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Thymol from *Trachyspermum ammi* as potent inhibitor for Protein Tyrosine Phosphate: *In silico* Analysis

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Abstract

Diabetes is one of the most serious metabolic conditions that affect people of all ages around the world. According to the World Health Organization (WHO), India is among the top three countries with 62 million diabetics. Without knowing the molecular mechanism, the plant *Trachyspermum ammi* was utilised as medicine in ancient times to treat diabetes. As a result, the chemical from the plant was evaluated for its oral pharmacological action using *insilico* techniques in this current work. The screening result projected that the compound Thymol would clear oral drug action and that the substance would have many pharmaceutical effects. Insulin hormones and leptin signal transduction are regulated by protein tyrosine phosphatase (PTP). The recent review in type 2 Diabetes revealed that the PTP as a novel target for type 2 diabetes and hence there is an urgent need for the discovery of novel natural anti-diabetic drugs against PTP without any side effects. The crystal structures of protein tyrosine phosphate was selected as target from the protein data bank of different ID's and docking analysis was carried out using online SwissDock. The compound thymol exhibited significant binding energy to most of 3D structures of the protein tyrosine phosphate. The future studies could be designed accordingly to highlight the efficiency of Thymol towards drug development in the treatment of diabetes.

Keywords: Diabetes, *Trachyspermum ammi*, Thymol, Protein Tyrosine Phosphate, Molecular Docking.

Introduction

Trachyspermum ammi, often known as Ajwain, is a plant native to India that is primarily grown in Gujarat and Rajasthan. Flatulence, atonic dyspepsia, diarrhoea, abdominal tumours, stomach aches, piles, bronchial issues, loss of appetite, galactogogue, asthma, and amenorrhoea have all been treated with the fruit, which has stimulant, antispasmodic, and carminative effects [Bairwa R*et al.,* 2012]. It has been shown to have antifungal, antioxidant, antimicrobial, antinociceptive, cytotoxic, hypolipidemic, antihypertensive, antispasmodic, broncho-dilating, antilithiasis, diuretic, abortifacient, antitussive, nematicidal, anthelmintic, and antifilarial properties in studies.[Sonal Dubey *et al.,* 2015]. Furthermore, studies reveal the presence of a variety of phytochemical constituents, including carbohydrates, glycosides, saponins, phenolic compounds, volatile oil (thymol, -terpinene, para-cymene, and - and -pinene), protein, fat, fibre, and mineral matter containing calcium, phosphorous, iron, and nicotinic acid [Ranjan Bairwa*et al.,* 2011]

Thymol is a colourless crystalline monoterpene phenol with the chemical name 2-isopropyl-5-methylphenol. In thyme species, it is one of the most essential nutritional ingredients [Angelica Escobar*et al.,* 2020]. It has been used in traditional medicine for generations and has been demonstrated to have pharmacological qualities such as antioxidant, free radical scavenging, anti-inflammatory, analgesic, antispasmodic, antibacterial, antifungal, antiseptic, and anticancer effects. Previous research has revealed the biochemical and molecular features of thymol, as well as its many therapeutic activities against cardiovascular, neurological, rheumatological, gastrointestinal, metabolic, and malignant illnesses. Thymol's anti-inflammatory, antioxidant, and antihyperlipidemic properties are mostly responsible for its notable effects [Nagoor Meeran MF*et al.,* 2017].

In the twenty-first century. Diabetes mellitus is a serious health disease that affects people all around the world [Paul Z Zimmet*et al.,* 2014]. According to the most recent Diabetes report, more than 70 million individuals worldwide, mostly in poor countries, have diabetes [Lefebvre P *et al.,* 2004]. Diabetes is a chronic metabolic condition characterised by changes in glucose, lipid, and protein metabolism caused by inadequate insulin secretion in the body [David M Nathan*et al.,* 2009]. The insulin hormone produced by the organ pancreas was primarily responsible for the incorrect glucose level in the blood, whether the body produces insufficient hormones or the cells in the human body do not react to the hormone [Ozougwu JC*et al.,* 2013].

Insulin is a crucial hormone that increases glucose uptake and storage in body tissues, particularly the liver, adipose tissue, and muscle (excluding smooth muscle) [Gisela Wilcox 2005]. As a result, a lack of insulin secretion in the body causes all of the symptoms of diabetes mellitus. Diabetes mellitus remains a mystery, despite the fact that environmental and genetic factors have a role [Rashmi B. Prasad*et al.,* 2015].

Protein Tyrosine Phosphatase (PTP) is responsible for removing phosphate from the tyrosine residues in the regulatory region of the insulin receptor, hence deactivation of the receptor is unknown [Yang H*et al.,* 2022]. Protein tyrosine kinases (PTK) are responsible for protein tyrosine phosphorylation, while protein tyrosine phosphatases are responsible for phosphate removal. PTP, like PTK, can influence cell activity in both positive and negative ways. PTP1B was the first purified and described protein tyrosine phosphatase [Chidambaram Ramachandran*et al.,* 2003].

Pharmaceutical companies nowadays use a number of computational methodologies, such as Bioinformatics tools and databases, to identify drug candidates based on efficacy and safety, as well as advance such molecules into clinical trial candidates [Sumudu P Leelananda *et al.,* 2016, Supreet Kaur Gill *et al.,* 2016]. The docking

methodology is one of the most essential and widely used strategies in structural-based drug discovery, predicting the binding affinity of small compounds to their appropriate target binding sites and thereby blocking the target functionalities [Xuan-Yu Meng*et al.,* 2011]. Molecular docking is widely used to predict the shape of a receptor-ligand complex [Chaudhary KK*et al.,* 2016], where the receptor is typically a protein or nucleic acid and the ligand is typically a small molecule or another protein.

The docking analysis was thought to be crucial in choosing the best pharmacological lead candidate for the target. The goal of this work is to use in silico docking to evaluate the tiny molecule Thymol as a diabetes inhibitor against the insulin receptor (Protein Tyrosine Phosphate).

Materials and Methods

Preparation of Ligand:

The pubchem database includes data on chemical structures and characteristics, biological activities, compound safety and toxicity, and more. Thymol's two-dimensional structure was retrieved in.sdf file format from Pubchem databases and transformed to.mol2 file format using Pymol software, making the compound ready for docking [Sunghwan Kim*et al.,* 2016].

Accession of target protein:

The Protein Data Bank (PDB) database (https://www.rcsb.org/) holds 3D structures and sequences of macromolecules such as proteins and nucleic acids. PDB IDs for 14 distinct Protein Tyrosine Phosphate 3D receptor structures (2AZR, 2BO7, 1C87, 2CMB, 1EEN, 2F6W, 2H4G, 2H4K, 1KAK, 1L8G, 1LN9, 1ONZ, 1PXH, 2VEU) were recovered [Stephen K. Burley*et al.,* 2017]. Except for chain A, other chains in receptors, metal ions attached to receptor molecules, water molecules in the structure, and ultimately heteroatoms were eliminated from 3D receptor structures using PyMol Software [Markus A. Lill*et al.,* 2011].

Analysis of target active binding sites

The CASTP database was used to estimate the active sites of 14 receptors. For protein-ligand interactions, the database predicts probable ligand binding sites on receptor surfaces [Thompson MA 2004]. The predicted locations were used to determine where the chemical Thymol might attach.

Docking of receptors with ligand:

A computational receptor-ligand docking studies were preformed to analyse the structural complexes of the PTP (receptor) withThymol (ligand) in order to diagnose the specify structural relationship with the ligand.SwissDock is a web service that allows tiny molecules to dock with target proteins. It's used in conjunction with setup scripts to solve common issues and prepare the target protein and ligand input files. Scientists may simply submit dockings and get anticipated complexes thanks to an efficient Ajax/HTML interface that was built and deployed. A programmatic SOAP interface has been put up for automated docking tasks, and template programmes in Perl, Python, and PHP can be downloaded. The website also has a database of hand curated complexes, which is based on the Ligand Protein Database. To encourage user participation, the community has access to a wiki and a forum. SwissDock's website can be found at http://www.swissdock.ch [Guntero, V.A *et al.,* 2021]. SwissDock is based on the docking software EADock DSS, which has the following steps in its algorithm:

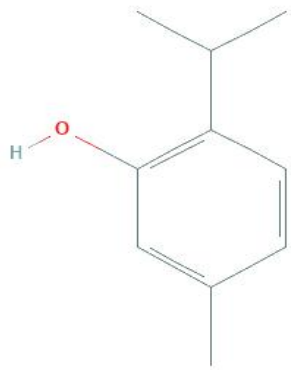
1. Many binding modes are formed in a box (local docking) or in the vicinity of all target cavities (global docking) (blind docking).
2. At the same time, their CHARMM energies are calculated on a grid. FACTS is used to analyse and cluster the binding modes with the most favourable energies.
3. The most advantageous clusters can be viewed and downloaded from the internet [Grosdidier A*et al.,* 2011]..

Results and Discussion

Structure of the ligand and target proteins:

The two dimensional structure of the Thymol with its Pubchem ID: 6989 were retrieved and further analysed for its oral drug activity using Lipinski Rule of Five database (Table 1). The three dimensional structure of 14 different targets were retrieved from the Protein Data Bank and all the structures were determined by X-Ray crystallography. The best ligand binding site was predicted for 14 proteins using CastP were listed below:**2AZR** (Ala 217, Arg 221, Asp 181, Cys 215, Glu 115, Lys 120, Phe 182, Ser 216, Tyr 46, Val 49).**2BO7** (ARG 266,ALA 216,,2BO7,GLU 213,GLY 214,, HIS 217, HIS 262,ILE 263,LYS 215, PRO 130, SER 105), **1C87** (ARG 24, ALA 27, ARG 254, ASP 29, ASP 48, GLN 262, HIS 25, ILE 219, SER 28, MET 258),**2CMB**(ALA 217, ASP 48, ASP 181,GLN 262, GLY 220,ILE 219, PHE 182, SER 216, TYR 46,VAL 49), **1EEN** (ALA 17, ALA 217, ARG 47, ASP 29,ASP 48, PHE 30, PHE 52.TYR 46, SER 28, VAL 49), **2F6W** (ALA 27,ALA 77, GLU 26,GLU 75,GLU 252,LEU 251, MET 74, SER 28, THR 230), **2H4G** (ALA 217, ARG 45, ARG 221,ASP 181, CYS 215,LYS 120,PHE 182, SER 216, TYR 46, VAL 49), **2H4K** (ARG 45,ARG 221, ASP 181, GLU 115, LYS 120, TYR 46, PHE 182, SER 216,VAL49), **1KAK (**ALA 27, ARG 24,ARG 254, ASP 29,GLN 21, GLU 26, GLN 262.HIS 25,SER 28TYR 20), **1L8G** (ALA 217,ARG 221, ASP 48,ASP 181, GLN 262,216ILE 219, LYS 120,MET 258,SER216,TYR 46). **1LN9 (**ALA 217, ARG 221,CYS 215, GLN 262, GLN 266,GLY 183, GLY 220,ILE 219, TYR 46, VAL 49), **1ONZ (**ARG 221, ASP 265, GLN 262, GLN 266.GLY 183,ILE 219, LYS 116,THR 263, TRP 179, VAL 184), **1PXH (**ALA 217,ASP 48,ILE 219, LYS120,PHE 182, TYR 46,MET 258, SER 50, SER 216, VAL 49), **2VEU (**ALA 27,ARG 24, ARG 254, ASP 29, GLN 21,GLN 262, PHE 52, MET 258, SER 28, TYR 20)

Table 1: 2D structure and Lipinski Rule of Five For Thymol



IUPAC Name: 5-methyl-2-propan-2-ylphenol, Isomeric SMILES: CC1=CC(=C(C=C1)C(C)C)O

Molecular properties	Value
miLogP	3.34
TPSA	20.23
Natoms	11
MW	150.22
nON	1
nOHNH	1
Nviolations	0
Nrotb	1
Volume	158.57

Docking analysis and its binding interaction between PTP with Thymol:

The above predicted active residues of the 14 proteins were used as the catalytic sites for small molecules Thymol for docking analysis. The results of the docking interaction between the binding site residues of target protein tyrosine phosphate and Thymol compound were shown in the Table 2.

Table 2: Docking energy and binding information of PTP with Thymol.

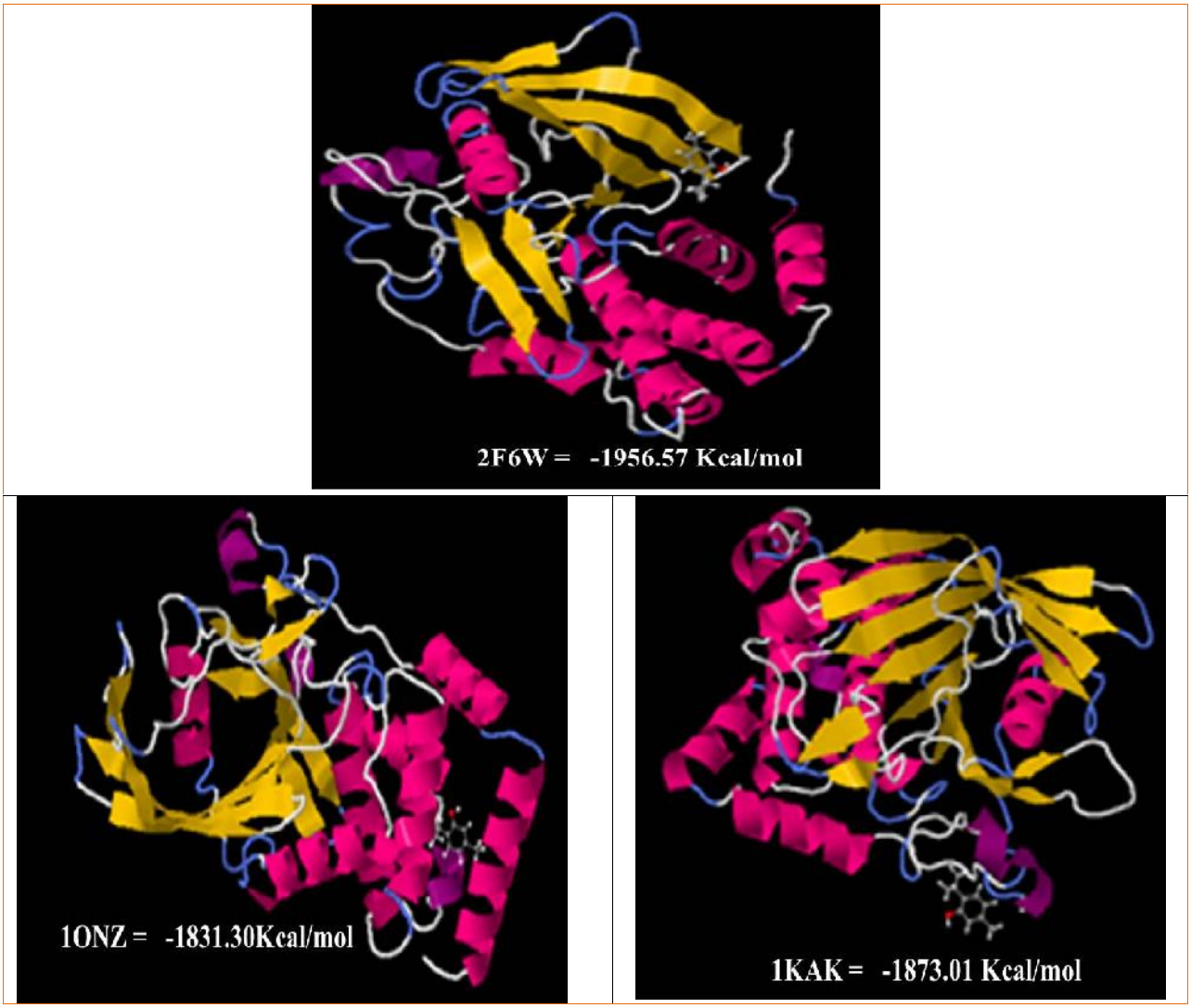
PDB ID of Protein Tyrosine Phosphate	FullFitness(kcal/mol)	Estimated ΔG (kcal/mol)
2F6W	-1956.57	-6.14
1ONZ	-1873.01	-6.17
1KAK	-1831.30	-6.05
1LN9	-1762.41	-5.96
1PXH	-1740.94	-5.96
2VEU	-1724.91	-6.18
1EEN	-1713.95	-5.93
2BO7	-1695.21	-5.99
2CMB	-1630.90	-6.10
1L8G	-1610.59	-5.80
2H4G	-1557.72	-5.94
2AZR	-1540.49	-6.48
2H4K	-1541.86	-6.17
1C87	-1536.28	-5.76

In general, the higher negative value of docking score predicted between receptor and ligand expected to hold more binding affinity towards each other especially through hydrogen bonding interaction [Pushpalatha R*et al.,* 2017]. By analysing the docking result it was revealed that:

- 3D structure of the protein 2F6W exhibited the higher negative value of -1956.57Kcal/mol with Thymol with strongest hydrogen bond interactions which indicates better binding affinity with the active sites of protein there by strongly inhibiting the function of the protein.
- 3D structure of 1ONZ and 1KAK exhibit the binding interaction -1873.01 Kcal/mol and -1831.30 Kcal/mol with better Hydrogen bond interaction.
- 3D structure of 1LN9, 1PXH, 2VEU and 1EEN exhibit the binding interaction -1762.41 Kcal/mol,-1740.94 Kcal/mol, -1724.91 Kcal/mol, -1713.95 Kcal/molwith good Hydrogen bond interaction.
- 3D structure of 2BO7. 2CMB, 1L8G exhibit the binding interaction -1695.21Kcal/mol, -1630.90Kcal/mol, -1610.59Kcal/mol, -with good Hydrogen bond interaction.
- 3D structure of 2H4G, 2AZR. 2H4K, 1C87exhibit the binding interaction -1557.72 Kcal/mol, -1540.49 Kcal/mol, -1541.86Kcal/mol, -1536.28 Kcal/mol,with least Hydrogen bond interaction.

From the result of Docking it was revealed that 14 three dimensional structure of PTP exhibited the better binding interaction with the Thymol. The previous *in silico* study of Thymol on angiotensin converting enzyme 2 [Imane Abdelli *et al.*, 2020] predicted the binding values >-7 Kcal/mol and they also concluded that the Thymol exhibited the good inhibitory activity of towards specific proteins.According to the findings of this investigation, the Thymol compound may be effective inhibitors of the diabetes protein tyrosine phosphate. The findings of the docking investigation could be useful in the development of new anti-diabetic drugs based on tiny compounds like Thymol.

Table 3: Best Docking interaction between Receptors and Ligand



Conclusion

The structural binding process between receptor and ligand was investigated using molecular docking analysis. Thymol may act as a unique chemical inhibitor for protein tyrosine phosphate, enhancing insulin
secretion in the human body, according to current *insilco* study on the substance as a diabetic inhibitor. Further *invivo* animal model research is needed to corroborate this current work, and the Thymol molecule may evolve as the best diabetes inhibitor in the future.

Conflict of interest:

The authors declare they have no competing interests.

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