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In-Silico Screening of Novel Urec Inhibitors from *Eupatorium odoratum* using Molecular Docking Study

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KEYWORDS

Eupatorium odoratum,
Ure C,
anti-bacterial activity,
anti-mycobacterial activity,
anti- tuberculosis activity, docking.

A B S T R A C T

Eupatorium odoratum belongs to the family *Asteraceae*, is well known as a traditional medicinal plant, which is used to treat wounds in skin. The compounds, such as 2,4,6-tris-(1-phenylethyl)-phenol, 2(E)-3,7,11,15-tetramethyl-2-hexadecen-1-ol, 1-tricosanol, tetra-O-methylscutellarin identified from the aqueous and methanol extracts of *Eupatorium odoratum* are said to possess anti-tuberculosis, anti-bacterial and anti-mycobacterial activity. Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* and it affects lungs and other parts of the body. UreC (Urease subunit alpha) is a protein present in *Mycobacterium tuberculosis*, which prevents the acidification of host phagosome and thereby preventing the eradication of *Mycobacterium tuberculosis* by the host immune system. The 3D structure of UreC for *Mycobacterium tuberculosis* was not available in PDB, Hence Homology modelling were done using Modeller to predict the 3D structure of UreC protein. Structure evaluation can also be done to refine the 3D structure. *In-silico* molecular docking were performed using AutoDock to analyse and identify the interaction of the above compounds of *Eupatorium odoratum* with UreC protein. The 3D structure of UreC protein was predicted. Docking study showed good score for 2,4,6-tris-(1-phenylethyl)-phenol, 2(E)-3,7,11,15-tetramethyl-2-hexadecen-1-ol, 1-tricosanol, tetra-O-methylscutellarin in *Eupatorium odoratum* against UreC protein. The good docking score of these compounds are said to be a good inhibitor of UreC protein. Thus, the above compounds of *Eupatorium odoratum* have potential anti-bacterial activity. In addition tetra-O-methylscutellarin showed anti-mycobacterial activity and 2(E)-3,7,11,15-tetramethyl-2-hexadecen-1-ol showed anti-tuberculosis activity. Hence, these compounds of *Eupatorium odoratum* showed potential anti-bacterial, anti-mycobacterial and anti-tuberculosis activity.

Introduction

Eupatorium odoratum (Chromoleana odorata) is folklore medicinal plant, belongs to the family of Asteraceae, is a perennial scandent or semi-woody shrub (Doss *et al*., 2011), being using to treat many microbial diseases since times immemorial (Panyaphu *et al*., 2011). Traditionally this plant is used in coughs and colds, treatment of skin diseases (Joshi, 2013), wound healing and as a local antiseptic agent (Joshi, 2013: Phan *et al*., 2001). In traditional medicine, a decoction of the leaf is used as a cough remedy and as an ingredient with lemon grass and guava leaves for the treatment of malaria (Doss *et al*., 2011). *E. odoratum* leaf was found to possess antibacterial (Lavanya and Brahmaprakash, 2011), anti-inflammatory activity (Ayyanar and Ignacimuthu, 2009; Owoyele *et al*., 2005; Pauillac *et al*., 2009) and the fresh leaf is ground into paste and applied topically on affected places to heal wounds (Kilani, 2006). In folk medicine, the aqueous leaf extracts of the plant is used as antiseptic wound dressing. It is sometimes grown as a medicinal and ornamental plant. It is used as a traditional medicine in Indonesia. It's potential therapeutic properties are still unknown (McClatchey, 2002) and is reported to have anti-bacterial, anti-viral, anti-fungal, anti-helminthic, analgesic, hypotensive, anti-inflammatory and immune enhancing effects (Duke *et al*., 2002; Liu *et al*., 2001). There is great demand for its fruit juice in treatment for different kinds of illness such as arthritis, diabetes, muscle aches, menstrual difficulties, heart diseases, cancers, gastric ulcers, blood vessel problems and drug addiction.

The GC-MS analysis of aqueous and organic extracts of *E.odoratum* having strong antibacterial compounds such as 2,4,6-tris-(1-phenylethyl)-phenol, (2E)-3,7,11,15-Tetramethyl-2-hexadecen-1-ol, 1-Tricosanol, Tetra-O-methyl scutellarin among the revealed 43 phyto-constituents and in addition, (2E)-3,7,11,15-Tetramethyl-2-hexadecen-1-olshows anti-tuberculosis activity and Tetra-O-methyl scutellarin shows anti-mycobacterial activity (Venkataraman *et al*., 2012).

Tuberculosis is an airborne disease caused by the bacterium *Mycobacterium tuberculosis (M. tuberculosis).*It a lung infection and is one of the contagious and deadly diseases which have added to the woes of the mankind. The main reason for the widespread of this disease is the population growth, emergence of multi–drug resistant TB strains, financial burden in the developing countries and unsuccessful attempt to synthesize a new drug with novel mechanism of action. *Mycobacterium tuberculosis* (MTB) is a pathogenic bacteria species in the genus *Mycobacterium* and the causative agent of most cases of tuberculosis (Ryanand Ray, 2004). It is a small bacillus that can withstand weak disinfectants and can survive in a dry state for weeks. Its unusual cell wall, rich in lipids (e.g., mycolic acid), is likely responsible for this resistance and is a key virulence factor (Murray *et al*., 2005).When in the lungs, *M. tuberculosis*is taken up by alveolar macrophages, but they are unable to digest and eradicate the bacterium. Its cell wall prevents the fusion of the phagosome with thelysosome, which contains a host of anti-mycobacterial factors(Keane *et al*., 1997).

UreC (Urease subunit alpha) is a gene present in *Mycobacterium tuberculosis*, which involves in the urea degradation pathway. Consequently, the bacteria multiply unchecked within the macrophage. The bacteria also carry the UreC gene, which prevents acidification of the phagosome (Bell 2005)and thereby it subverts the macrophage phagosome.

In molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using for example scoring functions (Bursulaya *et al*., 2003; Ewing *et al*., 2001). The protein structure and a database of potential ligands serve as inputs to a docking program. Molecular docking algorithms fit molecules together in complementary fashions. The technique has attracted increasing attention as a way to predict the geometries of bimolecular complexes (Irawin Kuntz *et al*., 1994). Most of docking programs in use account for a flexible ligand, and a rigid protein receptor. The present study has been carried out to test the efficiency of the compounds in *Eupatorium odoratum* against tuberculosis UreC using molecular docking studies.

Materials and Methods

UniProt

UniProt is the Universal Protein resource, a central repository of protein data created by combining the Swiss-Prot, TrEMBL and PIR-PSD databases. It provides comprehensive, high quality and freely accessible resources of protein sequence and functional information. The UniProt databases are the UniProt Knowledgebase (UniProtKB), the UniProt Reference Clusters (uniRef) and the UniProt Archive (UniParc) (www.uniprot.org/) (Amos Bairoch *et al*., 2004).

BLAST

BLAST for Basic Local Alignment Search Tool is an algorithm for comparing primary biological sequence information, such as the amino-acid sequences of different proteins or the nucleotides of DNA sequences. BLAST is one of the most widely used bioinformatics programs for sequence searching (Casey, 2005). A BLAST search enables a researcher to compare a query sequence with a library or database of sequences, and identify library sequences that resemble the query sequence above a certain threshold.

Protein Data Bank (PDB)

The PDB is the single, freely accessible, global archive for information about the 3D structure of bio-macromolecules (Helen Berman *et al*., 2000) and their complexes, as determined by X-ray crystallography, NMR spectroscopy and cryo-electron microscopy, and includes more than a few Nobel Prize winning structure.

Modeller

MODELLER is a computer program for comparative protein structure modeling (Fiser *et al*., 2000). It can be described as "Modeling by satisfaction of restraints" uses a set of restraints derived from an alignment and the model is obtained by minimization of these restraints. MODELLER uses Python as its control language. All input scripts to MODELLER are hence, Python scripts. Comparative modeling consists of four main steps (Marti-Renom *et al*., 2000): (i) fold assignment that identifies overall similarity between the target and at least one known template structure;(ii) alignment of the target sequence and the template; (iii) building a model based on the alignment with the chosen template ; and (iv) predicting the accuracy of the model.

PDBsum

PDBsum is a web based database providing a largely pictorial summary of key information on each molecular structure deposited at the PDB (Roman Laskowski 2001). PDBsum is a validation program validates the predicted structure by checking

various parameters. PROCHECK statistics, a structure verification program which fully depends on the Ramachandran plot, determines the quality of the predicted structure by assessing various parameters such as lengths, angles and planarity of the peptide bonds, geometry of the hydrogen bonds, and side chain conformations of protein structures as a function of atomic resolution.

Pubchem

PubChem (https://pubchem.ncbi.nlm.nih.gov) is a public repository for information on chemical substances and their biological activities, launched in2004 as a component of the Molecular Libraries Roadmap Initiatives of the US National Institutes of Health (NIH). For the past 11 years, PubChem has grown to a sizable system, serving as a chemical information resource for the scientific research community. PubChem consists of three inter-linked databases, Substance, Compound and BioAssay (Sunghwan Kim *et al*., 2015).As per the January 2011Pubchem consists, Total Compounds-31 million entries (all-PubChem Compound Results), Substances-75 million entries and Bioassay, bioactivity results from 1644 high-throughput screening programs with several million values (Kaiser *et al*., 2005).

Chemsketch

ACD/Chemsketch is a molecular modeling program used to create and modify images of chemical structures. It is the interfacial graphic software for ACD/Labs suite by advanced Chemistry Development. Chemsketch provides customer templates. It meets extensive task duty requirements in drawing, 3D, spectral information, physical, chemical properties and customer programming. Chemsketch has the function of generating structures from SMILES and also produce SMILES from structures (Zhenjiang Li *et al*., 2004).

Open Babel

Open Babel is free software, a chemical expert system mainly used for converting chemical file formats(O'Boyle *et al* 2011).Due to the strong relationship to informatics this program belongs more to the category Chem informatics than to molecular modeling. It is available for Windows, UNIX, and Mac OS. It is distributed under the GNU GPL.

AutoDock

In order to carry out the docking simulation, we used the AutoDock 4.0 suite as molecular-docking tool (Morris GM *et al*., 1998). AutoDock is molecular modeling simulation software and it is a flexible ligand-protein docking program. It is free and is available under the GNU General Public License. It is designed to predict how small molecules, such as substrates or drug candidates bind to a receptor of known 3D structures. AutoDock 4 actually consists of two main programs: autodock performs the docking of the ligand to a set of grids describing the target protein; autogrid pre-calculates these grids. It is very fast, provides high quality predictions of ligand conformations and good correlations between predicted inhibition constants and experimental ones. The docking results are more accurate and reliable (Gauet Morris *et al*., 2013).The current version of AutoDock, using the Lamarckian Genetic Algorithm and empirical free energy scoring function, typically will provide reproducible docking results for ligands with approximately 10 flexible bonds (Protein- ligand docking with AutoDock).

Pymol

PyMOL is an open source, three dimensional visualization tool to view the macromolecular structures like proteins and nucleic acids. It is freely available, since it is an open source visualization tool with python (programming language) interpreter. PyMol is used to visualize .pdb files, which is mostly available from the protein data bank (vlab.amrita.edu. 2012).

Result and Discussion

Protein structure preparation

Sequence Retrieval

The protein sequence for UreC of *Mycobacterium tuberculosis* was obtained from UniProt and its UniProt Id is P9WFF1.

Structure Retrieval

The 3D structure of UreC protein for *Mycobacterium tuberculosis* was not found in PDB, So homology modeling were done to generate the 3D structure of UreC protein.

The homologous structure of UreC was identified, which was used as template for the homology modelling. Using this sequence, protein BLAST (BLASTP) was done to identify the most suitable template for homology modeling of UreC. The structure of homologous template which has been used for homology modeling was downloaded from PDB database as pdb format and its Id is 1FWJ.

Homology modeling

Using the downloaded structure as template, the structure for UreC wasgenerated using the MODELLER program. This program finds the similarity between the target structure and the known template structure by aligning the two sequences. Then it builds a 3D model of UreC protein for *Mycobacterium tuberculosis*.

Structure validation

Protein structure validation were done to evaluate the UreC protein which is modeled in Modeller by using PDB sum, From using PROCHECK statistics, structure verification were done to predict the quality of the 3D structure of the protein. Ramachandran plot helps to refine the disallowed residues using loop refinement and thereby the protein is refined.

In the structure of UreC, red color represents alpha helix, yellow color represents beta sheets and green color represents loops.

Ligand structure preparation

The 2D structure of compounds such as 2, 4, 6-tris-(1-phenylethyl)-phenol, 2(E)-3, 7, 11, 15-tetramethyl-2-hexadecen-1-ol, 1-tricosanol, tetra-O-methyl scutellarin identified in *E.odoratum* were obtained from Pubchem Database.

The molecular properties of the ligands were analyzed using Molinspiration tool, which is an online tool used to analyze the molecular properties of the compounds. The 3Dstructure of the compounds is drawn using Chemsketch and it is saved in Mdlmol format. The 3D structure of the compounds is converted into pdb format from Mdl mol format using Open Babel, which is needed to run AutoDock.

Table.1 2D and 3D Structure of Ligands:

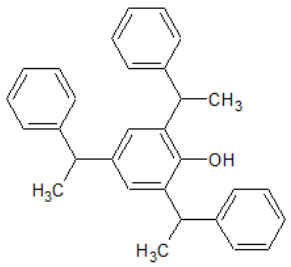
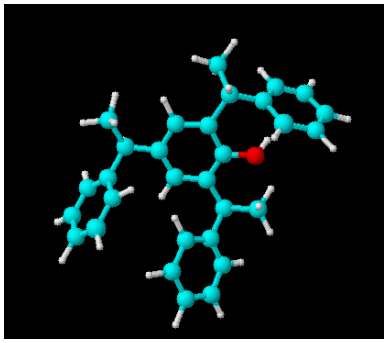
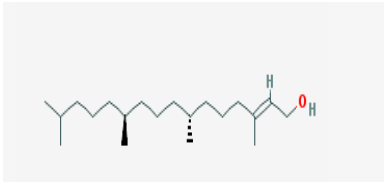
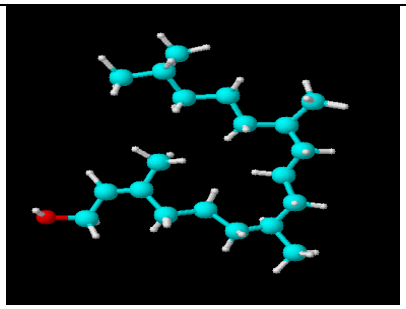
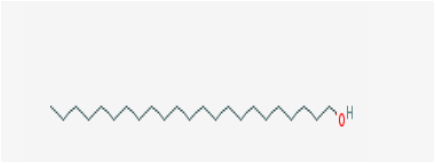
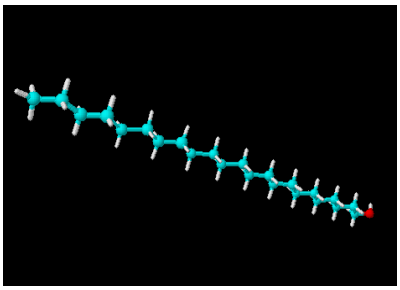
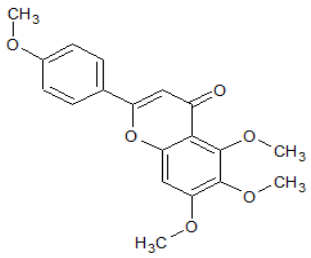
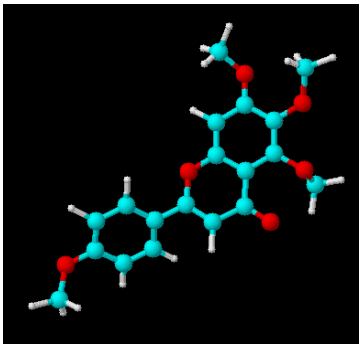
Compounds	2D structure	3D structure
2,4,6-tris-(1-phenylethyl)-phenol		
2(E)-3,7,11,15-tetramethyl-2-hexadecen-1-ol		
1-tricosanol		
Tetra-O-methyl scutellarin		

Table.2 Molecular Properties of the Ligands

Compounds	Molecular weight	Hydrogen bond acceptors	Hydrogen bond donors	Number of Atoms
2,4,6-tris-(1-phenylethyl)-phenol	406.57	1	1	31
2(E)-3,7,11,15-tetramethyl-2-hexadecen-1-ol	296.54	1	1	21
1-tricosanol	340.64	1	1	24
Tetra-o-methyl scutellarin	342.35	6	0	25

Table.3 Interaction between atoms of the ligands from *E.odoratum* and the amino acid residues of UreC protein along with the hydrogen bond distance and docking score

Ligand	UreC protein		Ligand Atom	Distance (Å)	Docking Score (kcal/mol)
	Residue	Atom			
2,4,6-tris-(1-phenylethyl)-phenol	SER190	OG	O	2.8	-8.0
2(E)-3,7,11,15-tetramethyl-2-hexadecen-1-ol	HIS226 ALA174	NE2 O	O H	2.8 2.2	-3.8
1-tricosanol	GLU124	OE2	H	1.8	-1.2
Tetra-O-methyl scutellarin	LYS173 LYS173 ARG343	NZ NZ NH1	O O O	2.8 3.1 3.2	-6.3

Table.4 Shows key residues of UreC, number of hydrogen bonds and docking score.

Compound	Key residues of UreC	No of hydrogen bonds	Docking score (kcal/mol)
2,4,6-tris-(1-phenylethyl)-phenol	SER190	1	-8.0
2(E)-3,7,11,15-tetramethyl-2-hexadecen-1-ol	HIS226,ALA174	2	-3.8
1-tricosanol	GLU124	1	-1.2
Tetra-O-methylscutellarin	LYS173,ARG343	3	-6.3

Fig.1 sequence retrieved in UniProt

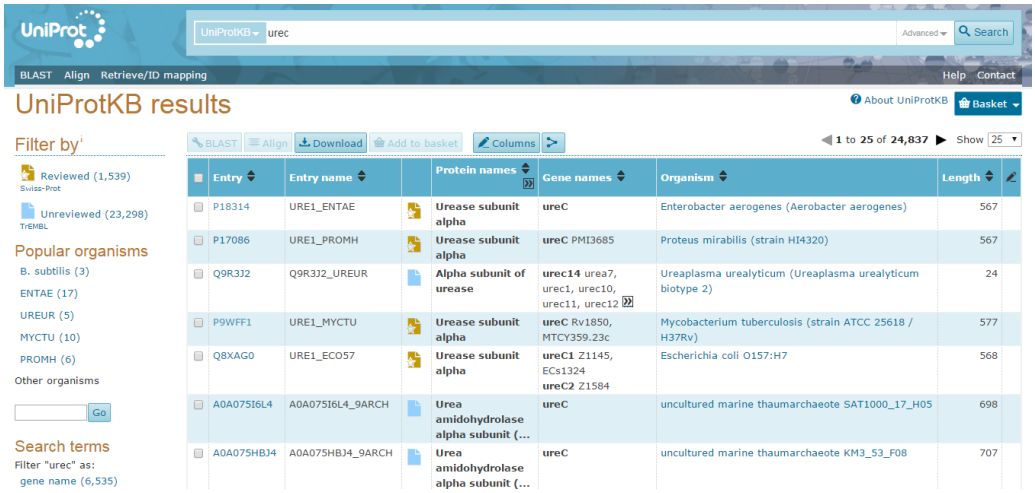


Fig.2 Homologous template identification in BLAST

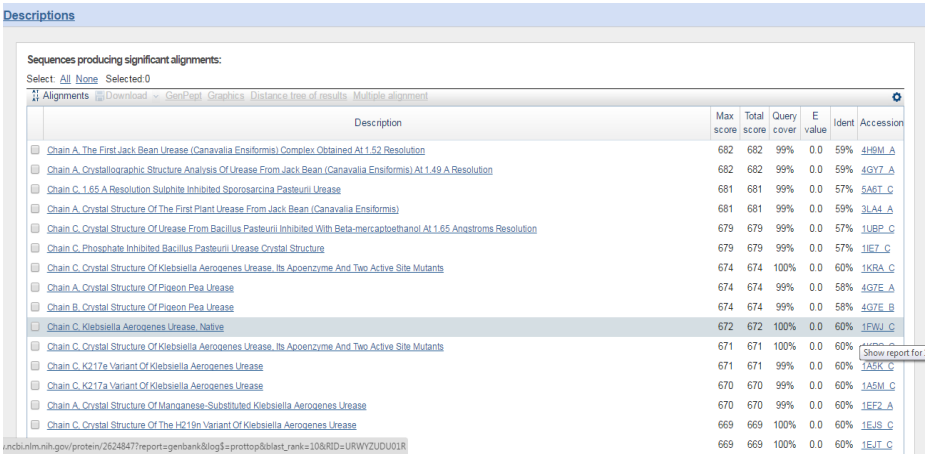


Fig.3 Template selection from PDB

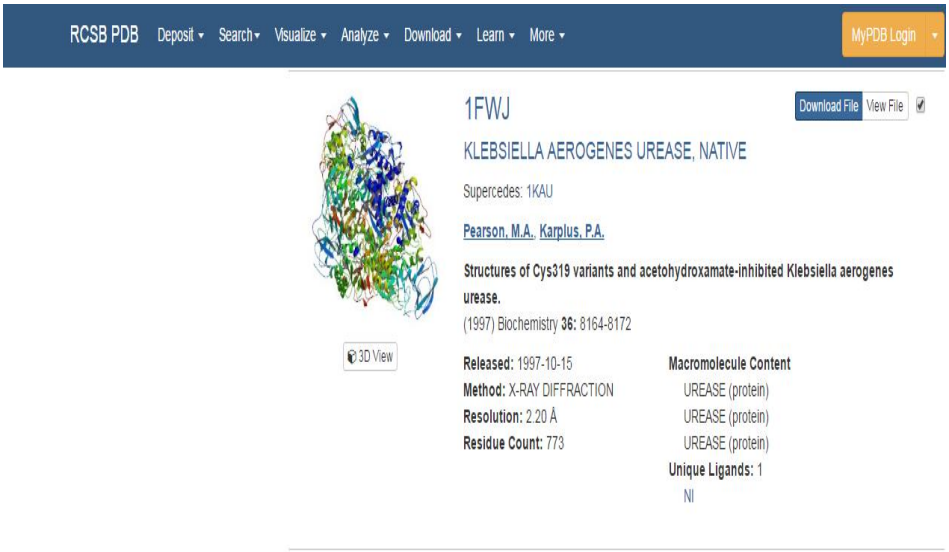


Fig.4 (a)Ramachandran plot before loop refinement
(b) Ramachandran plot after loop refinement

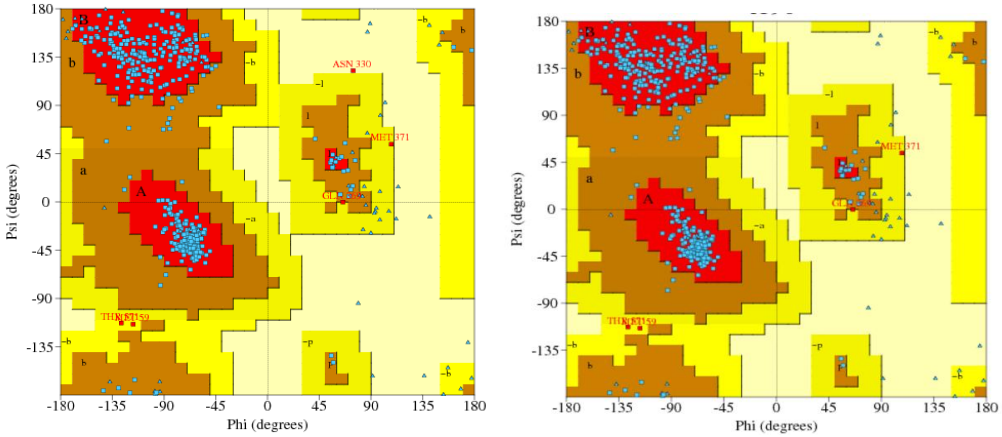


Fig.5 PROCHECK Statistics for UreC protein

PROCHECK statistics

1. Ramachandran Plot statistics

		No. of residues	%-tage
Most favoured regions	[A,B,L]	426	89.5%*
Additional allowed regions	[a,b,l,p]	47	9.9%
Generously allowed regions	[~a,~b,~l,~p]	3	0.6%
Disallowed regions	[XX]	0	0.0%
Non-glycine and non-proline residues		476	100.0%
End-residues (excl. Gly and Pro)		2	
Glycine residues		63	
Proline residues		36	
Total number of residues		577	

Based on an analysis of **118** structures of resolution of at least **2.0** Angstroms and *R*-factor no greater than **20.0** a good quality model would be expected to have over **90%** in the most favoured regions [A,B,L].

Fig.6 Crystal structure of UreC

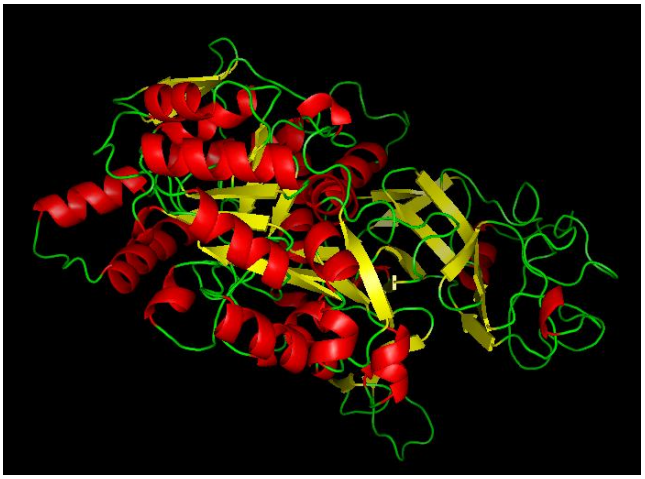
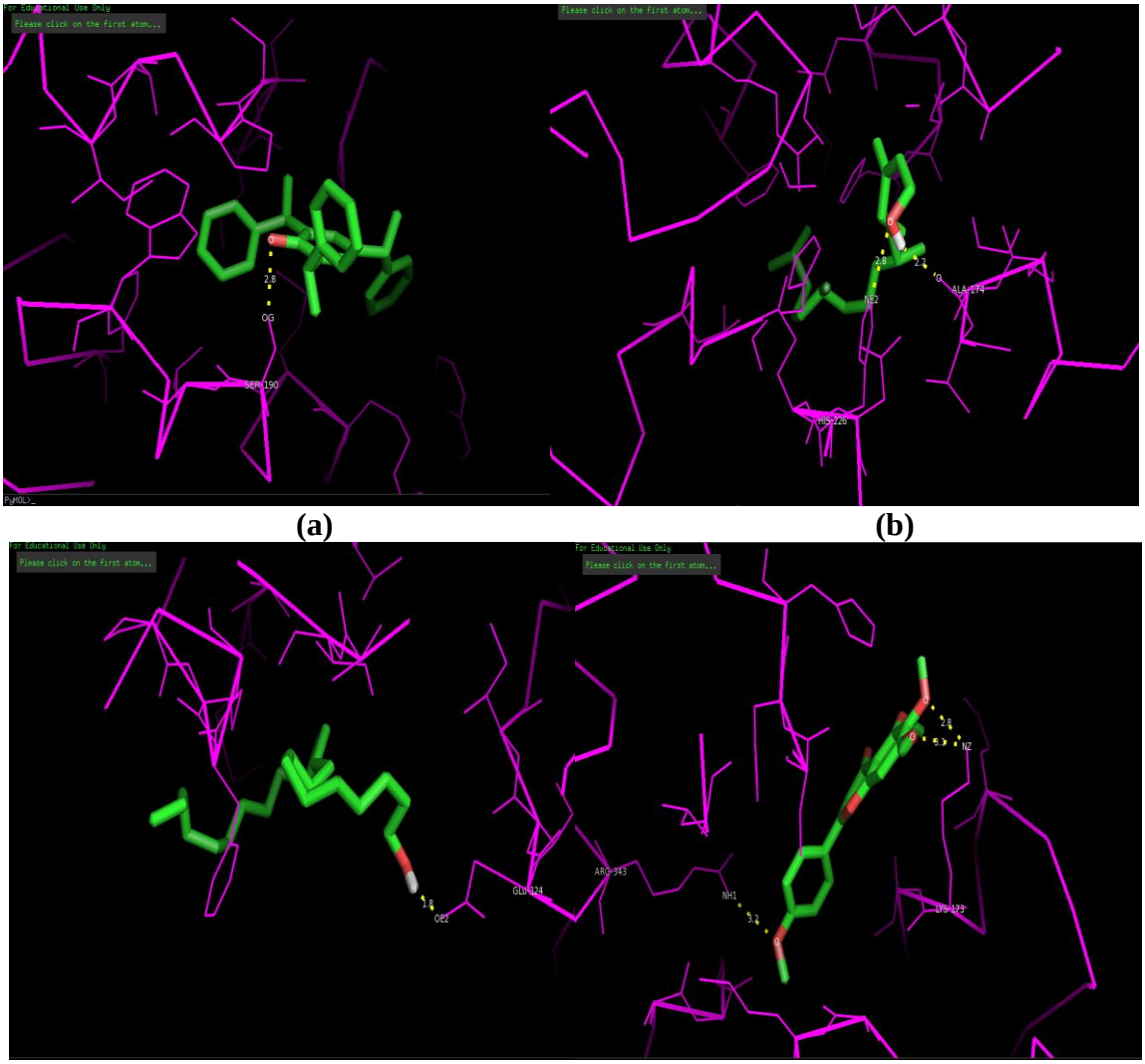


Fig.7 (a)Docking result shown between UreC and 2,4,6-tris-(1-phenylethyl)-phenol; (b)Docking result shown between UreC and 2(E)-3,7,11,15-tetramethyl-2-hexadecen-1-ol; (c)Docking result shown between UreC and1-tricosanol; (d)Docking result shown between UreC and Tetra-O-methylscutellarin.



(a) **(b)**

(c) **(d)**

Molecular docking studies

Molecular Docking is an effective and competent tool for *in silico* screening. It is playing an important and ever increasing role in rational drug design (Drews, 2000; Kuntz, 1992). Docking is a computational procedure of searching for an appropriate ligand that fits both energetically and geometrically the protein's binding site. In other words, it is a study of how two or more molecules e.g. ligand and protein, fit together. The problem is like solving a 3D puzzle (Kaapro and Ojanen, 2002). Molecular docking were done to determine the interaction between the ligands and the UreC protein, based on the docking score the inhibition of ligand against UreC were

predicted. AutoDock Tool assigned polar hydrogens, united atom Kollman charges, solvation parameters and fragmental volumes to the protein. AutoDock saved the prepared file in PDBQT format. AutoGrid was used for the preparation of the grid map using a grid box. A scoring grid is calculated from the ligand structure to minimize the computation time. AutoDock was employed for docking using protein and ligand information along with grid box properties in the configuration file. Then Lamarckian Genetic Algorithm (LGA) was chosen to search for the best conformations. AutoDock employs iterated local search global optimizer (Baxter J. 1981; Blum C2008).The docking results show the best interaction between the compounds and the UreC protein. For each compound maximum 10 conformations were obtained.

Once the Docking study is over, the results obtained from docking are analyzed in Pymol. Before it has been visualized in Pymol, the format of the file can be changed into pdb from pdbqt which is obtained from AutoDock using Open Babel. The interaction between the receptor and the ligand and the amino acids which is interacted and the distance of the interaction were analyzed.

The docking study between UreC and 2,4,6-tris-(1-phenylethyl)-phenol shows binding energy -8.0 kcal/mol, which has a interaction between the Ser190 residue's OG atom and O atom of 2,4,6-tris-(1-phenylethyl)-phenol.

The binding energy between UreC and 2(E)-3,7,11,15-tetramethyl-2-hexadecen-1-ol were -3.88 kcal/mol, which has two interactions between the HIS226 residue's HE2 atom and Oatom and ALA174 residue's O atom andH atom of2(E)-3,7,11,15-tetramethyl-2-hexadecen-1-ol.

The docking study between UreC and 1-tricosanol shows binding energy -1.2 kcal/mol, which has a interaction between the GLU124 residue's OE atom and H atom of 1-tricosanol and the docking study between UreC and Tetra-O-methyl scutellarin shows binding energy -6.23 kcal/mol, which has three interactions between the LYS173 residue's NZ atom and O atom, LYS173 residue's NZ atom and O atom and ARG343residue's NH1 atom and O atom of Tetra-O-methylscutellarin. The docking score of all the compounds are low and these shows the above compounds are potent UreC inhibitor.Among the four compounds, Tetra-O-methylscutellarin is a much potent inhibitor of UreC protein because it comes under Lipinski's rule of five and its docking score and interactions are also good between UreC and Tetra-O-methyl scutellarin.

Conclusion

In this study, Molecular docking were performed between UreC and four compounds from *Eupatorium odoratum*. These compounds have good docking energy and shows satisfactory yields and Tetra-O-methylscutellarin is a good inhibitor than all other compounds. Hence the compounds 2, 4, 6-tris-(1-phenylethyl)-phenol, (2E)-3, 7, 11, 15-Tetramethyl-2-hexadecen-1-ol, 1-Tricosanol, Tetra-O-methyl scutellarin identified from *Eupatorium odoratum* are good inhibitors of the UreC protein which prevents the acidification by host phagosome and thereby the activity of UreC protein by the compounds. Thus the study consummate, that these compounds possess good anti-bacterial activity and in addition Tetra-O-methyl scutellarin possess anti-mycobacterial activity and 2(E)-3,7,11,15-tetramethyl-2-hexadecen-1-ol possess anti-tuberculosis activity.

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