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IN SILICO STUDY OF ANTITUBERCULOSIS POTENTIAL OF PHYTOCOMPOUNDS OF ANDROGRAPHİS PANİCULATA AND THEIR ADMET ANALYSIS

Narayan Sarkar[1*], Dr. Namita Deka[2], Dr. Suresh Bharali[3], Bidyut Bikash Deka[4], Dipak konwar[5], Dr. Gunajit Kalita[6]

[1*]Msc.Botany student , Dept of Botany, Gauhati University (sarkarnarayn8@gmail.com)
[2]Assistant professor, Dept of Botany, Nalbari college (namitadeka8@gmail.com)
[3]Associate Professor, Dept of Botany, Tihu college (sureshbharali@gmail.com)
[4]Assistant Professor, Dept of Botany, Barama College (bidyutbikash.deka@gmail.com)
[5]Assistant Professor, Dept of Botany, Pub Kamrup College,Baihata (dipak@pubkamrupcollege.org)
[6]Assistant Professor, Dept of Botany,Nalbari College, Nalbari (gunajitkal@gmail.com)

***Corresponding Author:** Narayan Sarkar
[*]Msc.Botany student , Dept of Botany, Gauhati University (sarkarnarayn8@gmail.com)

Abstract:
Objectives: Tuberculosis is caused by the bacterium *Mycobacterium tuberculosis*. It is an infectious disease which affect the lungs adversely. There are several strains of *Mycobacterium tuberculosis* in India like MDR(Multi drug resistant TB) and XDR(extremely drug resistance TB).So, it is crucial to develop plant based new drugs.
Methodology: Several medicinal plants have been used traditionally in India to treat some Respiratory diseases like Cold, Cough etc. In this study, The phytocompounds of a traditionally used medicinal plant *Andrographis paniculata* was extracted by GC-MS analysis. The effectiveness of these compounds was screened against the enzyme 3-dehydroquinate dehydratase of Mycobacterial shikimate pathway . Molecular docking study was done to identify the phytocompounds which have highest binding affinity with this enzyme. Later Drug-likeness of these phytocompounds was studied followed by ADMET analysis.
Findings: The result of molecular docking showed that the compounds Andrographin has highest binding affinity with 3-dehydroquinate dehydratase. This compound has good drug-like properties and obeys Lipinski's rule of five. Later ADMET analysis reported that this compound have good absorption range , good bioavailabity score and less toxicity.
Novelty: By Molecular docking, one phytocompound Andrographin from Andrographis panicullata was identified which can inhibit the mycobacterial enzyme so that the pathogen can not synthesize aromatic amino acids through shikimate pathway and can not survive inside the host cell. So, this compound may be used as lead molecule for development of future anti-tuberculotic drug.

Keywords: Shikimate Pathway, Molecular docking, ADMET analysis, Lipinski's Rule of 5.

1. INTRODUCTION

Tuberculosis (TB) is one of the most lethal respiratory infections caused by the organism *Mycobacterium tuberculosis.* The organism primarily proliferates in lungs to stimulate the hostimmune system which specifically activates the phagocytes.[1] This result into a mass referred to as a granuloma, which consists of necrotic lung tissue and immune cells such as T-cells, B-cells and macrophages. Reactivation of TB occurs when those with latent TB infection progress to active infection, the organism can still persist for decades within a granuloma structure and as a result of an immune compromising

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events (Diabetes, HIV, Cancer) the bacteria can reactive to its infectious form.

Several drugs are available for the treatment of TB. These drugs can be classified into two categories: first line drugs such asisoniazid (INH), rifampin (RIF), pyrazinamide (PZA), ethambutol (EMB) etc. and second line drugs like para amino salicylate (PAS), kanamycin,cycloserine (CS), ethionamid (ETA), amikacin, capreomycin, thiacetazone, fluoroquinolones etc. An increase in the number of TB patients is attributable to the insufficient supply or low quality of anti TB drugs. In the treatment of tuberculosis one of the major hurdles has become the emergence of multi-drug resistance *Mycobacterium Tuberculosis*. In such circumstances, the second line drugs are prescribed in combination with DOTS which is very expensive, has to be administered for a longer duration and has significant side effects. Traditionally used drugs have earned a little success due to the time and cost involved in development of anti-tuberculosis drug. Numerous reports have demonstrated the cause and emergence of multidrug-resistance of *M. tuberculosis*. To improve the treatment of these strains there is a rising need to develop anti-TB effective drugs. The appearance of an incurable from of TB is a frightening prospect that has potentially disastrous consequences for humanity (WHO Global tuberculosis report, 2019). It is particularly worrying because only one new TB drug (Bedaquiline) has been approved by the FDA since the 1960s. Various pharmaceutical companies encounter hurdles for the discovery of drugs for TB treatment. Clearly, the development of new classes of anti-TB drugs is of global importance. New targets are a priority, since attacking the bacterium using multiple strategies provides the best means to prevent resistance. Compound acquisition, library-related data management and compound testing are in drug discovery are carried out by various software's.[2]

From ancient times natural products are being considered as potent sources of antimicrobials because of their amazing chemical diversity. Plants and microbes have the potentiality to fight against environmental infections using their chemical arsenal ofsecondary
metabolites and therefore many types of different structures have been reported to display an antimicrobial function.[3-4]. Present study includes screening of the potent ligands of traditionally used plant compounds *Andrographis paniculata* against the selected receptors 3-Dehydroquinate dehydratase through computer aided drug discovery. Although no single drug has been designed solely by computer techniques, the contribution of these methods to drug discovery could not be denied. All the world's major pharmaceutical and biotechnology companies use computational design tools. At their lowest level the contributions represent the replacement of crude mechanical models by displays of structure which are a much more accurate reflection of molecular reality, capable of demonstrating motion and solvent effects. Subsequently, theoretical calculations permit the computation of binding free energies and other relevant molecular properties. Compound acquisition, library-related data management and compound testing are in drug discovery are carried out by various software.

Mycobacterium metabolic pathways which do not appear in the host but present in the
pathogen are identified as pathways unique to mycobacterium as compared to the host. Enzymes in these unique pathways as well as enzymes involved in other metabolic pathways under carbohydrate metabolism, amino acid metabolism, lipid metabolism, energy metabolism, vitamin and cofactor biosynthesis and nucleotide metabolism are important to identify novel drug targets. An important question to be addressed while choosing potential drug targets is whether the biochemical pathway to be targeted is unique to bacteria. These biochemical pathways which are; Peptidoglycan biosynthesis, Mycobactin biosynthesis, d-alanine metabolism, thiamine metabolism and polyketide sugar unit biosynthesis, all absent in the host and therefore unique to the pathogen. Design and targeting inhibitors against these non-homologous sequences could be the better approach for generation of new drugs.[5]

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An attractive target for the development of antimicrobial agents is the Shikimate pathway because it is essential in bacteria, fungi, plants but absent from mammals. This involved seven enzymatic steps where phosphoenolpyruvate (PEP) and D-Erythrose -4-phosphate (E4P) are condensed to the branch point compound Chorismate. This chorismate is converted to tryptophan, tyrosine and phenylalanine (Nunes *et al.,* 2019)[6]. The mycobacterial genetic determinants allow these cells to overcome the host defense, which attempts to starve mycobacteria of tryptophan by a CD4 T-cell mediated killing mechanism. *M. tuberculosis* however can synthesize tryptophan (from chorismate precursor) under stress conditions and thus starvation fails. Accordingly, inhibition of any enzyme of the Mycobacterial shikimate pathway should preclude tryptophan biosynthesis and there by increase the likelihood of starvation as an efficient mechanism of killing afforded by the human host.

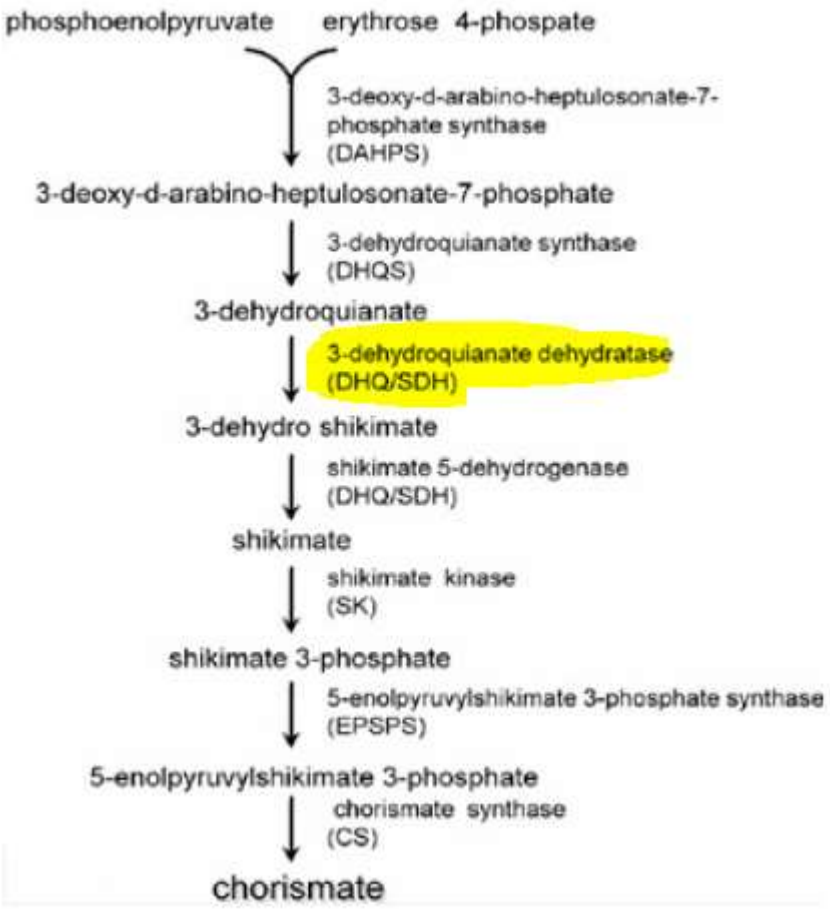

Fig.1: Shikimic acid Pathway

In silico drug discovery is the process of discovering and designing lead compounds against the specific target proteins of the disease causing organism. It includes target identification, target validation, lead identification, lead optimization and introduction of the new drugs to the public. This is a novel approach to analyze the causes of the disease and to configure all the possible ways for the remedy.

Therefore, the current project has been aimed to screen new ligands as drug candidates using different computationally based methods. It includes following objectives:

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1.To screen novel lead compounds of *Andrographis paniculata* against the target protein 3-Dehydroquinate dehydratase (3qbe) of *Mycobacterium tuberculosis* using DOCKING software package (AutoDock Vina).

2. To study the drug like properties of the selected molecules including ADME-Tox studies to establish the selected molecules as potential lead molecules for discovery of novel anti-tuberculosis drug(s).

2. MATERIALS AND METHODS

2.1. Preparation of Targat Proteins(Receptors):

From the literature it has found that 3 -dehydroquinate dehydratase is one of the good targets for the drug discovery.This target protein(enzyme) with PDB ID: 3QBE, was searched in Protein Data Bank(http://www.rcsb.org/pdb/home/home.do) . The structure of this protein was downloaded in PDB format. With the help of Chimera the water molecules and the binded ligands along with solvents were removed and added polar hydrogen.

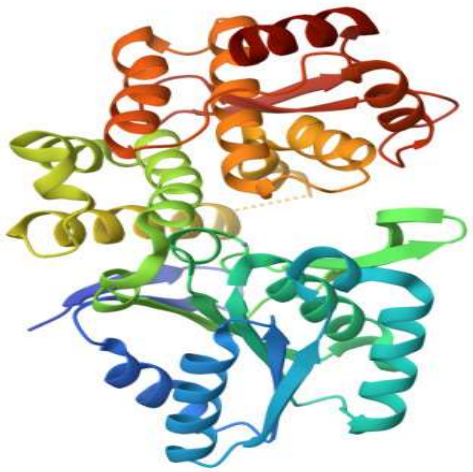

Fig.2: Structure of 3-Dehydroquinate dehydratase

2.2.Preparation of the Ligands:

The phytocompounds of Andrographis paniculata was extracted by GC-MS in outsource laboratory. 2D structures and Basic Chemical properties of the various *Curcuma longa* test compounds used in the present study are constructed in Accelrys Draw 4.2. The default root, rotatable bonds, and torsions of the ligand were set by TORSDOF utility in AutoDock Tools.

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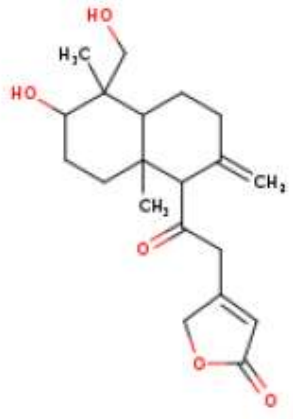

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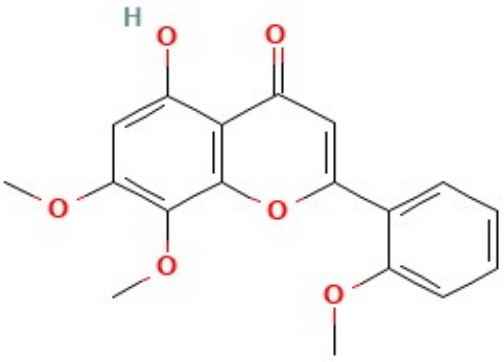

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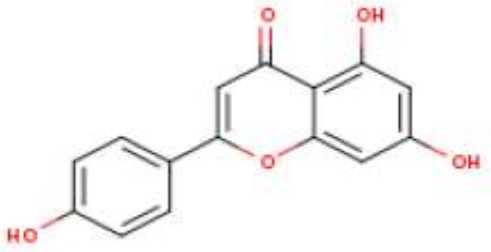

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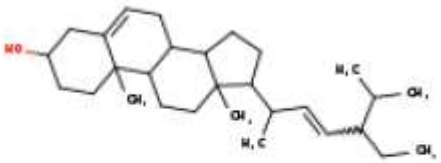

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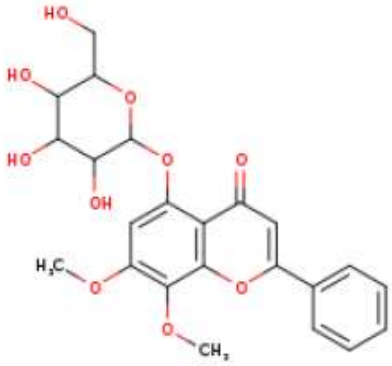

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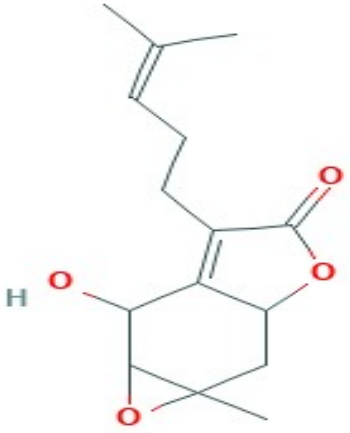

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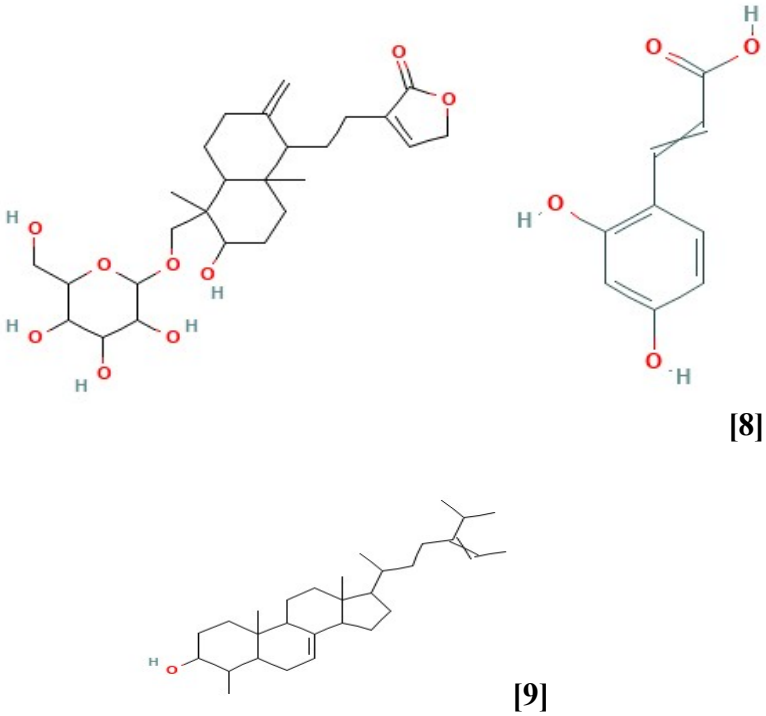

[7] **[8]**

[9]

Fig3:2D structures of the ligands

1. 14Deoxy-11-oxoandrographolide , **2.** Andrographin , **3**. Apigenin, **4.** Stigmasta-5,22-dien-3-ol
5. 7,8-Dimethoxy-2-phenyl-5-[3,4,5-trihydroxy-6- (hydroxymethyl)oxan-2-yl]oxychromen-4-one
6. 6-Hydroxy-1a-methyl-5-(4-methylpent-3-enyl)-2,2a,6,6a-tetrahydrooxireno[2,3-f][1]benzofuran-4-one
7. 4-[2-[6-hydroxy-5,8a-dimethyl-2-methylidene-5-[[3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxymethyl]-3,4,4a,6,7,8-hexahydro-1H-naphthalen-1-yl]ethyl]-2H-furan-5-one
8. (2E)-3-(2,4-Dihydroxyphenyl)acrylic acid
9. 4-Methylstigmasta-7,24(28)-dien-3-ol

2.3 Drug-likeness of the phytocompounds:
Drug like properties of the phytocompounds were calculated by uploading the SMILES to the SwissADME Online server.The properties such as molecular weight, hydrogen bond acceptors, hydrogen bond donors, Topological Polar Surface Area(TPSA) , MlogP, etc. were calculated to determine weather the compound obeys Lipinski's Rule of 5(RO5).

2.4 Molecular Docking:
The molecular docking study of 9 phytocompounds of *Andrographis paniculata* against the receptor 3-dehydroquinate dehydratase(3qbe) was done by Autodock vina.[7] The protein ligand interaction was visualized by PyMOL softwere[8] and 2D structure of protein –ligand interaction was visualized in Discovery Studio Visualizer. [9]

2.5.ADMET analysis:
Absorption , Distribution, Metabolism, Excretion and Toxicity of the compound was calculated by pkCSM online tool webserver (http://biosig.unimelb.edu.au/pkcsm/prediction.)
Bioactivity score was predicted by Molinspiration Online Tool. Again Drug like score was calculated

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by Molsoft Online server.[10-14]

3.RESULTS:

3.1.Drug likeness of the phytocompounds:

All the phytocompounds have Molecular weight <500, hydrogen bond donors <5, Hydrogen bond acceptor < 10, PSA<140. Therefore all of them have good drug like property and obeys lipinski's rule of 5. The drug likeness of the compounds is shown in table1

Table1: Drug likeness of the phytocompounds

Compound Name	MW	HBA	HBD	TPSA	MlogP	RO5	nVio
1. 14Deoxy-11-oxoandrographolide	348.43 g/mol	5	2	83.83 Å²	1.89	YES	0
2. Andrographis	328.32 g/mol	6	1	78.13 Å²	0.70	YES	0
3. Apigenin	270.24 g/mol	5	3	90.90 Å²	0.52	YES	0
4. Stigmasta-5,22-dien-3-ol	412.69 g/mol	1	1	20.23 Å²	6.62	YES	1
5. 7,8-Dimethoxy-2-phenyl-5-[3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one	460.43 g/mol	10	4	148.05 Å²	-1.18	YES	0
6. 6-Hydroxy-1a-methyl-5-(4-methylpent-3-enyl)-2,2a,6,6a-tetrahydrooxireno[2,3-f][1]benzofuran-4-one	264.32 g/mol	4	1	59.06 Å²	1.62	YES	0
7. 4-[2-[6-hydroxy-5,8a-dimethyl-2-methylidene-5-[[3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxymethyl]-3,4,4a,6,7,8-hexahydro-1H-naphthalen-1-yl]ethyl]-2H-furan-5-one	496.59 g/mol	9	5	145.91 Å²	0.48	YES	0
8. (2E)-3-(2,4-Dihydroxyphenyl)acrylic acid	180.16 g/mol	4	3	77.76 Å²	0.70	YES	0
9. 4-Methylstigmasta-7,24(28)-dien-3-ol	426.72 g/mol	1	1	20.23 Å²	6.82	YES	1

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MW- Molecular weight , **HBA**- Hydrogen bond acceptor , **HBD**-Hydrogen bond donor
TPSA- Topological polar surface area, **RO5**- Lipinski's Rule of 5, **nVio**- Number of violations

3.2.Molecular Docking:

Molecular docking results shows the different binding affinities of these ligands to 3-dehydroquinate dehydratase. The compound Andrographin has highest binding affinity (-9.1) to the receptor. The docking scores are shown in table 2.

Table2: molecular docking result

Compound Name	**Docking Score**
1. 14Deoxy-11-oxoandrographolide	-7.7
2. Andrographin	-9.1
3. Apigenin	-7.9
4. Stigmasta-5,22-dien-3-ol,	-6.9
5. 7,8-Dimethoxy-2-phenyl-5-[3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one	-8.6
6. 6-Hydroxy-1a-methyl-5-(4-methylpent-3-enyl)-2,2a,6,6a-tetrahydrooxireno[2,3-f][1]benzofuran-4-one	-6.9
7. 4-[2-[6-hydroxy-5,8a-dimethyl-2-methylidene-5-[[3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxymethyl]-3,4,4a,6,7,8-hexahydro-1H-naphthalen-1-yl]ethyl]-2H-furan-5-one	-8.4
8. (2E)-3-(2,4-Dihydroxyphenyl)acrylic acid	-5.7
9. 4-Methylstigmasta-7,24(28)-dien-3-ol	-9.0

3.3. Visualization of protein-ligand interaction:

The 2D structure of Protein-ligand interaction shows that the compound Andrographin can bind to the active centre of the enzyme 3-dehydroquinate dehydratase through different kind of interactions such as Hydrogen bonds, Van der walls interaction etc. Total 16 amino acids are invovled in this interaction which is shown in Fig.2.

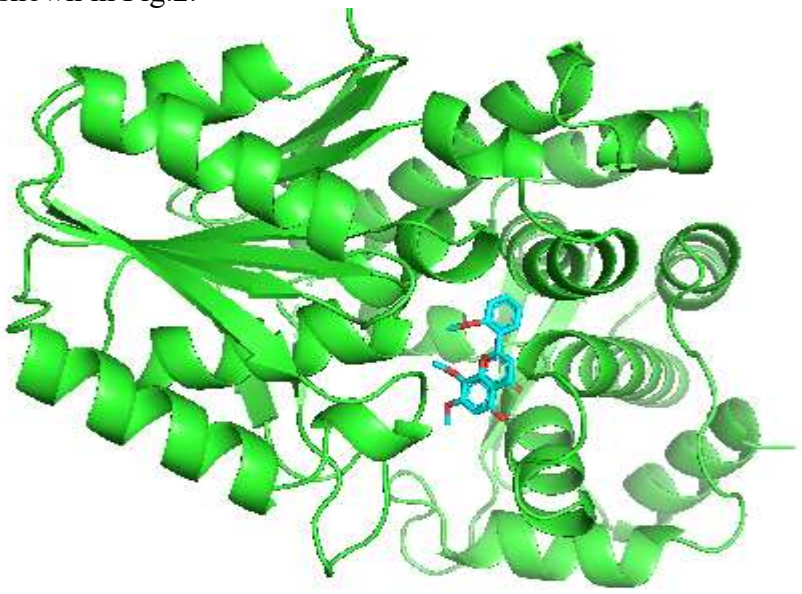

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Fig.2.a) Interactrion of 3-dehydroquinate dehydratase with Andrographin is visualized in pyMOL.

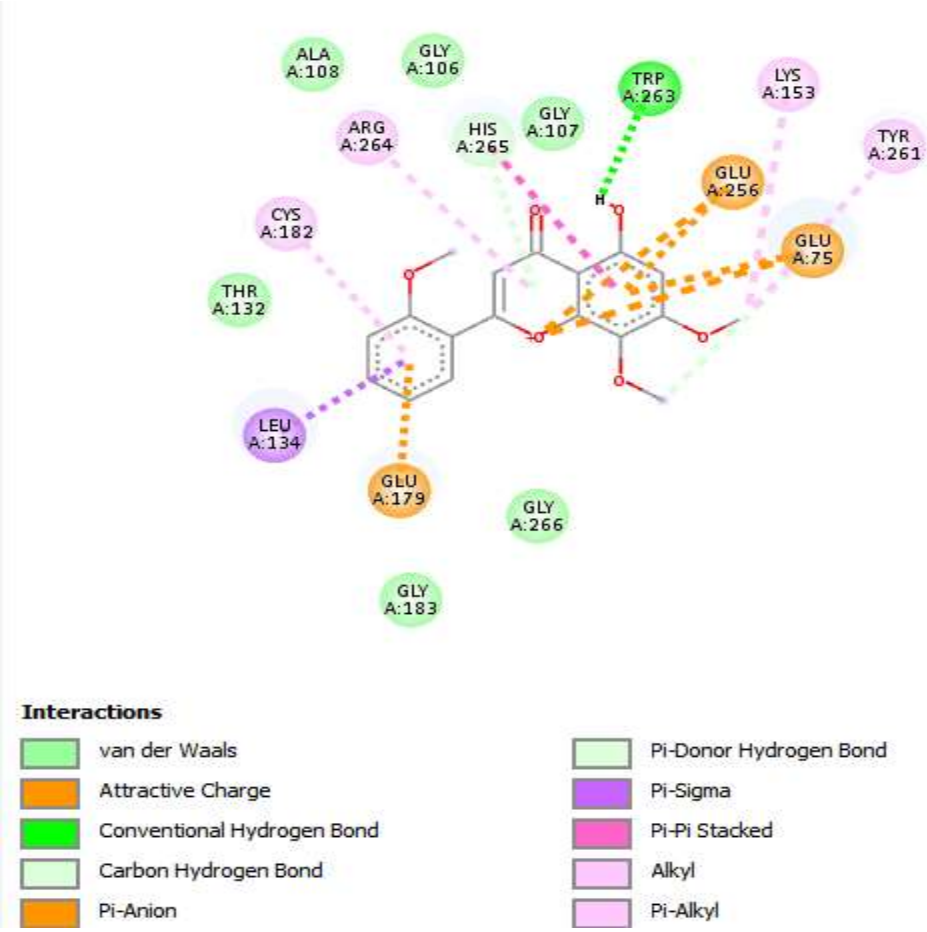

Fig2:b) Interactrion of 3-dehydroquinate dehydratase with Andrographin is visualized in Discovery studio visualizer.

3.4.ADMET analysis of Andrographin:
ADMET prediction using pkCSM

Prediction Test		ValuePrediction
1. Absorption		
Water solubility		-3.547
Caco2 permeability		1.229
Intestinal absorption (human)		95.965
Skin Permeability		-2.754
P-glycoprotein substrate		YES
P-glycoprotein inhibitor	I	NO

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P-glycoprotein II inhibitor		YES
2.Distribution		
VDss (human)		-
	0.159	
Fraction unbound (human)	0.124	
BBB permeability	-0.615	
CNS permeability		- 2.326
3.Metabolism		
CYP2D6 substrate		NO
CYP3A4 substrate	YES	
CYP1A2 inhibitior	YES	
CYP2C19 inhibitior	YES	
CYP2C9 inhibitior	NO	
CYP2D6 inhibitior	NO	
CYP3A4 inhibitior		NO
4.Excretion		
Total Clearance	0.374	
Renal OCT2 substrate		NO
5.Toxicity		
AMES toxicity	NO	
Max. tolerated dose (human)	0.143	
hERG I inhibitor	NO	
hERG II inhibitor	NO	
Oral Rat Acute Toxicity (LD50)	2.113	
Oral Rat Chronic Toxicity (LOAEL)	1.21	
Hepatotoxicity	NO	
Skin Sensitisation	NO	
T.Pyriformis toxicity	0.443	
Minnow toxicity		0.317

3.5.Boiled Egg analysis:

Gastrointestinal absorption and brain access are two pharmacokinetic behaviours crucial to estimate at various stages of the drug discovery process. The boiled egg analysis of Andrographin suggested that this compound could be absorbed by Gastrointestinal tract and it can cross the blood –brain –barrier.

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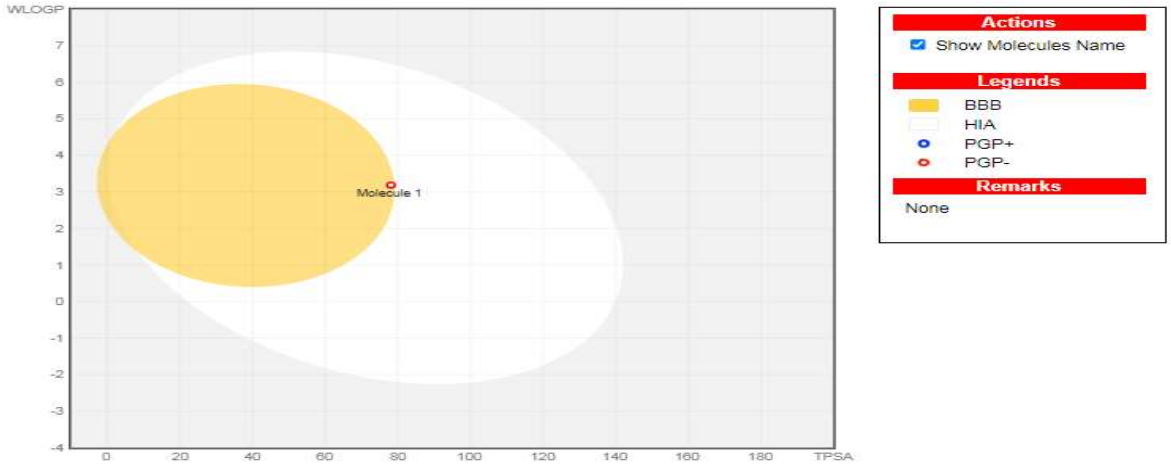
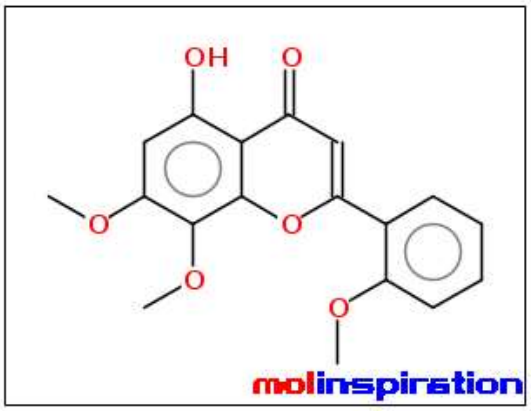


Fig3: boiled egg analysis of Andrographin

6.Bioactivity of Andrographin:

miSMILES: COc1ccccc1c3cc(=O)c2c(O)cc(OC)c(OC)c2o3
Andrographin



Molinspiration bioactivity score	v2022.08
GPCR ligand	-0.11
Ion channel modulator	-0.03
Kinase inhibitor	0.12
Nuclear receptor ligand	0.16
Protease inhibitor	-0.26
Enzyme inhibitor	0.24

Get data as text (for copy / paste).

Get 3D geometry BETA

7. Drug likeness of Andrographin as per Molsoft L.L.C

Molecular formula: C18 H16 O6

Molecular weight: 328.09

Number of HBA: 6

Number of HBD: 1

MolLogP : 3.35
MolLogS : -3.35 (in Log(moles/L)) 147.43 (in mg/L)

MolPSA : 61.00 A^2

MolVol : 332.57 A^3

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pKa of most Basic/Acidic group : <0. / 11.0
BBB Score : 3.57 The Blood-Brain Barrier (BBB)Score: 6-High,0-Low *(DOI: 10.1021/acs.jmedchem.9b01220)*

Number of stereo centers: 0
Drug-likeness model score: 0.29

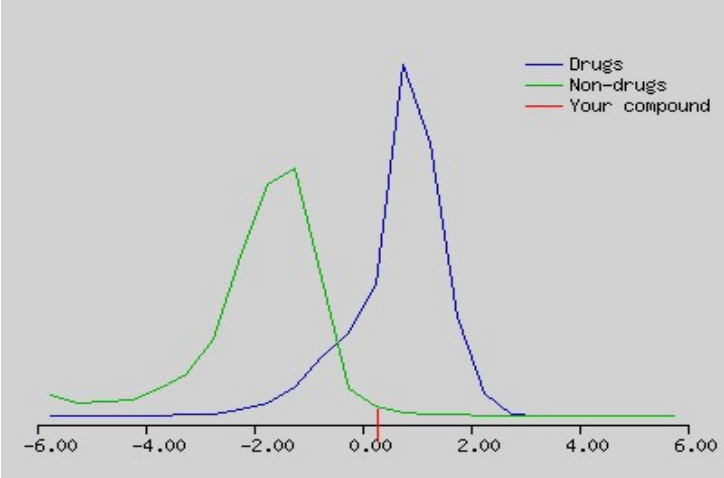

Fig4: The drug likeliness score of Andrographin is 0.29

4. DISCUSSION

4.1. Lipinski's Five Rule :

Computer aided drug discovery aims to discover a drug molecule to find new drug that can interact with the target receptor so that it can inhibit the function of the target protein. To apply the drug in human body ,it is mandatory to check wheather it obey Lipinski's Rule of 5. Based on these rules, 9 active compounds of the Andrographis plant were investigated to determine whether or not they matched the requirements of Rule Five using SwissADME. All the compounds obey Lipinski's Rule.

4.2. Docking Analysis and Visualization :

The result of molecular docking was visualized in Discovery studio visualizer. The compound Andrographin interact with the target enzyme 3-Dehydroquinate dehydratase through conventional hydrogen bond , carbon hydrogen bond , van der waal interaction etc. These bonds stabilize the receptor ligand interaction.

4.3. ADMET Prediction:

The compound Andrographin is difficult to dissolve in water, Caco2 permeability is high and intestinal absorption is also high. If absorption >80%, it is good and if <30% , it is bad.
(Chander et al., 2017). According to Pires et al., (2015), a compound is said to have relatively low skin permeability if it has a log value of Kp> -2.5. The compound Andrographin has skin permeability < -2.5.so, It has good skin permeability. This compound can be absorbed by P-glycoprotein and P-glycoprotein inhibitor II.
The compound is permeable to Blood brain barrier. This compound can not penetrate the CNS, this is said by Pires et al., (2015), the compound penetrates the CNS if the log PS is >-2.
AMES toxicity states that the compound Andrographin is not mutagenic. Maximum tolerated dose of this drug to human is 0.143.

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5.CONCLUSION

The compound Andrographin has a good binding affinity of -9.1 to the target enzyme 3-dehydroquinate synthase and the interaction is very good.This compound can inhibit the function of this enzyme of Mycobacterial shikimate pathway. This compound obey Lipinski's Rule of 5. Andrographin has good potential to exert antibacterial effect on *Mycobacterium tuberculosis* in the treatment of MDR-TB(Multi-drug resistant tuberculosis). It is necessary to conduct in vitro and in vivo tests to determine the activity of Andrographis plant compounds as an antibacterial for tuberculosis.

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