

In-silico Docking Analysis Reveals Thymol from *Plectranthus amboinicus* as a Potential Protein Tyrosine Phosphatase Inhibitor for Type 2 Diabetes

Submitted in partial fulfillment of the requirements for the award of
Master of Science in Bioinformatics and Data Science

By

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DEPARTMENT OF BIOINFORMATICS

SCHOOL OF BIO AND CHEMICAL ENGINEERING

SATHYABAMA

INSTITUTE OF SCIENCE AND TECHNOLOGY

(DEEMED TO BE UNIVERSITY)

Accredited with Grade "A++" by NAAC | 12B Status by UGC | Approved by AICTE

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APRIL - 2024



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BONAFIDE CERTIFICATE

This is to certify that this Project Report is the bonafide work of **U.GOWTHAMI (42739011)**, who carried out the final year project entitled **"In-silico Docking Analysis Reveals Thymol from Plectranthus amboinicus as a Potential Protein Tyrosine Phosphatase Inhibitor for Type 2 Diabetes"** under my supervision from September 2023 to April 2024.

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Internal Examiner

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External Examiner

DECLARATION

I **U.GOWTHAMI (42739011)** hereby declare that the Project Report entitled
**“In-silico Docking Analysis Reveals Thymol from Plectranthus amboinicus
as a Potential Protein Tyrosine Phosphatase Inhibitor for Type 2 Diabetes”**

done by me under the guidance of Dr. DANIEL ALEX ANAND at Sathyabama Institute of Science and Technology, Jeppiaar Nagar, Rajiv Gandhi Salai, Chennai –600 119, Tamil Nadu, India, and is submitted in partial fulfillment of the requirements for the award of Master of Science in Bioinformatics and Data Science.

DATE: 20.04.2024

PLACE: CHENNAI

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SIGNATURE OF THE CANDIDATE

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U.Gowthami

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. The chemical from the plant was evaluated for its oral pharmacological action using *in silico* 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 were selected as target from the protein data bank of different ID's and docking analysis was carried out using Discovery Studio to find the best Ligand Interactions and highlight with the RMSF value (4.8 (Å)) to find the fluctuation of target protein and docked structure.

Keywords: Diabetes, *Plectranthus amboinicus*, Thymol, Protein Tyrosine Phosphate, Molecular Docking, RMSF.

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LIST OF ABBREVIATIONS

PTP	PROTEIN TYROSINE PHOSPHATE
WHO	WORLD HEALTH ORGANIZATION
PTK	PROTEIN TYROSINE KINASES
PTP1B	PROTEIN TYROSINE PHOSPHATASE 1B
PDB	PROTEIN DATA BANK.
RMSF	ROOT MEAN SQUARE FLUCTUATION

CHAPTER 1

INTRODUCTION

1.1 PLECTRANTHUS AMBOINICUS

Plectranthus amboinicus belongs to the Lamiaceae family, it is also commonly known as Indian borage, and is a fleshy, succulent herb famous for its distinct oregano-like flavor and odor. It is one of the most cited species in the Lamiaceae family, especially for its medicinal properties, accounting for 68% of all customary applications of this genus. This herb is widely used by indigenous people of tropical rain forests, either in folk medicine or for culinary purposes. (Lukhoba C.W et al 2016) This is mainly due to its natural production of an essential oil with high amounts of bioactive compounds such as Carvacrol, Thymol, β -Caryophyllene, α -Humulene, γ -Terpinene, *p*-Cymene, α -Terpineol and β -Selinene, identified in the oil component of its leaves. (Leyva-López N et al 2017) The leaves of the plant are often eaten raw or used as flavoring agents, or incorporated as ingredients in the preparation of traditional food. The chopped leaves are also used as a substitute for sage (*Salvia officinalis*) in meat stuffing. (Arumugam G et al 2016)

It has been shown to have antifungal, antioxidant, antimicrobial, antinociceptive, cytotoxic, hypolipidemic, antihypertensive, antispasmodic, broncho-dilating, antilithiasis, diuretic, abortifacient, antitussive, nematocidal, anthelmintic, and antifilarial properties in studies. Furthermore, studies reveal the presence of a variety of phytochemical constituents, including carbohydrates, glycosides, saponins, phenolic compounds, volatile oil, protein, fat, fibre, and mineral matter containing calcium, phosphorous, iron, and nicotinic acid. (Sonal Dubey et al., 2015)

1.2 THYMOL

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. 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. Thymol's anti-inflammatory, antioxidant, and antihyperlipidemic properties are mostly responsible for its notable effects in the twenty-first century. (Angelica Escobaret al., 2020)

1.3 DIABETES MELLITUS

Diabetes mellitus is a serious health disease that affects people all around the world. According to the most recent Diabetes report, more than 70 million individuals worldwide, mostly in poor countries, have diabetes. Diabetes is a chronic metabolic condition characterized by changes in glucose, lipid, and protein metabolism caused by inadequate insulin secretion in the body. 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.(Sarwar N et al 2010) Insulin is a crucial hormone that increases glucose uptake and storage in body tissues, particularly the liver, adipose tissue, and muscle (excluding smooth muscle). 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.(Rahman MS et al 2021)

1.4 PROTEIN TYROSINE PHOSPHATASE

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. 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.(Sevillano J et al 2021)

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.(Vora LK et al 2023) The docking methodology is one of the most essential and widely used strategies in structural-based drug discovery, using the Lipinski rule of 5. Molecular docking is

widely used to predict the shape of a receptor-ligand, where the receptor is a protein and the ligand is a small molecule.

The Molecular Dynamic Simulation was thought to be crucial in choosing the best Receptor Ligand interaction for the target. The goal of this work is to use to evaluate the RMSF value as the compound Thymol as a diabetes inhibitor against the insulin receptor (Protein Tyrosine Phosphate).

1.5 PREVENTION AND TREATMENT

Positive energy balance, characterized by excess adiposity due to changes in dietary habits and decreased physical activity levels, has led to a global increase in weight among men and women.(Ezzati et al 2013) Excessive body mass index (BMI) is a significant risk factor for diabetes, with Asians exhibiting a lower BMI threshold for diabetes development compared to those of European descent.(Hu FB et al 2008) The risk of diabetes escalates with increasing body fat, starting from the lower end of a healthy BMI or waist circumference. Studies indicate that a higher waist circumference may pose a slightly stronger risk of diabetes than a higher BMI. Therefore, monitoring both BMI and waist circumference is crucial in clinical practice. Additionally, weight gain since young adulthood independently predicts diabetes risk, even after adjusting for current BMI. Lifestyle interventions, such as calorie restriction and exercise, have been shown to effectively promote weight loss and reduce the risk of diabetes. The Diabetes Prevention Program demonstrated a 58% reduction in diabetes conversion among high-risk patients with impaired glucose tolerance through such interventions. The effectiveness of lifestyle modifications in reducing diabetes risk has been documented across various populations, including multiethnic American, Finnish, Chinese,Indian.(Lancet et al 2008)

CHAPTER 2

REVIEW OF LITERATURE

Escobar et al. (2020) Thymol, a natural compound abundantly present in essential oils, has garnered considerable attention due to its remarkable bioactivity, as reviewed by Escobar et al. (2020). This comprehensive review underscores the multifaceted biological properties of thymol, ranging from its potent antimicrobial capabilities to its notable antioxidant, anti-inflammatory, and anticancer effects. Such a diverse array of biological activities positions thymol as a promising candidate for therapeutic interventions across various medical domains. In pharmacology, thymol holds promise as a potential therapeutic agent, offering avenues for the development of novel drugs aimed at combating microbial infections, mitigating inflammation, and even addressing certain cancer types. Furthermore, its application extends to dentistry, where its antimicrobial properties could be harnessed for oral care formulations, such as mouthwashes and toothpaste, to promote dental health and prevent oral diseases. The veterinary medicine field also stands to benefit from thymol's bioactivity, with potential applications in the development of veterinary drugs and products aimed at controlling microbial infections in animals. Moreover, the utility of thymol as an antimicrobial agent finds practical use in food preservation, where its ability to inhibit microbial growth could enhance the shelf life and safety of various food products. Escobar et al. (2020) highlights thymol's vast therapeutic potential and underscores its versatility across a spectrum of medical and industrial applications, positioning it as a valuable natural compound with broad-reaching benefits.

Yang et al. (2022) delve into the intricate mechanisms underpinning skeletal development, focusing particularly on the pivotal role of protein tyrosine phosphatases (PTPs). These enzymes emerge as central orchestrators in the intricate ballet of cellular activities governing bone formation. Through meticulous exploration, the study unveils the multifaceted contributions of PTPs, from steering osteoblast differentiation to fine-tuning the delicate process of bone mineralization. Such insights not only deepen our comprehension of skeletal biology but also illuminate promising avenues for therapeutic intervention in the realm of bone-related disorders. However, amidst the spotlight on PTPs, another intriguing player emerges: thymol. While seemingly distant from skeletal development, thymol's anti-inflammatory prowess presents a compelling narrative. By virtue of its ability to modulate inflammation-associated pathways, thymol could wield a subtle yet significant influence on overall bone health, hinting at a broader interplay between seemingly disparate biochemical phenomena. Thus, within the tapestry of skeletal development, the narrative expands to encompass not only the starring roles of PTPs but also the nuanced interconnections that weave together the intricate fabric of biological regulation.

Ramachandran and Kennedy (2003) intricate involvement in the complex pathophysiology of type 2 diabetes and obesity. At the heart of their investigation lies the recognition of PTP1B as a critical regulator within the intricate web of insulin signaling pathways. This enzyme, while seemingly diminutive in structure, wields substantial influence over cellular responses to insulin, thereby exerting profound effects on glucose homeostasis and metabolic equilibrium. The narrative of their research unfolds against the backdrop of a burgeoning global epidemic characterized by the insidious rise of diabetes and obesity. These metabolic maladies, once considered distinct entities, now stand united by a common thread: insulin resistance. PTP1B emerges as a key player in this unfolding drama, its aberrant activity implicated in the blunting of insulin signaling cascades, thereby perpetuating the vicious cycle of dysregulated glucose metabolism and adipose tissue dysfunction. Yet, amidst the bleak landscape of insulin resistance, a glimmer of hope arises in the form of therapeutic intervention. Ramachandran and Kennedy illuminate a promising avenue for combating

these metabolic scourges: inhibition of PTP1B activity. By targeting this pivotal phosphatase, researchers envision a transformative approach to restoring insulin sensitivity and reining in the ravages of diabetes and obesity. The prospect of pharmacological agents designed to selectively thwart PTP1B's deleterious actions holds tantalizing promise, hinting at a future where metabolic disorders may be tamed through precision medicine. While Ramachandran and Kennedy's exploration delves deep into the intricate workings of PTP1B, the spotlight remains fixed on its direct implications for diabetes and obesity. The tangential potential of natural compounds such as thymol remains largely uncharted territory within this particular narrative. Thymol, with its reputed antioxidant and anti-inflammatory properties, offers a compelling subplot within the broader saga of metabolic health. Though its direct effects on PTP1B are left unexplored in this narrative, one cannot help but wonder about the hidden synergies that may lurk beneath the surface. In this intricate dance of molecules and pathways, thymol's potential to modulate oxidative stress and dampen inflammatory cascades hints at a nuanced interplay between biochemical phenomena. While the direct link between thymol and PTP1B may remain elusive within the confines of Ramachandran and Kennedy's narrative, the tantalizing prospect of indirect modulation through antioxidant and anti-inflammatory mechanisms beckons further exploration.

Meng et al. (2011) provided an overview of molecular docking, Meng et al. (2011) embarked on a journey through the realm of structure-based drug discovery, illuminating the path paved by molecular docking—a computational technique that serves as a guiding light in the quest for novel therapeutic agents. Within the intricate landscape of drug development, molecular docking emerges as a beacon of hope, offering a window into the dynamic interplay between small molecules and their protein targets. At the heart of molecular docking lies the quest to decipher the intricate dance of molecular recognition—an elegant choreography wherein a small molecule, known as a ligand, seeks out its counterpart, the target protein or receptor, with exquisite precision. Through the lens of computational algorithms, researchers embark on a voyage of exploration, traversing the vast expanse of chemical space in search of the perfect fit—the elusive binding pose that heralds the dawn of pharmacological potential. The significance of molecular docking transcends mere prediction, extending its reach into the realm of understanding. By unveiling the intricate tapestry of binding interactions, molecular docking grants researchers unparalleled insights into the molecular mechanisms underpinning drug action. From the subtle nuances of hydrogen bonding to the sweeping arcs of hydrophobic interactions, each facet of the binding interface offers a glimpse into the inner workings of pharmacological efficacy. In the context of thymol bioactivity, the narrative takes on a new dimension—a convergence of computational prowess and natural product pharmacology. Within the vast repertoire of molecular targets that dot the cellular landscape, thymol seeks its partners in the dance of molecular recognition. Through molecular docking studies, researchers unravel the intricacies of thymol's interactions, shedding light on the pharmacological effects that underpin its reputed bioactivity. With each computational simulation, a new chapter unfolds—a tale of molecular affinities and therapeutic potential. From the bustling streets of inflammatory pathways to the tranquil shores of enzymatic cascades, thymol navigates the complex terrain of biological regulation with finesse. And as the binding poses emerge from the digital ether, so too do the prospects for therapeutic innovation—a tantalizing glimpse into a future where natural compounds stand poised to revolutionize the landscape of drug discovery. In the crucible of computational simulation, thymol's journey unfolds—a testament to the power of molecular docking to

unravel the mysteries of bioactivity and therapeutic potential. As researchers continue to probe the depths of chemical space, armed with algorithms and insights, the promise of structure-based drug discovery looms large—a beacon of hope in the ongoing quest for novel therapeutics.

(M. et al., 2022) In his explores the phytochemical profile and various biological properties of the essential oil, providing valuable insights into its potential applications in medicine, cosmetics, and other industries. The study conducted by M. et al. (2022) delves into the chemical composition and diverse biological activities of the essential oil extracted from *Plectranthus amboinicus* (Lour.) Spreng., a plant cultivated in Egypt. With meticulous attention to detail, the researchers unravel the intricate phytochemical profile of this essential oil, shedding light on its multifaceted potential across various domains, including medicine, cosmetics, and beyond. At the heart of their investigation lies a comprehensive analysis of the constituents that constitute the essential oil of *Plectranthus amboinicus*. Through advanced analytical techniques, the researchers decipher the complex array of volatile compounds that lend this oil its distinctive aroma and therapeutic properties. From aromatic terpenes to potent phenolic compounds, each constituent emerges as a testament to the rich biochemical diversity harbored within this botanical treasure. Through a series of rigorous experiments, the researchers unveil the multifaceted pharmacological potential of this oil, ranging from antimicrobial and antioxidant properties to anti-inflammatory and analgesic effects. Such findings not only underscore the traditional medicinal uses of *Plectranthus amboinicus* but also open new vistas for exploration in modern pharmacology and biotechnology. Moreover, the implications of this study extend far beyond the laboratory bench. By elucidating the diverse biological activities of *Plectranthus amboinicus* essential oil, M. et al. (2022) provide valuable insights for a wide array of stakeholders. Researchers stand poised to capitalize on these findings, leveraging the unique chemical constituents and pharmacological properties of this oil to develop novel therapeutic agents. Pharmacologists, in particular, may find inspiration in the potential applications of *Plectranthus amboinicus* in combating infectious diseases, oxidative stress-related disorders, and inflammatory conditions. In essence, the work of M. et al. (2022) serves

as a beacon of enlightenment, illuminating the profound potential harbored within the essential oil of *Plectranthus amboinicus*. Through their meticulous exploration of its chemical composition and biological activities, they invite us to embark on a journey of discovery, where ancient wisdom converges with modern science to unlock the secrets of nature's pharmacy. As we navigate this uncharted terrain, we stand poised to reap the bountiful harvest of botanical bounty, transforming age-old traditions into cutting-edge therapies for the betterment of humanity.

Zheng et al. (2020) focuses on exploring the potential of 4-thiazolinone derivatives as inhibitors of Protein Tyrosine Phosphatase 1B (PTP1B), a key enzyme involved in insulin signaling and a promising target for treating type 2 diabetes mellitus (T2DM). In the pursuit of novel therapeutics, the researchers synthesized seventeen new derivatives of 4-thiazolinone and evaluated their biological activity against PTP1B. These derivatives were subjected to comprehensive evaluation, including ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction, to assess their drug-like properties. Encouragingly, the synthesized compounds demonstrated favorable drug-like characteristics, indicating their potential for further development. In vitro assays were conducted to assess the inhibitory activity of these derivatives against PTP1B. Among them, compound 7p emerged as particularly noteworthy, exhibiting a potent inhibition of PTP1B with an IC₅₀ value of 0.92 μ M. This highlights the promising inhibitory potential of certain derivatives in modulating PTP1B activity, which could have significant implications for T2DM treatment. Moreover, the researchers delved into the molecular mechanisms underlying the inhibitory activity of compound 7p through detailed binding mode analysis and molecular dynamics simulations. These computational techniques provided insights into the interactions between the inhibitor and the target enzyme, shedding light on the structural basis of their interaction and elucidating the mechanism of action. Overall, the study underscores the potential of 4-thiazolinone derivatives as promising candidates for T2DM therapy by targeting PTP1B. The synthesis, biological evaluation, and molecular dynamics studies collectively contribute to expanding the repertoire of PTP1B inhibitors and pave the way for further research in developing effective treatments for T2DM.

CHAPTER 3

AIM AND SCOPE

3.1 AIM

The aim of this comprehensive study is to evaluate the potent inhibitor of plants *Plectranthus amboinicus* for the treatment of type 2 diabetes. This overall goal is to clarify the pharmacological characteristics of thymol and determine whether it is a suitable natural chemical for treating PTP-related illnesses.

3.2 SCOPE

The study into thymol from *Plectranthus amboinicus* as inhibitors for Protein Tyrosine Phosphatase (PTP) represents a comprehensive exploration with broad implications for medical therapeutics. Beginning with chemical characterization, researchers meticulously examine thymol's properties, ensuring its purity and structural integrity. Subsequent assessment of inhibitory activity involves experimental assays to gauge thymol's effectiveness in blocking PTP enzymatic function. Molecular dynamics simulations further elucidate the intricate interactions between thymol and PTP at a molecular level, offering insights into its mechanism of action. Comparative analyses against reference inhibitors validate thymol's potency and specificity, bolstering its candidacy as a therapeutic agent. Investigating therapeutic applications, particularly in conditions like diabetes and cancer, underscores thymol's potential to mitigate disease progression. Safety evaluations are paramount, ensuring thymol's suitability for clinical use through rigorous toxicity assessments. Formulation optimization endeavors to enhance thymol's bioavailability and stability for efficient delivery. Ultimately, preclinical and clinical studies validate thymol's efficacy and safety, paving the way for translational applications in medicine. This multidisciplinary approach seeks to unlock thymol's therapeutic potential, offering promise in addressing diseases linked to dysregulated PTP activity and advancing medical treatment paradigms.

CHAPTER 4

METHODOLOGY

4.1 TARGET IDENTIFICATION

Uniprot Database include the data of Amino acid length, Gene, Organisms, Domain, PTP Protin structure, Protein's resolution. Thus, by following all these criteria we selected 5 PDB ID 1EEN , 1PXH, 2CMA, 2F6W,1L8G with least resolution and Domain present in it. Using all these Protein Id in PDBSum we can find the Disallowed region from Ramachandran plot

4.2 LIGAND IDENTIFICATION

In the process of ligand identification, by using IMPPAT database we can identify the phytochemical compounds of a selected plant (*Plectranthus amboinicus*). Among these compound Thymol is selected because it has an oral drug action and that the substance would have many pharmaceutical effects. Now using Pubchem we download Thymol compound in .sdf file format.

4.3 PHARMOKINETICS AND DRUGLIKENESS

Pharmokinetics and Drug likeness information are gathered in SWISS ADME Database. Pharmacokinetics is the study used to know about and plant / drug's absorption, distribution, metabolism, and excretion (ADME).

By using Lipinski's rule of five we found the Drug-Likeness of a selected compound's Canonical Smiles from Pubchem Database and check whether it has any violations in it.

4.4 MOLECULAR DOCKING

A computational receptor-ligand docking studies were performed to analyse the structural complexes of the PTP (receptor) with Thymol (ligand) in order to diagnose the specify structural relationship with the ligand. Molecular Docking is done using Discovery Studio.

It consists to 3 types of docking Algorithms Libdock , CDocker , GOLD Dock. Using Discovery studio we can visualize the Ligand-Receptor Interaction its 2D Diagram.

4.5 MOLECULAR DYNAMIC SIMULATION

Molecular Dynamic Simulation is done using Discovery Studio through Standard dynamic Cascade and RMSF plot is done using Cabsflex 2.0

Cabsflex is a server for fast modeling of protein structure flexibility. CABS-flex 2.0 implements an efficient simulation engine that allows for modeling of large-scale conformational transitions of protein systems.

CHAPTER 5

RESULTS AND DISCUSSION

5.1 TARGET IDENTIFICATION

The Co-crystal structure of the target protein was retrieved from the PDB Database. The target protein is (1EEN) Protein tyrosine phosphatase 1B (PTP1B), Classification - Hydrolase, Organisms – HomoSapeins. It consists of 2 chain A,B and a LIGAND ACY and MG and most importantly its Domin region ranges from 3-227(PTP) and by using PDBSum from Ramachandran plot we can visualize that it has 0 disallowed region.

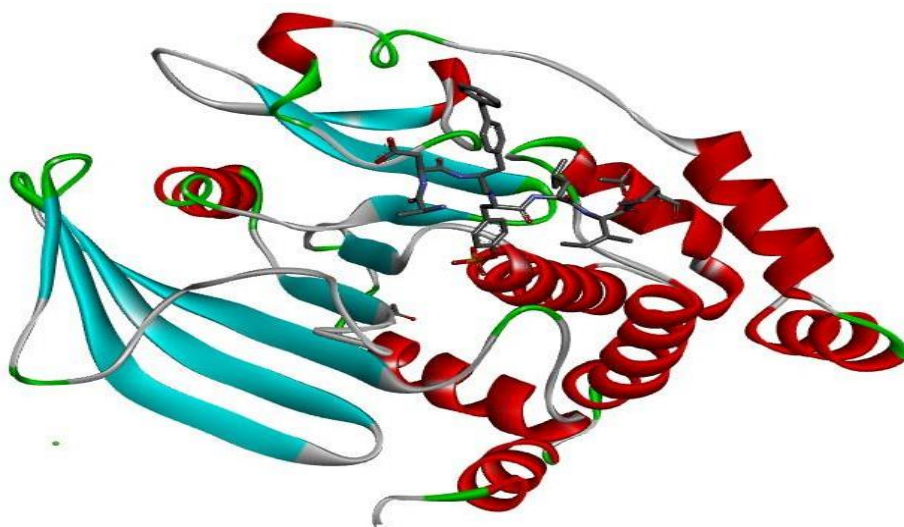


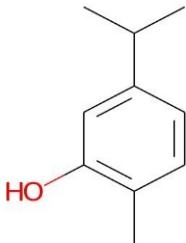
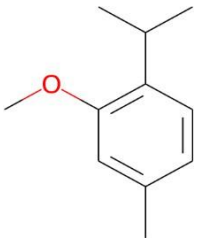
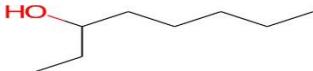
FIGURE 5.1.1: Target protein

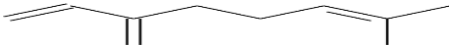
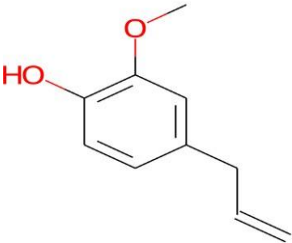
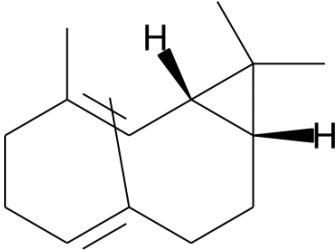
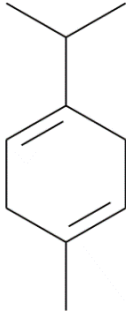
5.2 LIGAND IDENTIFICATION

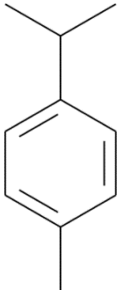
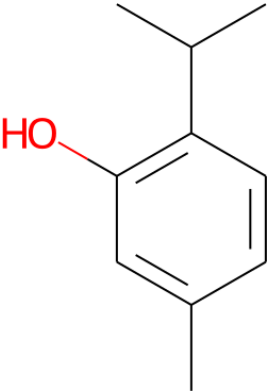
Medicinal plants have been used for centuries to treat human ailments in different systems of traditional medicine across the world. Phytochemicals are the chemical factors behind the therapeutic action of such plants and the medicinal formulations prepared from them. Consequently, significant research has been directed toward the identification of phytochemicals of medicinal plants to discover novel and biologically relevant molecules. (Vivek-Ananth RP et al 2023)

Ligand present in IMPPAT database can identify the phytochemical compounds of a selected plant (Plectranthus amboinicus). Among these compound “Thymol” is selected because it has an oral drug action that the substance has many pharmaceutical effects and it has 0 violation according to Lipinski Rule of five.

TABLE 5.2 : LIGAND IDENTIFICATION

PLANT NAME	ID / MOLECULAR NAME	MOLECULAR STRUCTURE
Plectranthus amboinicus 	<u>IMPHY001246 Carvacrol</u>	
	<u>IMPHY001658 Thymol methyl ether</u>	
	<u>IMPHY001828 3-Octanol</u>	

	<u>IMPHY003485</u> Myrcene	
	<u>IMPHY003536</u> Eugenol	
	<u>IMPHY003616</u> <u>Bicyclogermacrene</u>	
	<u>IMPHY003982</u> gamma- <u>Terpinene</u>	
	<u>IMPHY005345</u> 1-Octen-3- <u>OL</u>	

	<u>IMPHY006145</u> p-Cymene	
	<u>IMPHY006550</u> Thymol	

5.3 PHARMOKINETICS AND DRUGLIKENESS

SwissADME is the process of assessing the pharmacokinetic and drug-likeness properties of a compound . Thymol, a naturally occurring compound found in several plants, has garnered attention for its potential therapeutic properties. Utilizing SwissADME, researchers can explore various pharmacokinetic parameters, drug-likeness, Lipophilicity, Physicochemical Properties, Water Solubility, Medicinal Chemistry.

TABLE 5.3: PHARMOKINETICS AND DRUGLIKENESS

COMPOUND PROPERTIES		THYMOL
Lipophilicity	Log Po/w (iLOGP)	2.32
	Log Po/w (XLOGP3)	3.30
	Log Po/w (WLOGP)	2.82
	Log Po/w (MLOGP)	2.76
	Log Po/w (SILICOS-IT)	2.79

	Consensus Log Po/w	2.80
COMPOUND PROPERTIES		THYMOL
Drug-likeness	Lipinski	Yes; 0 violation
	Ghose	No; 1 violation: MW<160
	Veber	Yes
	Egan	Yes
	Muegge	No; 2 violations: MW<200, Heteroatoms<2
	Bioavailability Score	0.55
COMPOUND PROPERTIES		THYMOL
Pharmacokinetics	GI absorption	High
	BBB permeant	Yes
	P-gp substrate	No
	CYP1A2 inhibitor	Yes
	CYP2C19 inhibitor	No
	CYP2C9 inhibitor	No
	CYP2D6 inhibitor	No
	CYP3A4 inhibitor	No
	Log Kp (skin permeation)	-4.87 cm/s
COMPOUND PROPERTIES		THYMOL
Physicochemical Properties	Formula	C ₁₀ H ₁₄ O
	Molecular weight	150.22 g/mol
	Num. heavy atoms	11
	Num. arom. heavy atoms	6
	Fraction Csp ³	0.40
	Num. rotatable	1

	bonds	
	Num. H-bond acceptors	1
	Num. H-bond donors	1
	Molar Refractivity	48.01
	TPSA	20.23 Å²
COMPOUND PROPERTIES		THYMOL
Water Solubility	Log S (ESOL)	-3.19
	Solubility	9.74e-02 mg/ml ; 6.49e-04 mol/l
	Class	Soluble
	Log S (Ali)	-3.40
	Solubility	5.97e-02 mg/ml ; 3.98e-04 mol/l
	Class	Soluble
	Log S (SILICOS-IT)	-3.01
	Solubility	1.46e-01 mg/ml ; 9.71e-04 mol/l
	Class	Soluble
COMPOUND PROPERTIES		THYMOL
Medicinal Chemistry	PAINS	0 alert
	Brenk	0 alert
	Leadlikeness	No; 1 violation: MW<250
	Synthetic accessibility	1.00

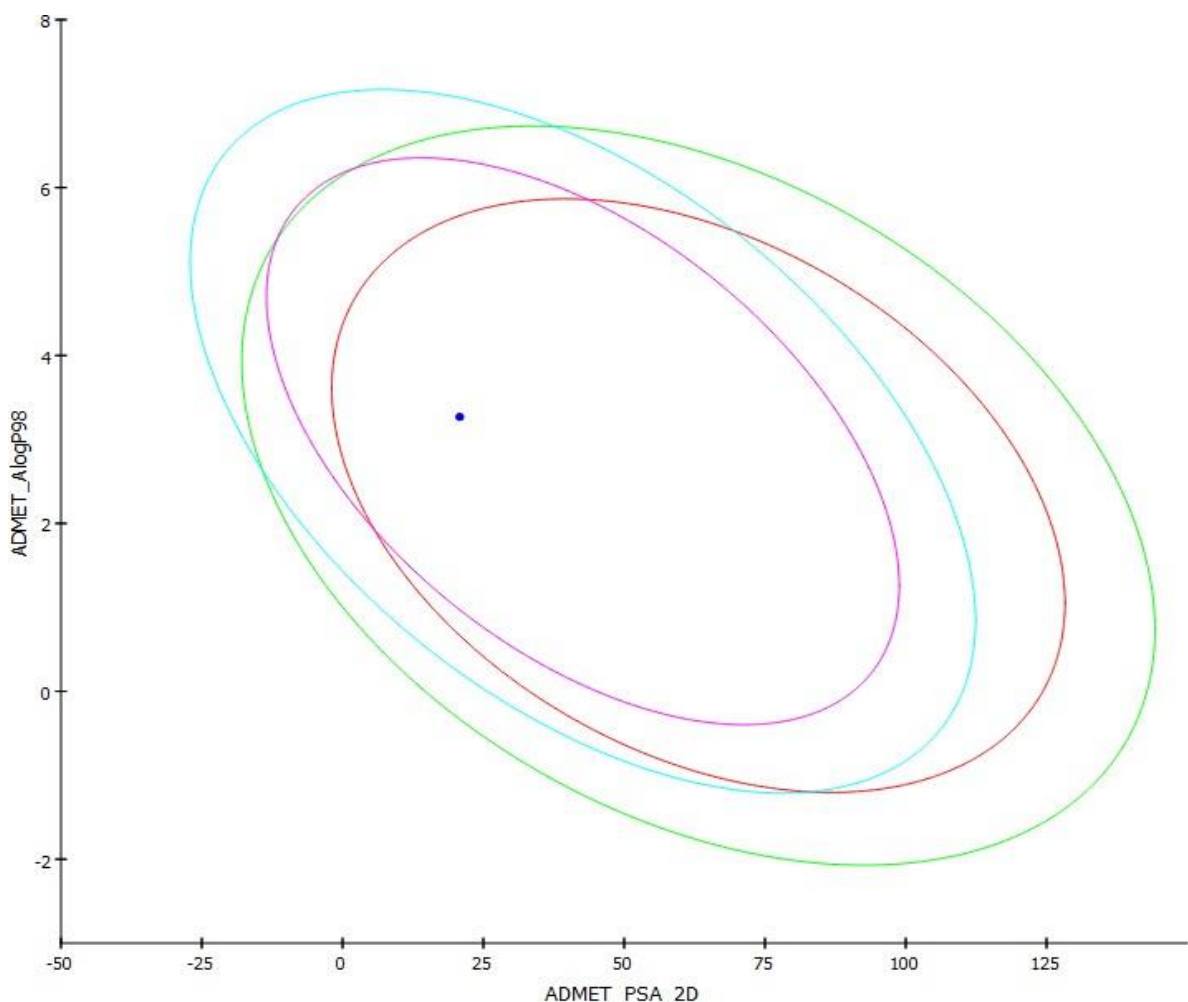


FIGURE 5.3.1 ADMET PREDICTION

5.4 MOLECULAR DOCKING

Molecular docking is done using Discovery studio.

The first step is to remove water, Hetatm and extra chains and Ligands present in the structure. After removing all these we need to do Minimization energy and calculate energy to check the least energy value because lesser the energy more the stability. By checking we got all protein ID with minimized value. After this we need to check the RECEPTOR CAVITIES and PDB SITE RECORD to check where it binds with the protein structure after we undergo the docking process . Discovery Studio employs a variety of docking algorithms, such as CDOCKER, GOLD, and LibDock, to generate a set of possible binding poses for the ligand, and to rank them based on their predicted binding energy.

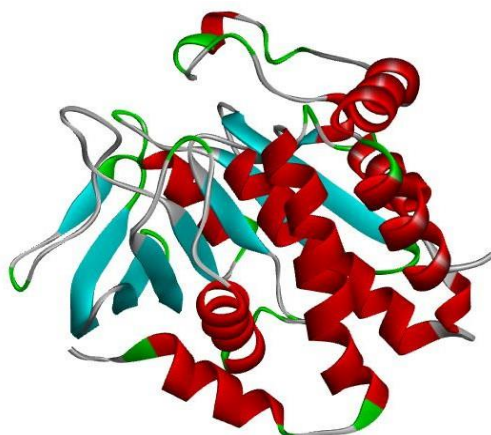


FIGURE 5.4.1: Calculate Energy

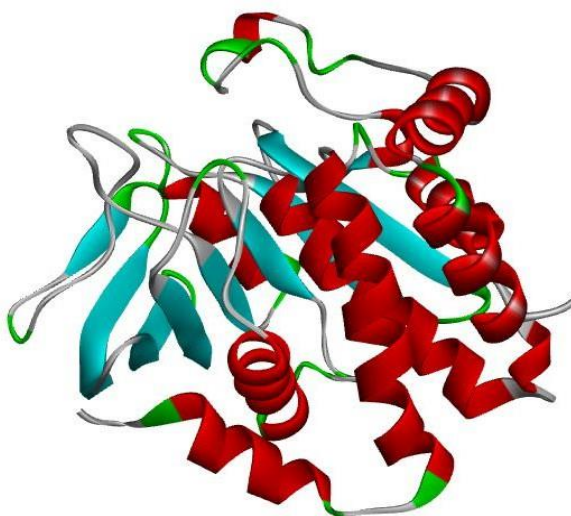


FIGURE 5.4.2: Minimization Energy

Calculate Energy Value: -6678.17610 and Minimization value : -11334.38309. Thus Minimization energy has least energy value . So Minimization energy value is further choosen for Docking.

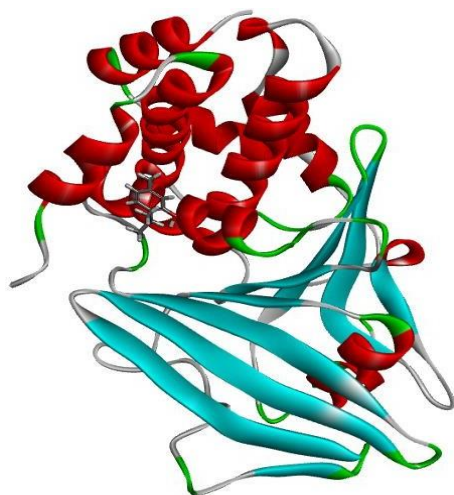


FIGURE 5.4.3: Docked Structure

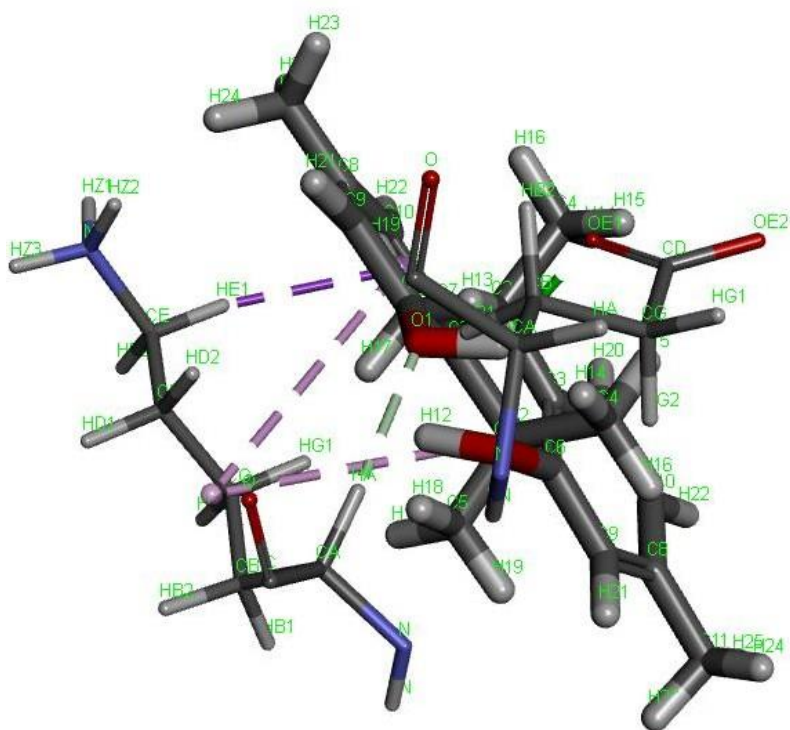


FIGURE 5.4.4: RECEPTOR LIGAND INTERACTION

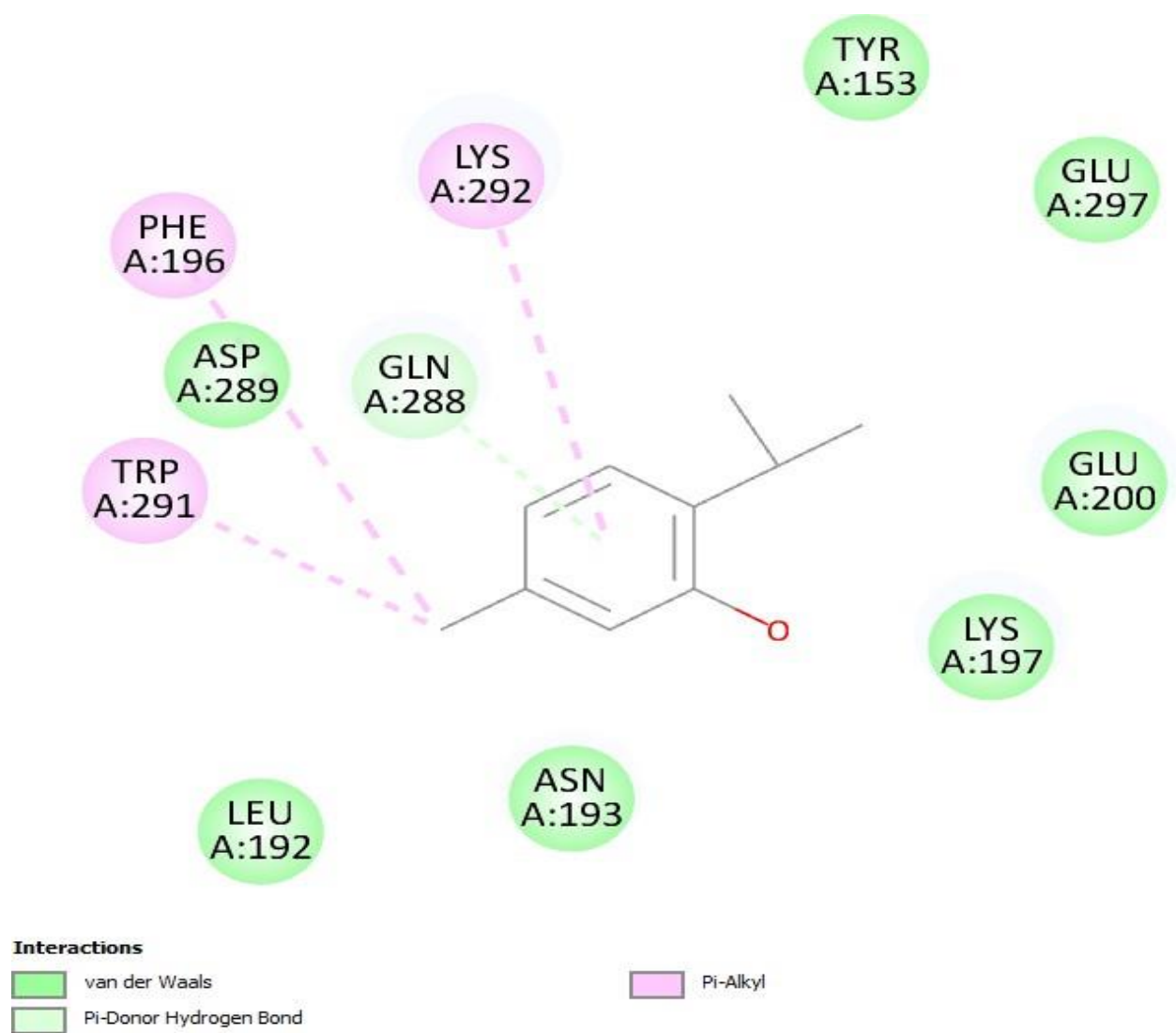


FIGURE 5.4.5 : RECEPTOR LIGAND INTERACTION 2D DIAGRAM

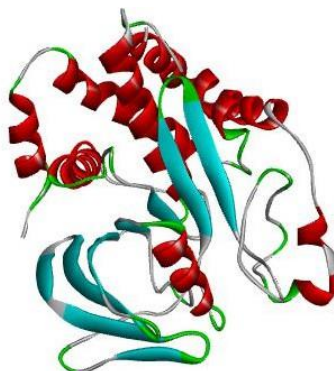


FIGURE 5.4.6 SOLVATION

5.5 MOLECULAR DYNAMIC SIMULATION

The investigated protein and ligand complex resulting from molecular docking and the pose optimization were submitted to MD simulations. Through the application of MD simulations, the insight gained through the molecular docking was extended, as MD is considered to serve as a more profound basis for molecular analysis of ligand recognition using default parameters.

(Stefan M. Noha et al 2017)

The CABS-flex method follows our earlier work where we demonstrated that the consensus view of protein near-native dynamics obtained from 1.5 ns MD simulations is consistent with dynamics from the CABS model. The CABS-flex simulation length has been optimized to obtain the best possible convergence with the 1.5 ns MD simulations.(Jamroz M et al 2014)

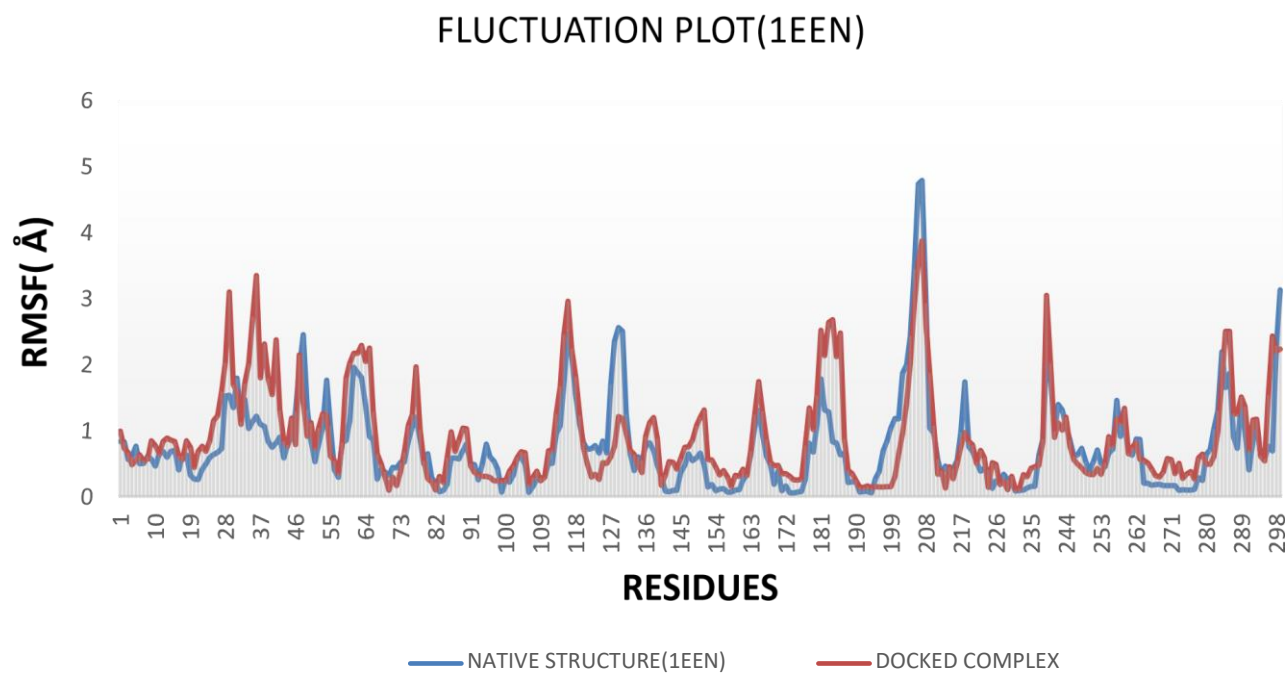


FIGURE 5.5.1: RMSF

CHAPTER 6

SUMMARY AND CONCLUSION

6.1 SUMMARY

The project aims to identify potential therapeutic avenues for treating type 2 diabetes by investigating the interaction between Protein Tyrosine Phosphatase (PTP) and Thymol, a compound found in *Plectranthus amboinicus*, a plant known for its antidiabetic properties. Initially, 6 PDB IDs of PTP were selected for molecular docking studies with Thymol. These proteins were analyzed for structural features, domain composition, and resolution using UniProt and PDB databases to ensure their suitability for docking experiments. Thymol's drug-likeness was evaluated through computational tools like SWISS ADME and IMPPAT. Molecular docking simulations, carried out using Discovery Studio, focused on the 1EEN PDB structure, revealing promising interactions between Thymol and PTP, particularly with 1EEN and Solvation is done using docked structure. Furthermore, molecular dynamics simulations provided dynamic insights into the stability of the Thymol-PTP complex, as indicated by Root Mean Square Fluctuation (RMSF). The findings suggest that Thymol from *Plectranthus amboinicus* holds potential as a treatment for type 2 diabetes due to its favorable interaction with PTP. Further research is essential to validate these computational findings and explore Thymol's therapeutic efficacy in clinical settings.

6.2 CONCLUSION

The study aimed to elucidate Protein Tyrosine Phosphate (PTP) as a promising therapeutic target for type 2 diabetes treatment, leveraging the potential interaction with Thymol, a compound derived from *Plectranthus amboinicus*. Methodologically, the research involved meticulous steps encompassing protein and compound selection, docking analysis, and comprehensive evaluation of structural aspects including domain characterization, disallowed regions, and resolution. Moreover, the investigation extended to assessing drug-likeness and small molecule interactions to gauge Thymol's pharmacological potential. Notably, the docking analysis, executed across seven selected PDB IDs of PTP and Thymol compound, was executed with particular focus on the 1EEN PDB structure, yielding insightful results. After Docking to check the water molecules present we undergo Solvation . Subsequently molecular dynamics (MD) simulation utilizing the computation of essential metrics such as Root Mean Square Fluctuation (RMSF) for the target protein. The findings underscored promising interactions between Thymol and PTP, suggesting its candidacy as a therapeutic agent for type 2 diabetes. The successful docking and MD simulation outcomes substantiate the plausibility of Thymol binding to PTP and potentially modulating its activity, thus paving the way for further exploration and development of novel antidiabetic therapeutics.

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