MOLECULAR DOCKING OF ANTITRYPANOSOMAL INHIBITORS FROM EUCALYPTUS TERETICORNIS FOR SLEEPING SICKNESS

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ABSTRACT

Objectives: This study aims to investigate the antitrypanosomal inhibitors of Eucalyptus tereticornis for sleeping sickness through molecular docking and studies on Absorption distribution metabolism excursion and toxicology (ADMET).

Methods: In silico molecular docking in ArgusLab software and ADMET analysis in AdmetSAR software was performed for the antitrypanosomal inhibitors of E. tereticornis for sleeping sickness.

Results: Interactions were studied for the ten proteins responsible for sleeping sickness with the 50 antitrypanosomal inhibitors of E. tereticornis. Docking was performed to see the interaction and the best binding energy of compounds with the proteins involved in sleeping sickness. The docking scores were highest for betulonic acid with −15.66 kcal/mol followed by euglobal with −12.24 kcal/mol, B-pinene with −10.31 kcal/mol, A-pinene with −10.34 kcal/mol, and the least docking score for P-cymene with −10.60 kcal/mol. Docking results showed that only betulonic acid and euglobal showed that hydrogen bond interaction was as b-pinene, a-pinene, and p-cymene yielded no hydrogen bond interactions so we will be taking the former docking results for further studies. The best docking result was shown by betulonic acid with trypanothione reductase giving binding energy of −15.66 kcal/mol with hydrogen bond interaction of 2.9, so this result was taken for further analysis.

Conclusion: The results of the compound extracted from E. tereticornis will become physiological relevant only when (i) the pure compounds of this plant is available in large quantities; (ii) the Eucalyptus is biochemically stabilized to avoid degradation and enhance absorption in the gastrointestinal tract; and (iii) special delivery methods for this drug to reach the areas of treatment. In this work, the efficacy of E. tereticornis to act against trypanosomal protein was initiated and thus further research in this process would help us to take full advantage of the remedial effects of the compounds extracted from this plant.

Keywords: Antitrypanosomal Inhibitors, Eucalyptus tereticornis, Sleeping sickness, Molecular Docking, ADMET studies.

INTRODUCTION

Human trypanosomiasis, also known as “sleeping sickness,” is caused by microscopic parasites of the species Trypanosoma brucei. At present, about 10,000 new cases each year are reported to the World Health Organization occurred in India in 2007 and re-emerging these days; however, it is believed that many cases go undiagnosed and unreported. Sleeping sickness is curable with medication but is fatal if left untreated [1]. A report on a case of a 37-day-old infant from Uttar Pradesh who was presented with fever, lethargy, and convulsions, and who had a history of painful insect bite the day before admission [2]. In some cases, a pregnant woman can pass the infection to her fetus. In theory, the transmission of infection can also be by the transference of blood or sexual contact, but such cases were rarely documented [3]. The course of untreated infection rarely lasts longer than 6–7 years and more often kills in about 3 years [4]. The widely used criteria for defining the second stage in disease are the observation of trypanosomes in CSF or a white blood cell count of six or higher. Other indications of the second-stage disease include elevated protein and trypanosomes in CSF or a white blood cell count of six or higher. Other indications of the second-stage disease include elevated protein and trypanosomes in CSF or a white blood cell count of six or higher. Other indications of the second-stage disease include elevated protein and trypanosomes in CSF or a white blood cell count of six or higher. Other indications of the second-stage disease include elevated protein and trypanosomes in CSF or a white blood cell count of six or higher.

The goal of the current study was to identify the protein targets that the medicinal plants target selectivity for phytochemical classes. In doing so, we have theoretically identified the strongly interacting plant chemicals and their biomolecular targets. These results should lead to further research to verify the efficacy of phytochemical agents [8]. In silico screening of small molecules has been at the forefront of drug discovery in recent years. There are various drug targets in T. brucei. These include trypanothione reductase (TR), rhodanese, triosephosphate isomerase (TIM), and farnesyl diphosphate synthase, in line with the fact that target-based drug discovery efforts remain a front runner in lead identification [9,10]. The clinical significance of the young febrile infant was malaria, bacterial sepsis, or viral fever. The clinical diagnosis of trypanosomiasis was surprising and incidental because this parasitic infection in humans is very rare in India. The characteristic morphology and the polymerase chain reaction made the diagnosis unequivocal. However, a causal association between the parasite and the febrile illness is difficult to establish [11]. The patient was treated with suramin, a drug used for the treatment of human African trypanosomiasis. The authors hypothesized that the patient was infected by a wound in the index finger while delivering an infected cattle or a bite by the flies of Tabanidstriatus to transmit infection in animals. Subsequently, a serologic study was conducted in the same village, and it illustrated that the sera of 81 of 1806 people (4.5%)
METHODS

Bioinformatics is vital to significantly improve the position and function of molecules in binding and simulation. In bioinformatics, the process of computer-aided drug design (CADD) exists as a specialized discipline to use the computational [12] methods to simulate the interactions between a drug and a receptor. CADD methods are heavily dependent on bioinformatics tools, applications, and databases. The small molecules used in this study have been taken from literature survey; they have been selected on the criteria that these ligands have not been used prior as antitrypanosomal studies. The structures of the ligand were downloaded directly from PubChem.

Retrieval of the target protein

The 3D structures of the target trypanosomal proteins were downloaded from the Protein data bank database (PDB) in.pdb format.

Protein preparation

Protein-ligand docking studies [13] were carried out based on the crystal structures of *T. brucei* adenine kinase, TbAK (PDB 2xb and PDB 3tox). *T. brucei* pteridine reductase 1 (TbPTR1, PDB 3jq7). *T. brucei* dihydrofolate reductase (TbDHFR, TbDHFR (PDB 3rg9) and PDB 3sfq), *T. brucei* trypanothione reductase, *T. brucei* cathepsin B, *T. brucei* heat shock protein 90 (TbHSP90), TbHSP90 (PDB 3z0a and PDB 3opd), *T. brucei* sterol 14α-demethylase, *T. brucei* nucleoside dehydrogenase (TbNH), TbNH (PDB 3sf0), *T. brucei* TIM (TbTIM), and TbTIM (PDB 1ih, *T. brucei* nucleoside 2-deoxynucleoside 5'-triphosphatase, and *T. brucei* ornithine decarboxylase, TbODCPDB 1nj)). The solvent molecules and the co-crystallized ligands were removed from the crystal structure. To be used as a receptor for docking, protein structures should be processed. Some of the typical operations include (i) addition of hydrogen atoms, (ii) elimination of water molecules that are not involved in ligand binding, and (iii) making binding groups. This was done in ArgusLab.

Protein-ligand interaction using ArgusLab

The compounds isolated from the plants were docked against the proteins using ArgusLab, to find the reasonable binding geometries and explore the protein-ligand interactions. Docking of the protein-ligand complex was mainly targeted to the predicted active site only. The selected residues of the receptor were defined to be a part of the binding site. All the compounds in the dataset were docked into the active site of the protein following the same procedure. After docking, the docked protein (protein-ligand complex) was analyzed to investigate the type of interactions. The poses of docking were saved for each compound and ranked according to their function. The pose having the highest dock score was selected for further analysis [14] (QSAR studies).

RESULTS

This study was conducted to understand the interactions between the proteins and the ligand to discover their binding affinity. This docking study was executed using ArgusLab. The 3D structure of the trypanosomal protein was downloaded from PDB and used as a target for docking. The results are as follows.

Protein’s binding site prediction

CASTp was used for predicting the binding site of the protein. The active site of protein comprises of amino acid for 3OTX, 3QFX, 3JSQ, 3FZO, 2XTB, 1NJ, 3RG9, and 11IH is listed in Tables 1-8.

In Table 1, the position of amino acids in the active sites of the protein with PDB id 3OTX was analyzed by CASTp server.

In Table 2, the position of amino acids in the active sites of the protein with PDB id 3QFX was analyzed by CASTp server.

In Table 3, the position of amino acids in the active sites of the protein with PDB id 3JSQ was analyzed by CASTp server.

In Table 4, the position of amino acids in the active sites of the protein with PDB id 3FZO was analyzed by CASTp server.

In Table 5, the position of amino acids in the active sites of the protein with PDB id 2XTB was analyzed by CASTp server.

| S. No. | Amino acid | Active sites |
|-------|------------|-------------|
| 1     | Cystine    | 12, 123, 239|
| 2     | Arginine   | 7, 34, 58, 70, 94, 132, 156, 223, 245, 265, 316, 332 |
| 3     | Asparagine | 13, 56, 67, 195, 222, 231, 295 |
| 4     | Leucine    | 15, 16, 39, 134, 138, 286 |
| 5     | Aspergin   | 17, 92, 238, 266, 287, 289, 293, 299 |
| 6     | Serine     | 19, 64, 197, 269 |
| 7     | Alanine    | 20, 37, 78, 112, 113, 156, 158, 157, 221, 297, 300, 326 |
| 8     | Histidine  | 21, 105, 114, 224, 323 |
| 9     | Glucine    | 33, 101, 104, 106, 131, 160, 225, 279, 268, 241, 288, 328, 339 |
| 10    | Glycine    | 35, 62, 63, 81, 107, 129, 298, 296 |
| 11    | Threonine  | 36, 85, 172, 264, 270, 280, 325 |
| 12    | Isoleucine | 38, 90, 106, 127, 267, 292, 330 |
| 13    | Proline    | 55, 61, 199, 282, 284, 338 |
| 14    | Valine     | 57, 60, 68, 71, 98, 109, 283, 240, 125, 278, 291, 329 |
| 15    | Tyrosine   | 59, 79, 95, 165 |
| 16    | Glutamine  | 73, 77, 203, 285, 288, 327 |
| 17    | Tryptsin   | 74 |
| 18    | Isoleucine | 80, 82, 97, 100, 130, 227, 340 |
| 19    | Methionine | 110, 294, 302 |
| 20    | Phenylalanine | 169, 200, 301 |

| S. No. | Amino acid | Active sites |
|-------|------------|-------------|
| 1     | Arginine   | 59, 84, 95, 100, 107, 183 |
| 2     | Leucine    | 90, 97, 105 |
| 3     | Aspergin   | 43, 45, 54, 88, 120 |
| 4     | Serine     | 89, 98, 106, 108, 192, 216 |
| 5     | Alanine    | 34, 226 |
| 6     | Histidine  | 182 |
| 7     | Glycine    | 42, 44, 45, 83, 136, 161, 162, 163 |
| 8     | Threonine  | 46, 86, 164, 184 |
| 9     | Isoleucine | 41, 47, 51, 118, 160, 165 |
| 10    | Proline    | 48, 52, 91, 92119 |
| 11    | Valine     | 32, 33, 195 |
| 12    | Glutamine  | 50, 234 |
| 13    | Tryptsin   | 57, 166 |
| 14    | Lysin      | 85, 93, 123, 235 |
| 15    | Methionine | 55, 82 |
| 16    | Phenylalanine | 58, 94, 233 |

| S. No. | Amino acid | Active sites |
|-------|------------|-------------|
| 1     | Arginine   | 89, 98, 106, 108, 192, 216 |
| 2     | Leucine    | 90, 97, 105, 137, 168 |
| 3     | Aspergin   | 46, 86, 164, 184 |
| 4     | Serine     | 43, 45, 54, 88, 120 |
| 5     | Alanine    | 34, 226 |
| 6     | Histidine  | 52, 60, 101 |
| 7     | Glycine    | 42, 44, 45, 83, 136, 161, 162, 163 |
| 8     | Threonine  | 46, 86, 164, 184 |
| 9     | Isoleucine | 41, 47, 51, 118, 160, 165 |
| 10    | Glutamine  | 50, 234 |
| 11    | Tryptsin   | 30, 168 |
| 12    | Lysin      | 85, 93, 123, 235 |
| 13    | Methionine | 55, 90, 100, 105 |
| 14    | Phenylalanine | 55, 98, 133 |
In Table 6, the position of amino acids in the active sites of the protein with PDB id 1NJJ was analyzed by CASTp server.

In Table 7, the position of amino acids in the active sites of the protein with PDB id 3RG9 was analyzed by CASTp server.

In Table 8, the position of amino acids in the active sites of the protein with PDB id 1I1H was analyzed by CASTp server.

Docking of proteins with plant compounds

In this study, the interactions between the ligands and various trypanosomal proteins were explored to check their binding affinity; docking study was performed using ArgusLab. The interaction between the protein and ligand was analyzed on the basis of binding energy and the results are compiled in Tables 9-17.
In Table 1, P-Cymene has the minimum binding energy with ornithine decarboxylase.

In Table 2, alpha-pinene has the minimum binding energy with dihydrofolate reductase.

In Table 3, Euglobal has the minimum binding energy with dihydroorotate dehydrogenase.

In Table 4, the binding energy is given in kcal/mol.

In Table 5, alpha-pinene has the minimum binding energy with HSP90.

In Table 6, P-Cymene has the minimum binding energy with adenosine kinase.

In Table 7, Euglobal has the minimum binding energy with tyrosine kinase.

In Table 8, alpha-pinene has the minimum binding energy with HSP90.

In Table 9, the binding energy is given in kcal/mol.

In Table 10, P-Cymene has the minimum binding energy with adenosine kinase.

In Table 11, P-Cymene has the minimum binding energy with ornithine decarboxylase.

In Table 12, alpha-pinene has the minimum binding energy with dihydrofolate reductase.

In Table 13, Euglobal has the minimum binding energy with dihydroorotate dehydrogenase.

In Table 14, alpha-pinene has the minimum binding energy with TR.

In Table 15, alpha-pinene has the minimum binding energy with HSP90.

In Table 16, P-Cymene has the minimum binding energy with adenosine kinase.

In Table 17, Euglobal has the minimum binding energy with tyrosine kinase.

In Table 18, alpha-pinene has the minimum binding energy with HSP90.

In Table 19, alpha-pinene has the minimum binding energy with triosephosphate isomerase.

In Table 20, alpha-pinene has the minimum binding energy with tyrosine kinase.

In Table 21, the binding energy is given in kcal/mol.

In Table 22, alpha-pinene has the minimum binding energy with HSP90.

In Table 23, the binding energy is given in kcal/mol.

In Table 24, alpha-pinene has the minimum binding energy with adenosine kinase.

In Table 25, Euglobal has the minimum binding energy with tyrosine kinase.

In Table 26, alpha-pinene has the minimum binding energy with HSP90.

In Table 27, alpha-pinene has the minimum binding energy with triosephosphate isomerase.

In Table 28, alpha-pinene has the minimum binding energy with tyrosine kinase.

In Table 29, the binding energy is given in kcal/mol.

In Table 30, alpha-pinene has the minimum binding energy with HSP90.

In Table 31, the binding energy is given in kcal/mol.

In Table 32, alpha-pinene has the minimum binding energy with adenosine kinase.

In Table 33, Euglobal has the minimum binding energy with tyrosine kinase.

In Table 34, alpha-pinene has the minimum binding energy with HSP90.

In Table 35, alpha-pinene has the minimum binding energy with triosephosphate isomerase.

In Table 36, alpha-pinene has the minimum binding energy with tyrosine kinase.

In Table 37, the binding energy is given in kcal/mol.

In Table 38, alpha-pinene has the minimum binding energy with HSP90.

In Table 39, the binding energy is given in kcal/mol.

In Table 40, alpha-pinene has the minimum binding energy with adenosine kinase.

In Table 41, Euglobal has the minimum binding energy with tyrosine kinase.

In Table 42, alpha-pinene has the minimum binding energy with HSP90.

In Table 43, alpha-pinene has the minimum binding energy with triosephosphate isomerase.

In Table 44, alpha-pinene has the minimum binding energy with tyrosine kinase.

In Table 45, the binding energy is given in kcal/mol.

In Table 46, alpha-pinene has the minimum binding energy with HSP90.

In Table 47, the binding energy is given in kcal/mol.

In Table 48, alpha-pinene has the minimum binding energy with adenosine kinase.

In Table 49, Euglobal has the minimum binding energy with tyrosine kinase.

In Table 50, alpha-pinene has the minimum binding energy with HSP90.

In Table 51, alpha-pinene has the minimum binding energy with triosephosphate isomerase.

In Table 52, alpha-pinene has the minimum binding energy with tyrosine kinase.

In Table 53, the binding energy is given in kcal/mol.

In Table 54, alpha-pinene has the minimum binding energy with HSP90.

In Table 55, the binding energy is given in kcal/mol.

In Table 56, alpha-pinene has the minimum binding energy with adenosine kinase.

In Table 57, Euglobal has the minimum binding energy with tyrosine kinase.

In Table 58, alpha-pinene has the minimum binding energy with HSP90.

In Table 59, alpha-pinene has the minimum binding energy with triosephosphate isomerase.

In Table 60, alpha-pinene has the minimum binding energy with tyrosine kinase.

In Table 61, the binding energy is given in kcal/mol.

In Table 62, alpha-pinene has the minimum binding energy with HSP90.

In Table 63, the binding energy is given in kcal/mol.

In Table 64, alpha-pinene has the minimum binding energy with adenosine kinase.

In Table 65, Euglobal has the minimum binding energy with tyrosine kinase.

In Table 66, alpha-pinene has the minimum binding energy with HSP90.

In Table 67, alpha-pinene has the minimum binding energy with triosephosphate isomerase.

In Table 68, alpha-pinene has the minimum binding energy with tyrosine kinase.

In Table 69, the binding energy is given in kcal/mol.

In Table 70, alpha-pinene has the minimum binding energy with HSP90.

In Table 71, the binding energy is given in kcal/mol.

In Table 72, alpha-pinene has the minimum binding energy with adenosine kinase.

In Table 73, Euglobal has the minimum binding energy with tyrosine kinase.

In Table 74, alpha-pinene has the minimum binding energy with HSP90.

In Table 75, alpha-pinene has the minimum binding energy with triosephosphate isomerase.

In Table 76, alpha-pinene has the minimum binding energy with tyrosine kinase.

In Table 77, the binding energy is given in kcal/mol.

In Table 78, alpha-pinene has the minimum binding energy with HSP90.

In Table 79, the binding energy is given in kcal/mol.

In Table 80, alpha-pinene has the minimum binding energy with adenosine kinase.

In Table 81, Euglobal has the minimum binding energy with tyrosine kinase.

In Table 82, alpha-pinene has the minimum binding energy with HSP90.

In Table 83, alpha-pinene has the minimum binding energy with triosephosphate isomerase.

In Table 84, alpha-pinene has the minimum binding energy with tyrosine kinase.

In Table 85, the binding energy is given in kcal/mol.

In Table 86, alpha-pinene has the minimum binding energy with HSP90.

In Table 87, the binding energy is given in kcal/mol.

In Table 88, alpha-pinene has the minimum binding energy with adenosine kinase.

In Table 89, Euglobal has the minimum binding energy with tyrosine kinase.

In Table 90, alpha-pinene has the minimum binding energy with HSP90.

In Table 91, alpha-pinene has the minimum binding energy with triosephosphate isomerase.

In Table 92, alpha-pinene has the minimum binding energy with tyrosine kinase.

In Table 93, the binding energy is given in kcal/mol.

In Table 94, alpha-pinene has the minimum binding energy with HSP90.

In Table 95, the binding energy is given in kcal/mol.

In Table 96, alpha-pinene has the minimum binding energy with adenosine kinase.

In Table 97, Euglobal has the minimum binding energy with tyrosine kinase.

In Table 98, alpha-pinene has the minimum binding energy with HSP90.

In Table 99, alpha-pinene has the minimum binding energy with triosephosphate isomerase.

In Table 100, alpha-pinene has the minimum binding energy with tyrosine kinase.

In Table 101, the binding energy is given in kcal/mol.

In Table 102, alpha-pinene has the minimum binding energy with HSP90.

In Table 103, the binding energy is given in kcal/mol.

In Table 104, alpha-pinene has the minimum binding energy with adenosine kinase.

In Table 105, Euglobal has the minimum binding energy with tyrosine kinase.

In Table 106, alpha-pinene has the minimum binding energy with HSP90.

In Table 107, alpha-pinene has the minimum binding energy with triosephosphate isomerase.

In Table 108, alpha-pinene has the minimum binding energy with tyrosine kinase.

In Table 109, the binding energy is given in kcal/mol.

In Table 110, alpha-pinene has the minimum binding energy with HSP90.

In Table 111, the binding energy is given in kcal/mol.

In Table 112, alpha-pinene has the minimum binding energy with adenosine kinase.

In Table 113, Euglobal has the minimum binding energy with tyrosine kinase.
crucial information concerning the orientation of the inhibitors in the binding pocket of the target protein. Several potential inhibitors have been identified. The results of our present study suggested that it can be used for the design and development of novel compounds having better inhibitory activity against several types of trypanosomiasis. These potential drug candidates can be further be validated in wet lab studies for its proper function. In other words, the results of the present study can be concluded in the following points. Betulonic acid was better ligands of choice that inhibits TR antitypanosomal protein than other ligands showing the best affinity to bind with the protein and showed outstanding score and energy when compared to all other compounds. By applying QSAR studies to the best-scored compounds, it also stands for both properties (drug likeness and orally bioavailability).

CONCLUSION

Human trypanosomiasis or sleeping sickness currently is a common disease among the rural regions though found rare in the city sides causing deaths in humans as well as livestock. Although continuing to decline in the city sides, yet incidence rates remain level in rural regions following an increase in India since 2007. Trends in human trypanosomiasis related death trends due to livestock and causative agents over the past several decades. In this field of structure-based drug designing, there is a growing interest in the human trypanosomiasis protein study for the screening of putative leaf compounds. This approach involves the structure-based study of trypanosoma proteins and the antitypanosomal properties of the selected plant compounds based on the literature available. The active sites of the trypanosoma proteins were found out and the molecular docking of the plant compounds was performed. The five compounds were docked, from based on the binding energy and the number of hydrogen bonds. Among them betulonic acid, a compound in E. tereticornis is found to have the best binding affinity and strong hydrogen bond interaction with trypanosoma protein. Euglobal, B-pinene, A-pinene, and P-cymene also gave good scores.

The results of the compound extracted from E. tereticornis will become a physiological relevant only when (i) the pure compounds of this plant are available in large quantities; (ii) the Eucalyptus is biochemically stabilized to avoid degradation and enhance absorption in the gastrointestinal tract; and (iii) special delivery methods for this drug to reach the areas of treatment. In this work, the efficacy of E. tereticornis to act against trypanosomal protein was initiated and thus further research in this process would help us to take full advantage of the remedial effects of the compounds extracted from this plant. Solving these issues in the future would help the in vitro and in vivo studies to enhance the possibility of using Eucalyptus in clinical practice. The below mentioned wet lab studies were possible that can be carried out in future can be listed as below: (i) The synergistic effect of TR can be tested with other compounds; (ii) to test how far these are useful in combinatorial chemotherapy; (iii) its role in targeting multiple arms of the immune system machinery; (iv) Identification and effect of structurally modified E. tereticornis compounds as trypanosomal inhibitors; and (v) real-life challenges and possibility in bringing up these inhibitors as orally available drugs or even as energy drinks.

AUTHORS’ CONTRIBUTIONS

Aarthi Rashmi B guided the research. Vasanth Nirmal Bosco supervised the research. Priyanka K interpreted the results. Harishchander A prepared the manuscript with a highlight on critical points.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Table 19: Selected compounds with the least binding energy

| S. No | Protein                          | Ligand   | Binding energy (kcal/mol) | No. of h-bond interactions (angstroms) |
|-------|---------------------------------|----------|--------------------------|---------------------------------------|
| 1     | Trypanothione reductase (3QFX)  | Betulonic acid | -15.66                  | 1 (2.90000)                           |
| 2     | Adenosine kinase (3OTX)         | Euglobal  | -12.24                   | 3 (7.15618, 2.947590, and 2.544139)   |
| 3     | Adenosine kinase (3OTX)         | B-pinene  | -10.31                   | 0                                     |
| 4     | Adenosine kinase (3OTX)         | A-pinene  | -10.3418                 | 0                                     |
| 5     | Adenosine kinase (3OTX)         | P-cymene  | -10.6045                 | 0                                     |