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An In Silico Study to understand the effect of Dihydrohelenalin against Tyrosine-protein phosphatase non-receptor Type 6 for the Treatment of Rheumatoid Arthritis

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Abstract
Rheumatoid arthritis is an autoimmune disease causing chronic inflammation which affects the joints, connective tissues, muscle, tendons and fibrous tissue. It is more common in females than males. This disease is not the result of action of genes, it is a person's autoimmunity which cause them this disease. This further cause medical problems with lungs, nerves, skin, eyes, heart. This cannot be cure but treated by using anti-rheumatic drugs and we are in great demand of such drugs. So, the current research was carried to study the effect of receptor Tyrosine Protein phosphatase (RPTPs) on the target protein molecule with the help of molecular docking to treat the rheumatoid arthritis (RA). Therefore, different compounds or ligands were selected for the treatment of RA. To screen the RPTPs target protein with ligand compounds using computer aided molecular modelling. Ligand with the target protein was docked using molecular docking software. The protein structure was retrieved by online databases and molecular docking of Dihydrohelenalin compounds with RPTPs was performed by Autodock Vina. This it is remarkable to consider the ligand for further validation and future process for the treatment of RA. Therefore, ligand can be used for further study through in vivo and in vitro studies.

Keywords: *Rheumatoid Arthritis, Autoimmune, Autodock Vina, Molecular Docking, Ligand*

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I. INTRODUCTION

Rheumatoid Arthritis which is also known as RA is autoimmune disease which causes immense pain in joints and bones. As there is no cure for RA, the treatment goals are to reduce the pain and stop/slow further damage. The cause of deaths in RA patients are different from general population which are as were infectious diseases (20.5%), respiratory diseases (16%, mainly interstitial pneumonia and chronic obstructive lung diseases), and gastrointestinal diseases (14.7% chiefly perforation or bleeding of peptic ulcer) [4]. In the West, the prevalence of RA is believed to be 1–2% [1,2], and 1% worldwide [3]. RA is a Autoimmune disease that initially affects small joints, progressing to larger joints, and eventually the skin, eyes, heart, kidneys, and lungs. Often, the bone and cartilage of joints are destroyed, and tendons and ligaments weaken [5]. Patients with RA are at greater risk for serious infection, respiratory disease, osteoporosis, cardiovascular disease, cancer, and mortality than the general population [6].

Seropositive, seronegative and juvenile idiopathic arthritis are three different types of RA which classified on the basis of the presence of the Ab/protein which produce when immune system is attacked. The diagnosis is based on the presence or absence of the Ab/protein in the body through different diagnostic tool kits. In seropositive and seronegative the factor known as rheumatoid factors (RF) is presence and absence respectively. RF factors is determined by the presence of the Ab/protein in the body. Juvenile idiopathic arthritis is the common among all three types of RA which found in children below the age of 17.

Fibroblast Like Synoviocytes (FLS) plays an important role in the mediating the action of inflammation and joint destruction in the body of RA patient. The FLS cells enter through the extracellular matrix which further produce cartilage degrading proteases and inflammatory cytokines [7]. The behaviour of FLS is controlled by multiple interconnected signal transduction pathways involving reversible phosphorylation of proteins on tyrosine residues. In this in silico study we deal with the PTPs (protein tyrosine phosphatase) which is our target protein and three different natural occurring compounds to find the best protein-ligand complex which can be helpful in the treatment of RA through molecular Docking.

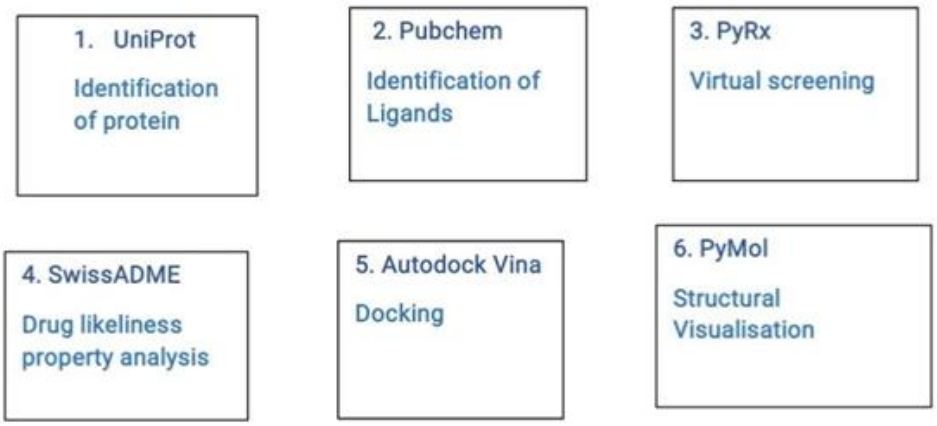


Figure1: Software and Tools

1.1 Methodology

1.1.1 Identification of Protein

Protein tyrosine phosphatases (PTPs) have emerged as a new class of signalling molecules and Based on their cellular localization they are also classified as receptor-like or intracellular PTP [9]. Protein Tyrosine Phosphatase (PTPs) has a role in the FLS activity which are the meditators of inflammation and joint destruction. In this study we take Tyrosine Protein phosphatase non-receptor type 6 which play a key role in haematopoiesis. This protein modulates signalling by tyrosine phosphorylated cell surface receptors such as KIT and the EGF receptors [8].

Obtained the tyrosine-protein phosphatase non-receptor type 6 structure from Protein Data Bank (PDB) https://www.rcsb.org/ and downloaded protein in pdb format.

1.1.2 Identification of Ligands

There are three natural compunds- sulfonamides, Thiophenes, Dihydrohelenalin which are selected and used as a ligand in the study.

- Sulfonamides represent a large class of antibiotics. Antibiotics has been used in treating the RA since 1930s and it begins from the use of sulphonamide [10]. Sulphonamides were derived from the sulfor containing chemical- sulfanilamide. This is a natural product which was isolated from a marine sponge, and the remainder isolated from the streptomyces species [11].
- Thiophenes represent the class of compound with biological activities. Various tri and tetra substituted thiophene Derivatives and their anti-inflammatory activity are Well documented in literature [12,13]. This compund has a anti-inflammatory property due to which it has a great effect in the RA treatment.
- Dihydrohelenalin Is a alcoholic extracts prepared form Arnicae flos, which also known as flowerheads from Arnica montana and A. chamissonis ssp. Foliosa, is an anti-inflammatory remedies which are used therapeutically [15].

All-natural compounds have been selected according to the literature. By using PubChem https://pubchem.ncbi.nlm.nih.gov/., These natural compounds are retrieved in SDF format. After that Online SMILES translator https://cactus.nci.nih.gov/translate/, is Used for converting all ligands, from SDF to pdb format and downloaded.

1.1.3 Virtual Screening by PyRx

Virtual screening of the ligands has been done through PyRx software. The PyRx software has shown the affinity and binding Energy of every ligand using virtual screening. Firstly, open a PyRx window and loaded the protein molecules which were in pdb Format. The protein molecule was converted from pdb format to pdbqt format. Then, ligand molecules that have sdf format were Also imported. Minimized all the energies of ligands and converted all ligands molecules from sdf format to pdbqt format. On the Basis of their binding affinity, the results were analyzed.

1.1.4 Drug Likeliness property analysis

Based on drug likeliness properties, natural compounds were selected for studies of molecular docking. Based on the Five rules of Lipinski screened the ligands.

Following Lipinski's rules of five states are [14]:-

1. Hydrogen bond [H-bond] acceptors less than 10.
2. Hydrogen bond [H-bond] donors less than 5.
3. Molecular mass not more than 500Da.

4. Must be less than 5 partitions co-efficient (LogP).
5. More than one rule cannot be violated.

Analyzed the five Lipinski's rules using SwissADME http://www.swissadme.ch/., an online web server. Firstly copy the SMILE Notation of ligands from PubChem. This SMILE notation was submitted on SwissADME and the analysis of the five rules of Lipinski.

1.1.5 Docking by AutoDock Vina through MGL tools

Load the protein targets on the graphical window of Auto dock Vina in pdb format. Water molecules of protein molecules were Deleted. The polar hydrogen atoms and Kollman charges are also added to protein molecules. Then, the protein molecule was Converted into pdbqt format and saved. The ligand molecule in pdb format was imported. Convert the ligand molecule from pdb Format to pdbqt format. Protein molecules, as well as ligand molecules, were loaded on a graphical screen and set the boundaries Of the grid box. Both protein and ligand molecule to be docked, using command prompt was carried out and analyzed the result And grid box was analyzed and prepared as shown in figure 2.

1.1.6 Structural Visualisation

Structural visualization of protein was done by PyMol software which is freely available on the internet. The protein Pdbqt format That automatically saved with the name of the output pdbqt file in a selected folder after Auto dock vina were loaded on the Graphical screen of the PyMol tool. After that protein and ligand interaction was visualized and analyzed.

II. RESULT AND DISCUSSION

The results obtained are as discussed below.

The tyrosine protein phosphatase non-receptor type 6 was retrieved in pdb format from Protein Data Bank [Figure 3] and The 3D structure of the protein [figure 4].

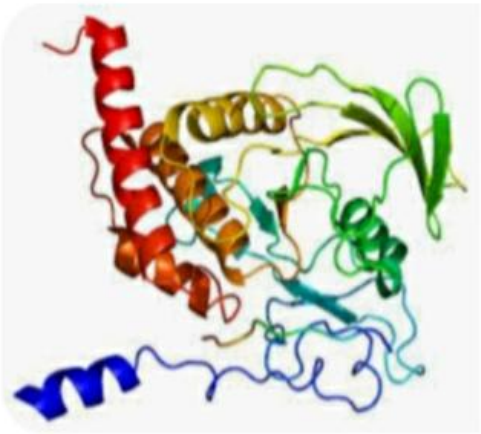


Figure 3: 2D Structure of Tyrosine-protein phosphatase protein non-receptor type 6.
type 6

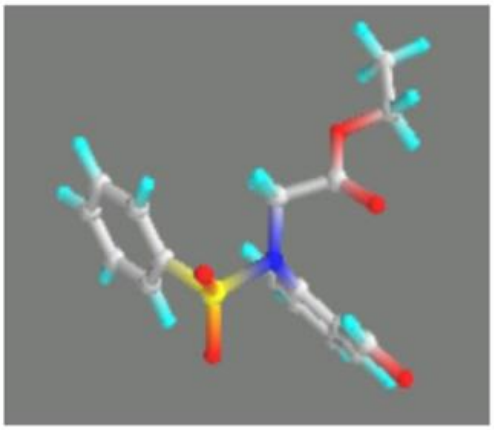


Figure 4: 3D Structure of Tyrosine-Phosphatase non-receptor

Sulfonamides (CID: 91392493), Thiophenes (CID: 8030), Dihydrohelenalin (CID: 3032910) were downloaded in sdf format and 2D And 3D structure [Table: 1].

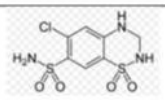
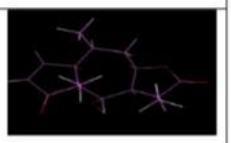
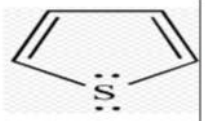
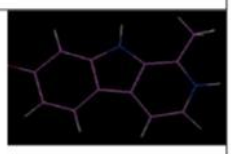
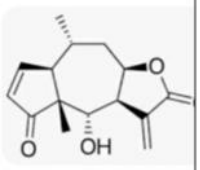
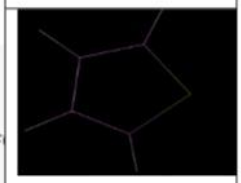
Ligands	CID	Molecular Weight	Molecular Formula	2D structure	3D structure
Sulfonamides	91392493	170.21 g/mol	RSO2 NH2		
Thiophenes	8030	84.14 g/mol	C4H4S		
Dihydrohelenalin	3032910	262.30 g/mol	C15H20O4		

Table 1: Structure of Ligands

Through PyRx software, the virtual screening of all three ligand molecules such as sulfonamides, Thiophenes, and Dihydrohelenalin was done. The binding affinity values of all three ligands are: sulfonamides was -3.2, Thiophenes was -3.2, and Dihydrohelenalin was -1.5 [Table: 2]. After the PyRx result, the selected ligands were Thiophenes and Dihydrohelenalin. After that drug likeliness Properties were analyzed of these selected ligands. The drug-likeness property analysis of these ligands was done with the help Of SwissADME software [Table: 3]. According to Lipinski's Rule of Five, the ligands were screened. The SwissADME result Showed that Dihydrohelenalin was qualified for all Drug properties.

Name of Compunds	Ligands	Binding Affinity	Mode	RMSD Lower Bond	RMSD Upper Bond
Sulfonamides	Protein_c1_uff_E =610.92	-3.2	0	0	0
Thiophenes	Protein_c2_uff_E= 355.54	-3.2	0	0	0
Dihydrohelenalin	Protein_c3_uff_E=212.66	-1.5	0	0.0	0.0

Table 2: PyRx Result

Ligands	Molecular weight	No of H-bond acceptors less than 5	No of H-bond donors less than 5	Log Po/w (MLOGP) less than 5	Lipsinki
Thiophenes	84.14 g/mol	0	0	1.12	0 violation
Dihydrohelenalin	262.30 g/mo	4	1	1.62	0 violation

Table 3: SwissADME Table

The qualifying molecule Dihydrohelenalin was docked with target protein Tyrosine-protein phosphatase non-receptor type 6 through Auto dock Vina (MGL tool). The Auto Dock Vina results show 9 different values of binding affinity, (RSMD lower bound), (RMSD upper bound) [Table 4]. The protein target Tyrosine-protein phosphatase non-receptor type 6 and Dihydrohelenalin interaction was visualized through PyMol software [Figure 5].

Mode	Binding Affinity (K cal/mol)	Distance from best mode RMSD Lower Bond	Distance from best mode RMSD Upper Bond
1	-8.6	0	0
2	-8.5	22.023	24.020
3	-8.5	12.511	13.642
4	-8.4	11.806	13.336
5	-8.4	18.415	26.158
6	-8.4	15.055	19.115
7	-8.4	12.037	17.971
8	-8.3	18.056	19.850
9	-8.3	15.915	22.455

Table 4: Result of AutoDock Vina

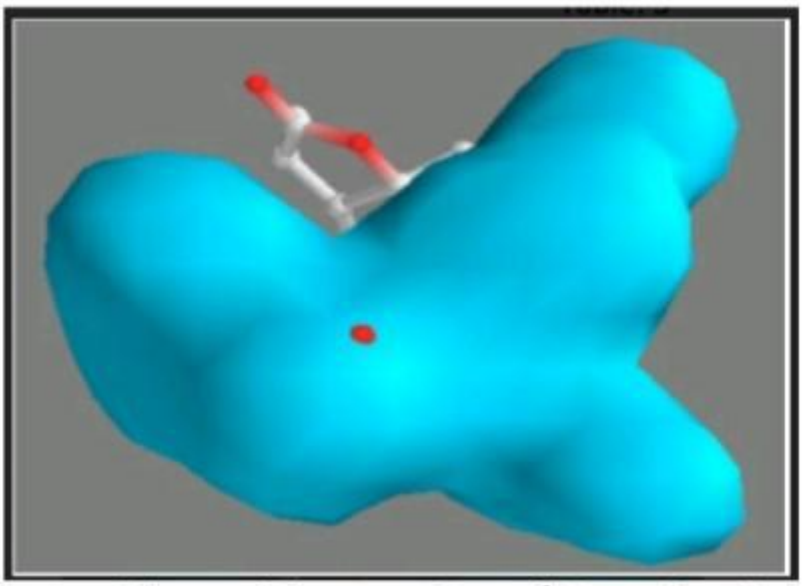


Figure 4: Interaction of Tyrosine Protein and Dihydrohelenalin Ligand

III. CONCLUSION

Tyrosine-protein phosphatase non-receptor type 6 was used for docking studies. Molecular docking is a useful tool for the drug discovery. This approach was used to study the potential of naturally occurring compounds such as sulfonamides, Thiophenes and Dihydrohelenalin with target Tyrosine-protein. Docking results were analysed for the best ligands on the basis of drug likeliness property analysis. In this study, Dihydrohelenalin was found as the best ligand with minimum binding affinity value and this compound is also qualified Lipsinki's rule of five. The result of this study was helpful in understanding the structure characteristics required to improve inhibiting activities. Dihydrohelenalin may act as a drug against the rheumatoid arthritis. After both in vivo as well as in vitro, Dihydrohelenalin may be a promising drug for treating the rheumatoid arthritis disease in the future.

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