sterols, etc, which have various anti-cancer, anti-diabetic, and neuroprotective properties. Because of their neuroprotective properties, they were selected in the treatment of Tay-Sachs disease. Their phytocompounds were retrieved from the IMPPAT Database. From there about 110 phytocompounds were retrieved. From them, about 10 compounds were screened for molecular docking as shown in Figure 1 [13].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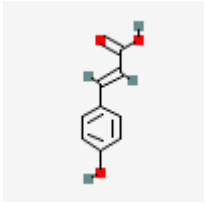
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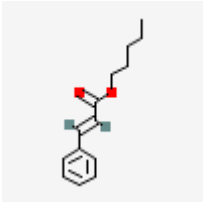
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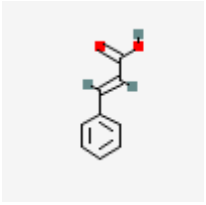
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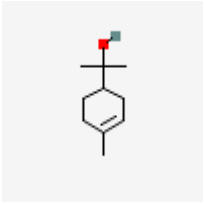
Abieta-7,13-dien-18-oic acid; P-coumaric acid; pentyl cinnamate; and cinnamic acid.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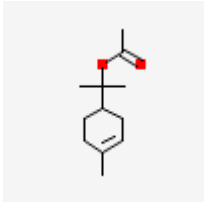
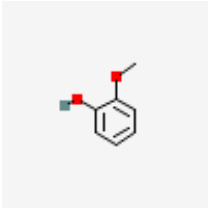

CID:111037


CID:61060


CID:2537

Alpha-terpineol; terpinyl acetate 124-76-5; isoborneol, and camphor.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Guaiacol

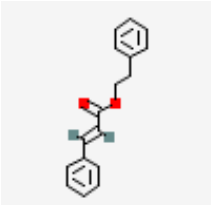

CID:5369459
Phenethyl cinnamate

Figure 1. Compounds with their PubChem ID.

Protein Structure Validation

Before completing molecular docking, the quality of the protein had to be determined. To find prospective therapeutic candidates, molecular docking predicts how ligands interact with target proteins. Therefore, the purified protein structure was validated through the Ramachandran plot. Ramachandran analysis helps us understand the structural architecture, topology, and irregularities in the protein. Hence, it is used to understand the protein structure before it is used for docking. The purified protein of GJX from the Ramachandran plot had 85.7% residues in the favorable regions,

14.3 % residues in the unfavorable region and 0% in the generously allowed region, and 0% in the disallowed region. The total number of residues was 492 out of which the residues in which the number of non-glycine and non-proline residues was 427 and the number of glycine and proline residues was 31 each and the number of end residues was 3 (Figure 2).

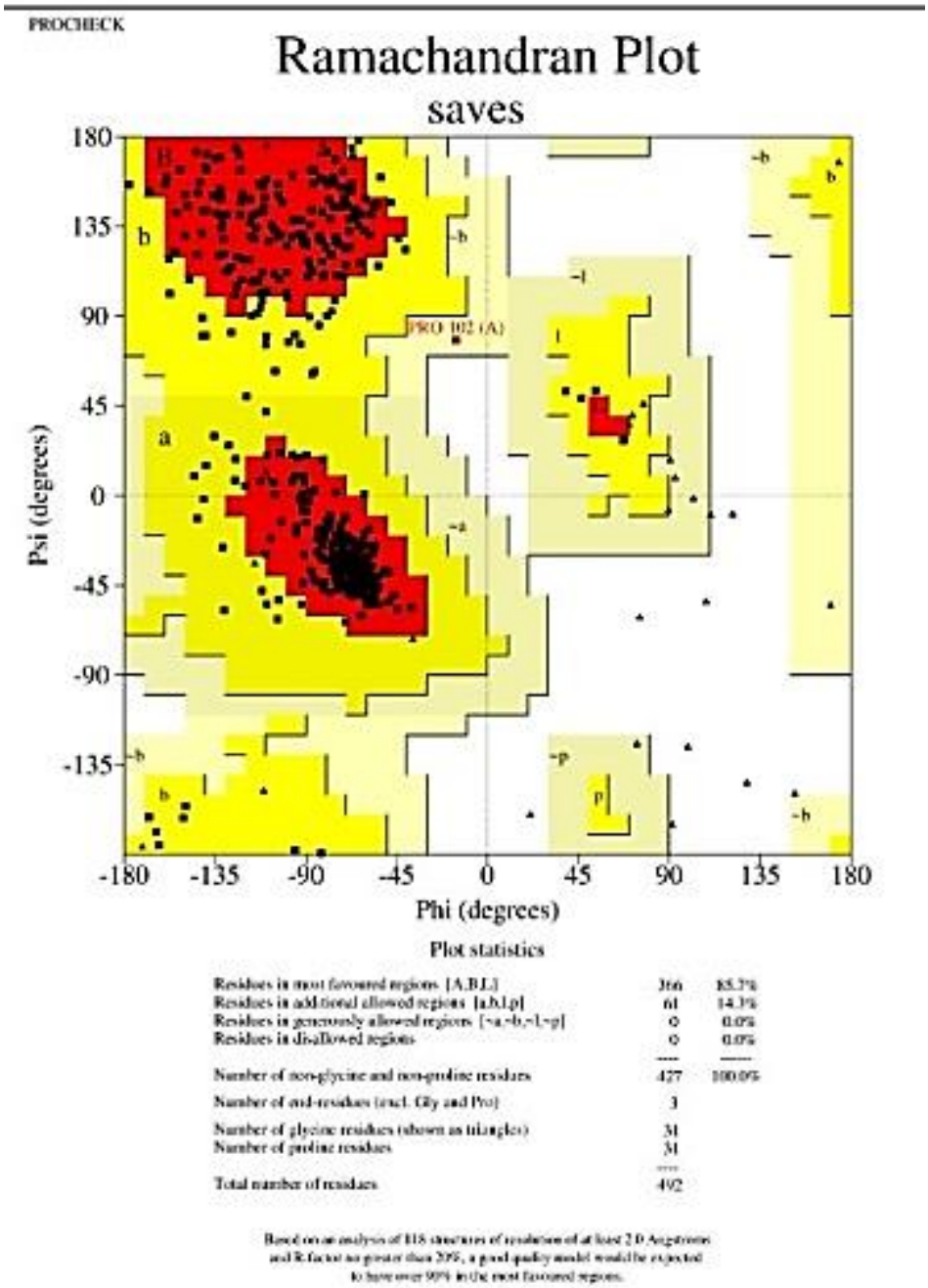


Figure 2. Ramachandran plot.

Molecular Docking

The docking of the ligands was done using the PyRx software. We then retrieved the binding affinities of all the ligands with the target molecules. About 100 binding affinities were retrieved out of which the one with zero RMSD values were taken. From these, the top 6 binding affinities were

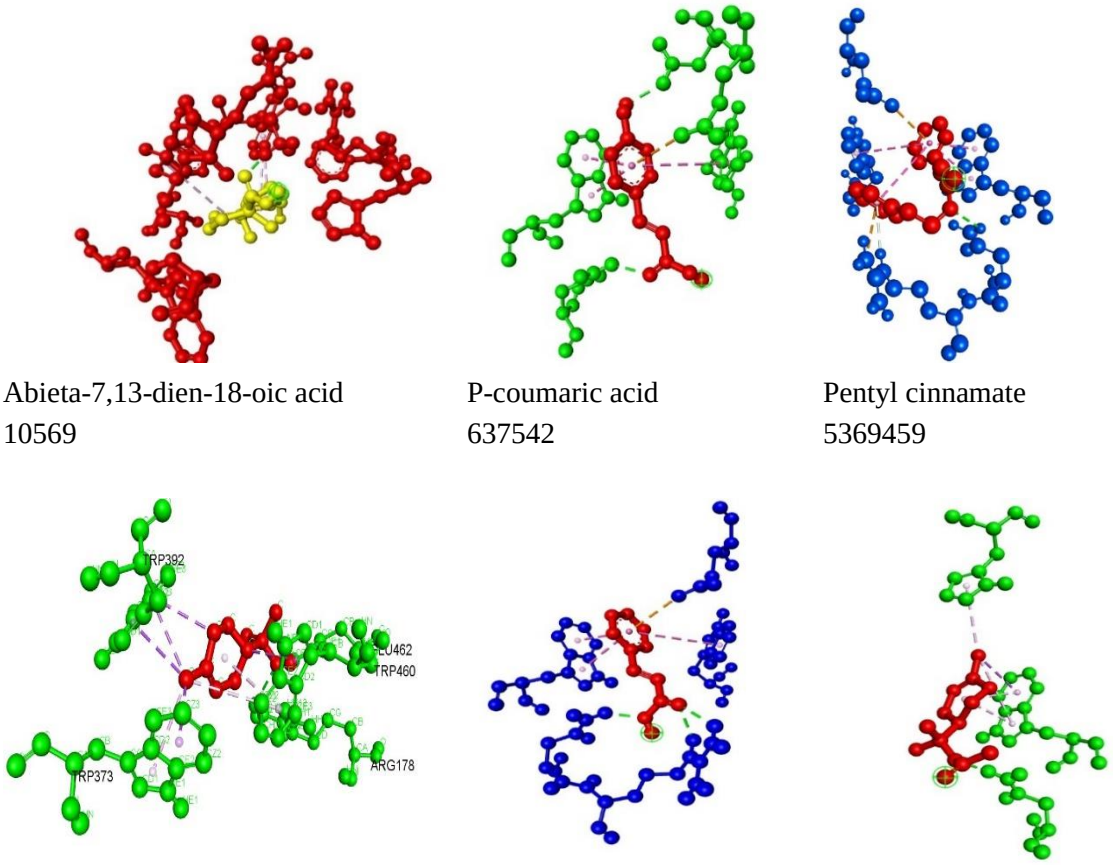
taken. The one with the highest binding affinity was Abieta-7,13-dien-18-oic acid (10569) with the binding energy of –7.4. The table below shows the binding energies of the top 6 ligands that were taken for further investigation (Table 1).

Table 1. Binding energies of the top 6 ligands.

S.N.	Ligand	PubChem ID	Binding Energy
1.	Abieta-7,13-dien-18-oic acid	10569	–7.4
2.	P-coumaric acid	637542	–6.7
3.	Pentyl cinnamate	5369459	–6.4
4.	Cinnamic acid	444539	–6.3
5.	Alpha-terpineol	17100	–6.3
6.	Alpha-terpinyl acetate	111037	–6.0

Molecular Visualization

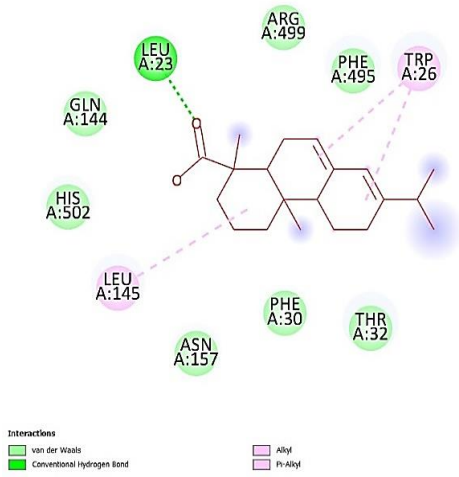
The top 6 ligands that had the best binding affinity with the molecular target "2GJX" were then taken for visualization using BIOVIA Discovery Studio. For the target protein GJX, the ligands with the PubChem CID: 10569, 637542, 5369459, 444539, 17100, 111037 demonstrated binding affinity less than 7.5 from Table 1. The visualization its shown that the ligands interacted with the target protein through hydrogen bonds and other non-covalent interactions predominantly with TRP 26, LEU 145, GLU 323, and ARG 424 (Figures 2, 3, and 4).



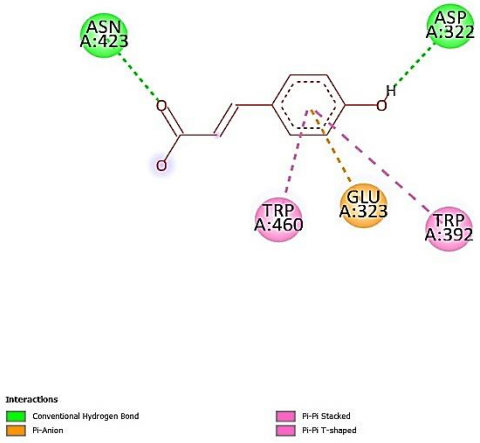
Abieta-7,13-dien-18-oic acid 10569 | P-coumaric acid 637542 | Pentyl cinnamate 5369459

Cinnamic acid 444539 | Alpha-terpineol 17100 | Alpha-terpinyl acetate 111037

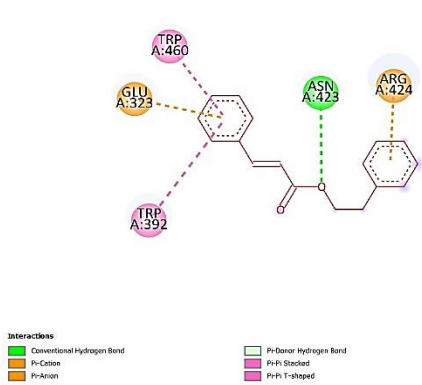
Figure 3. Molecular interactions of *H. indicus* compounds with molecular target 2GJX 2D interactions.



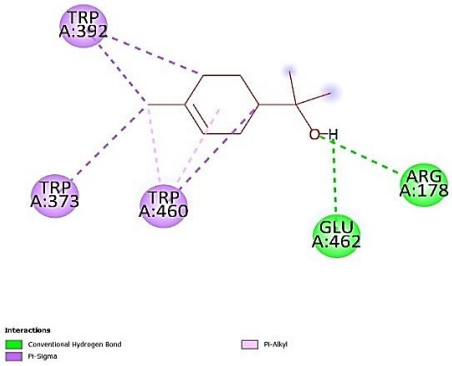
Abieta-7,13-dien-18-oic acid
10569



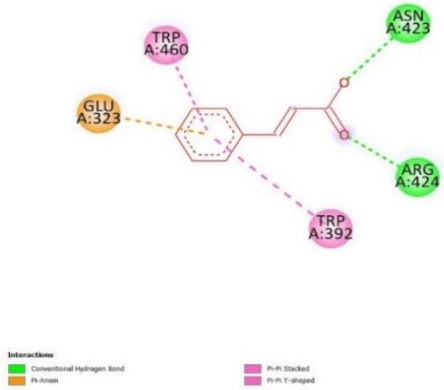
P-coumaric acid
637542



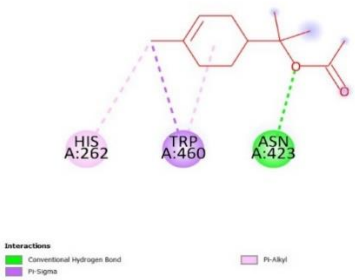
5369459 Pentyl cinnamate



444539 Cinnamic acid



17100 Alpha-terpineol



111037 Alpha-terpinyl acetate

Figure 4. Molecular interactions of *H. indicus* compounds with molecular target 2GJX 3D interactions.

Pharmacological Studies

The medicinal and therapeutic potential of *H. indicus* is studied based on ADMET properties as the bioactive compounds must contain drug-like properties. The top 6 ligands that were screened for docking were investigated for their physiochemical properties (Table 2), drug-like properties (Table 3), and their medicinal chemistry (Table 4).

Table 2. Physiochemical properties of *H. indicus* phytocompounds.

Phytocompound	PubChem	M.W	Rot bonds	M.R	TPSA
Abieta-7,13-dien-18-oic acid	10569	302.5 g/mol	2	92.22	37.3
P-coumaric acid	637542	164.16 g/mol	2	45.13	57.3
Alpha-tyerpineol	17100	154.25 g/mol	1	48.8	20.3
Cinnamic acid	444539	148.16 g/mol	2	43.11	37.3
Pentyl cinnamate	5355854	218.29 g/mol	7	66.66	26.3
Alpha-terpinyl acetate	111037	196.29 g/mol	3	58.33	26.3

Table 3. Drug-like properties of *H. indicus* phytocompounds.

Ligands	H bonds	H acceptor	Lipinski	Ghose rule	Bioavailability
Abieta-7,13-dien-18-oic acid	1	2	0	1	0.85
P-coumaric acid	2	3	0	0	0.85
Alpha-terpineol	1	1	0	1	0.55
Cinnamic acid	1	2	0	2	0.85
Pentyl cinnamate	0	2	0	0	0.55
Alpha-terpinyl acetate	0	2	0	0	0.55

Table 4. Medicinal chemistry of *H. indicus* phytocompounds.

Ligands	GIA	BBB	PAINS	Solubility
Abieta-7,13-dien-18-oic acid	High	Yes	0	Moderately soluble
P-coumaric acid	High	Yes	0	Soluble
Alpha-terpineol	High	Yes	0	Soluble
Cinnamic acid	High	Yes	0	Soluble
Pentyl cinnamate	High	Yes	0	Soluble
Alpha-terpinyl acetate	High	Yes	0	Soluble

DISCUSSION

The protein biomarker used was 2GJX-hexosaminidase. This enzyme breaks down GM2 Ganglioside and hence lack of this enzyme or underexpression of this enzyme causes accumulation of GM2 gangliosides which causes degeneration. This research hence focused on studying the interactions between phytocompounds in Anantmul to the target protein 2GJX to increase its expression. Out of the 110 compounds present in Anantmul, 11 compounds were screened based on their pharmacological properties and toxicity for molecular docking. Out of these, the top 6 ligands with the highest binding affinity were taken. The six compounds were Abieta-7,13-dien-18-oic acid, p-coumaric acid, alpha-terpineol, cinnamic acid, pentyl cinnamate, alpha-terpinyl acetate. Out of these the one with the highest binding affinity was Abieta-7,13-dien-18-oic acid with a binding affinity of –7.4. It is a diterpenoid with anti-neurodegenerative and anti-neuroinflammatory properties in a study done by Juan Xiong et al. 12 new Ent-abietene were isolated from roots of Chloranthus old Ami and showed anti-neuroinflammatory properties by inhibiting the nitric oxide production in lipopolysaccharide murine BV-2 microglial cells. The next compound with the second highest binding affinity was p coumaric acid with a binding affinity of –6.7. In a study done by Pratibha Atul Daro et al. using p-coumaric acid on a mouse, the study showed a protective effect of p-coumaric acid in neuroinflammation, cognitive impairment, and apoptosis that was induced by LPS through its anti-

oxidant activity, ache inhibitory activity, anti-inflammatory and anti-apoptotic properties which was y determined by behavioral, biochemical, and histopathological measures. The third compound with the highest binding affinity was alpha-terpineol with a binding affinity of -6.4. In a study performed by Hamid-Reza Alipour et al. alpha-terpineol was used on rat models. Aβ1-42 was injected into the hippocampus of wiser rats. It was shown to improve neurogenesis and long-term memory while reducing Amyloid plaque counts and ameliorating biochemical factors. The fourth phytocompound with the highest binding affinity was cinnamic acid with the binding affinity of -6.3. In a study done by Shung Huan et al. oral administration of cinnamic acid was shown to reverse LPS-induced memory disturbance and normalize glucose uptake in mice. It was also revealed that it was bound to the MAPK signaling pathway resulting in its downstream signaling pathway by blocking neuroinflammatory progression. Docking studies also showed that it could be inserted into an active pocket of interleukin-1. The fifth compound with the highest binding affinity was pentyl cinnamate with a binding affinity of -6.3. Pentyl cinnamate is an alkaloid that has various neuroprotective and neurodegenerative effects. The sixth compound was alpha-tepinyl acetate with a binding energy of -6.0. In a study done by Chowdhury and Kumar, they demonstrated the therapeutic potential of alpha-terpinyl acetate as it bonded to multiple drug targets causing inhibition of acetyl esterase inhibition, reduced beta-amyloid induced toxicity, reduced hydrogen peroxide-induced oxidative stress

CONCLUSIONS

Tay-Sachs disease is an unfortunate disease that affects many infants and children although there has not been a proper treatment and cure for this disease from our research and studies the Ayurvedic medicinal plant Anantmul or *H. indicus* has been proven to help cure and alleviate the symptoms of Tay-Sachs disease from the phytocompounds present in it. Among 110 compounds present 6 compounds had the best interaction with the target protein HEX A and among them the compound Abieta-7,13-dien-18-oic acid had the best interaction with the binding energy of –7.4. Hence from our research and studies, Abieta-7,13-dien-18-oic acid has shown potential in the treatment of Tay-Sachs disease and other neurodegenerative diseases. However, still additional research and studies need to be done to understand its mechanism and interaction and its possible use for clinical purposes in the future.

Conflict of Interest

- The authors declare no conflict of interest.
- Authors contribution.
- All the authors have contributed equally to the manuscript.

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