NETWORK PHARMACOLOGY BASED APPROACH ON POTENTIAL TARGETS OF *OCIMUM SANCTUM*

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Abstract

Holy basil, or Ocimum sanctum, is a herb widely utilized in traditional medicine for various health advantages, such as a potential reduction of cholesterol. The single most important risk factor for heart disease is high cholesterol, and although statins and other medications similar to them are widely used, they have unwanted side effects. Consequently, the interest in natural remedies has increased. It is still not known precisely how Ocimum sanctum contributes to cholesterol management, however Holy basil, or Ocimum sanctum, is a herb widely utilized in traditional medicine for various health advantages, such as a potential reduction of cholesterol. In this research, we examined the interactions between the bioactive compounds of Ocimum sanctum and key proteins that play a role in cholesterol metabolism through network pharmacology and molecular docking. With the aid of bioinformatics tools such as IMPPAT, STITCH, STRING, ADMETLab, AutoDock Vina (molecular docking), and Discovery Studio, we examined the compounds of the plant and their effect on cholesterol-related target proteins. Based on our Studies, we have six key target proteins that are linked to oxidative stress, inflammation, and lipid metabolism: AMPK, MAPK, PPARa, PPARγ, CYP2C9, and ALOX12.Through molecular docking studies, it was discovered that Ocimum sanctum compounds were binding well to these proteins, suggesting potential cholesterol regulation. The ancient use of Ocimum sanctum in cholesterol control is complemented by computational data provided in this work. By the combination of molecular docking and network pharmacology, we highlight its possible multi-target activity. These findings extend our understanding of plant medicine and pave the way for further research in the laboratory to study the plant's possible role as a natural cholesterol-reducing agent

Keywords*: Ocimum Sanctum, Cholesterol, Molecular Docking, Inflammation, Oxidative Stress.*

Introduction

2.1 Hypercholesterolemia:

Hypercholesterolemia is a clinical syndrome that has high levels of cholesterol (≥200 mg/dl) and is also associated with atherosclerosis and cardiovascular disease (Rachmawati, et al., 2019). Globalization negatively affects nutritional transitions in general society of many nations around the globe, leading to changes in food intake from high carbohydrate and fiber to high fat, salt, and cholesterol. One recent study revealed that elevated cholesterol levels in adults are related to increased risk of CVD (Cardiovascular Disease), in comparison

with individuals having normal or low cholesterol levels. Even though cholesterol level changes cannot be ascertained, we suppose that such lowered cholesterol levels will be obtained by lifestyle intervention or through statin medication Unhealthy food habits due to globalization have added risks for cholesterol (Chu, A., et al ., 2016).Lifestyle control by diet and exercise is useful.

2.2 Statin Treatment and Side Effects:

Hydroxymethyl glutaryl coenzyme A reductase (HMG-CoA) inhibitors commonly known as statins is mostly widely prescribed drug acroos the world since their introduction to the market which is more than twenty year ago . Currently, there are six statin drugs available on the market they are pitavastatin, atorvastatin, rosuvastatin, pravastatin, simvastatin and fluvastatin. Because pitavastatin is more commonly prescribed in Asian patients, trial results are more generalizable to the wider Asian population (Saku, K.,et al ., 2011)

Statin therapy is effective in lowering low density lipoprotein cholesterol (LDL-C) levels 20-50%, as well as lowering triglyceride levels 10-20% and it can increase the high density lipoprotein cholesterol (HDL-C) levels (5-10%) (Huang, W. C., et al ., 2013, Odden, M. C., et al .,2015, Taylor, F., et al.,2013). Nearly all of the statin drugs are associated with musculoskeletal side effects (Pedro-Botet, J., et al ,. 2015). Most common symptom is Myalgia , and less common is myositis and is associated with a rise in creatine kinase (CK) (Pedro-Botet, J., et al ,. 2015) .Statin therapy is associated with increase in hepatic transaminases up to 1-3% of patients. This is usually dose dependent and it occurs within the first three months of the therapy, and is not associated with long-term hepatic dysfunction.Out of 20,000 patients on pitavastatin, two had abnormal liver tests, and seven experienced other liver issues. However, most had no symptoms, and serious liver failure from statins is extremely rare (Yokote, K., et al ., 2011). Statins can cause increase to get diabetes mellitus in patients , when they can disrupt insulin signalling pathways, affect pancreatic beta cell function and may also contribute to increased insulin resistance. (Bang, C. N., & Okin, P. M. (2014) , Cederberg, H., et al (2015))Statins may affect the kidney in two primary mechanisms. Statin therapy may be related to a benign proteinuria with inhibition of tubular reabsorption of low molecular weight proteins. (Brown, W. V. (2008).)

Given these challenges, there is increasing interest in natural products and plant-based therapies as alternative or complementary treatments. In certain regions, the utilization of traditional medicine through the use of medicinal plants has a very significant role, determined by a number of factors, such as contemporary health care that does not have appropriate and fair health services, constraints on the economic status pertaining to quick population increase, and weak economic performance (Kairanova, G. K., (2024) , Yeshiwas, Y., et al (2019).)

2.3 Medicinal Plants and Their Therapeutic Importance

Medicinal plants, a centuries-old medicine, possess bioactive compounds with anti-inflammatory and hypolipidemic activity (Davis et al., 2002; Rates, 2001).Even though used for centuries, a mere 16% have been clinically tested (Allkin & Willis, 2017).

2.4 Ocimum sanctum: A Cholesterol-Lowering Herb:

Ocimum sanctum (Holy Basil) contains antioxidant, polyphenolic, and flavonoid compounds that are useful in lowering cholesterol levels (Mahmoud et al., 2017; Grassi et al., 2009). It was found to lower LDL and total cholesterol levels as per studies (Waji & Surgani, 2009; Rachmawati et al., 2019). O. sanctum contains flavonoids, phenolics, and terpenoids possessing hypolipidemic activity (Maurya et al.; Mahajan et al., 2013; Pattanayak et al., 2010). It increases the excretion and metabolism of cholesterol, prevents oxidative stress, and decreases hypercholesterolemia.

2.5 Network Pharmacology Approach:

Figure 1Ocimum sanctum (Tulsi)

Network pharmacology utilizes bioinformatics in pursuing drug-target interaction. It reveals the major molecular targets of O. sanctum in cholesterol control (Dong et al., 2021). The method speeds up drug research and explains mechanisms (Zhou et al., 2020; Noor et al., 2022). The model departs from single-target therapy to multi-target therapy, and thus it is suitable for plant medicine research (Lee et al., 2019; Zhang et al., 2020).

Matreials and methods:

3.1 Compound Identification and Selection IMPPAT

IMPAAT database has been utilized for identification of bioactive compounds in Ocimum sanctum (Mohanraj et al., 2018). Interactions among plant part-phytochemical-therapeutic application are reported in IMPPAT 2.0, the largest database of medicinal plants in India. Ocimum sanctum search, screening for medicinal compounds, chemical structure inspection, patent searching, literature checking, and molecular docking tools form a part of it.

3.2 Target Prediction and Interaction Analysis

STITCH (Szklarczyk et al., 2016) and STRING (Szklarczyk et al., 2019) were employed to identify protein targets of cholesterol metabolism. STITCH treats chemical-protein interactions in terms of experimental and evidence-based data from databases. The method utilized was querying Ocimum sanctum, extracting chemical-protein interactions, filtering with confidence score (>0.7), and interaction network study and validation for bioactive compounds. STRING was utilized for the construction of protein-protein interaction (PPI) networks for relationship mapping of the targets.

3.3 Drug-Likeness and ADMET Analysis

SWISS ADME evaluated drug-likeness, solubility, and bioavailability. Identified compounds were retrieved from literature or databases (PubChem, ChEMBL) and submitted in SMILES or InChI format. Filters such as Lipinski's Rule of Five and Veber's Rule assessed drug potential. ADMETlab predicted pharmacokinetic features such as absorption, metabolism, excretion, and toxicity. The findings offered information on solubility, permeability, metabolic stability, and toxicity potential

3.4Data Retrieval and Structural Preparation

Protein sequences were retrieved from UniProt and 3D structures were retrieved from PDB. Conformations of ligands were downloaded from PubChem and minimized in energy by Chimera for docking analysis.

3.5 Molecular Docking and Interaction Analysis

AutoDock Vina was used to perform docking (Trott & Olson, 2010) in order to search for ligand-protein interactions. Water molecules and heteroatoms were removed from proteins while pre-processing using Chimera. Significant residues were selected, and the docking site was assigned. Binding affinity was computed and outputs verified using Discovery Studio (Dassault Systèmes, 2020) to display hydrogen bonding, hydrophobic contacts, and π-π stacking for confirmation.

Result and disscussion

4.1 Compound Identification and Selection IMPPAT

By using IMPPAT database, a total of about 587 phytochemicals were identified and these compounds were retrieved, which gives the foundation for further compound Identification and selection.

4.2 Stitch and string analysis With STITCH and STRING, interaction networks were constructed on the connections of Ocimum sanctum bioactive substances with the potential protein targets (Figures 1-2).

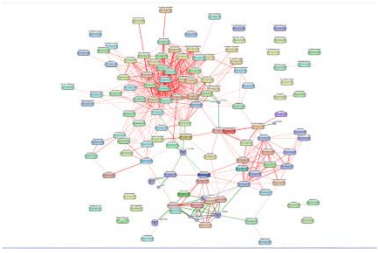


Figure 2 STITCH analysis

4.3 SITCH Compound-Target Interaction Network

This network shows the interactions between the target proteins of the bioactive chemicals found in Ocimum sanctum.Large chemicals with multiple target interactions are symbolized by the heavily interconnected nodes. Red edges represent strong correlations, whereas green and blue edges represent other types of interaction

4.4 STRING Protein-Protein Interaction Network.

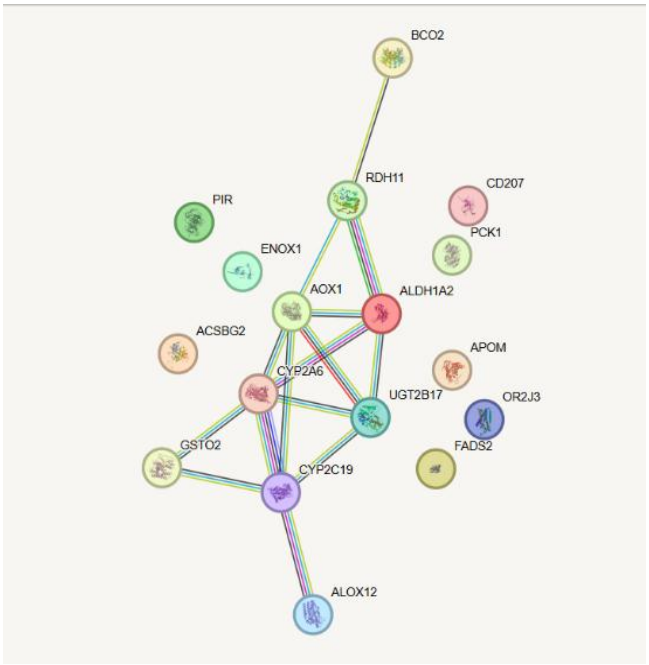


Figure 2 STRING analysis

PPIs between the top targets identified in the study are identified through STRING analysis.The network exhibits strong relationships among PPARα, PPARγ, CYP2C19, MAPK, AMPK, and ALOX12 and plays a significant role in lipid metabolism, inflammation, and cholesterol regulation. Center nodes of the network indicate the significance of these proteins in the hypocholesterolemic effect of Ocimum sanctum. These findings raise questions regarding the molecular pathways through which Ocimum sanctum may be exhibiting its ability to decrease cholesterol.

4.5 ADME and Toxicity Evaluation for Lipid-Lowering Activity

To investigate the pharmacokinetic potential and safety of Ocimum sanctum phytochemicals as lipid metabolism modulators, ADME-Tox studies were conducted using SwissADME and ADMETlab 3. The data show that a number of compounds have good drug-like properties, making them candidate as lipid lowering drugs.

4.6 SwissADME Predictions

SwissADME analysis of the chosen phytochemicals demonstrated molecular weights between 98.14 and 222.37 Da, indicating good drug-like characteristics

Lipophilicity (LogP): The majority of compounds had moderate logP values, providing optimum membrane permeability and aqueous solubility, which are required for systemic circulation and target interaction.The potential for effective oral treatment of some substances in lipid metabolic diseases is demonstrated by their considerable absorption via the gastrointestinal tract (GI).

Permeability of the Blood-Brain Barrier (BBB): It was discovered that some phytochemicals have BBB permeability, which is crucial for the main regulatory mechanisms of lipid metabolism.The molecules were recognized as P-glycoprotein (P-gp) substrates, a finding with relevance to drug bioavailability and transport.

CYP Enzyme Inhibition: Some of the phytochemicals were recognized as CYP2D6 inhibitors, which would influence drug interactions and metabolic stability. Water Solubility: Although the compounds showed a range of solubility trends, most showed positive solubility that would be conducive to improved bioavailability and systemic activity.

4.7 ADMETlab 3 Toxicity Predictions

The toxicity evaluation showed that the greater majority of the phytochemicals possess a good safety margin, with hardly any risk for toxicity at doses used therapeutically. Carcinogenicity & Mutagenicity: Most of the compounds exhibited minimal carcinogenicity and mutagenicity, affirming their innocuity for indefinite lipid-lowering therapy. Hepatotoxicity: While a few showed slight hepatotoxicity, many were found not to be hepatotoxic, proving their utility for lipid metabolism in the absence of harmful hepatic effects. Acute Aquatic Toxicity: The environmental toxicity risks were minimal for the majority of compounds, with a safer ecological imprint. All these toxic compounds were removed and is not included them in further studies.

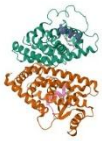
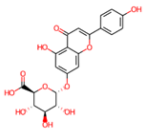
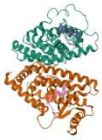
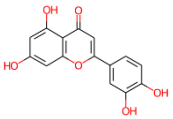
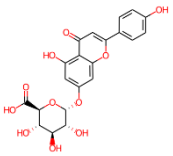
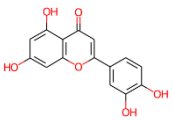
4.8 ADME-Tox Implications in Lipid-Lowering Activity

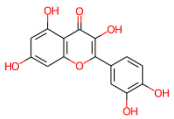
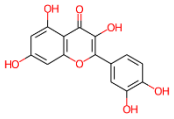
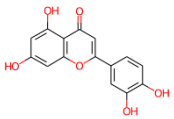
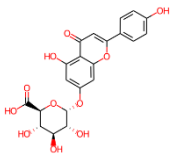
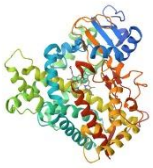
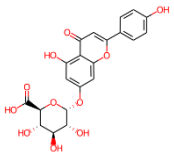
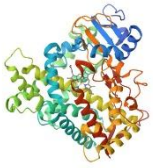
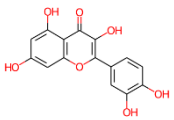
The good GI absorption, moderate lipophilicity, and low toxicity of Ocimum sanctum phytochemicals are pharmacokinetic attributes with positive connotations, and therefore, they are good prospects for lipid-lowering drugs. The fact that they can engage key lipid metabolism targets like PPARα, PPARγ, and AMPK, coupled with acceptable ADME profiles, hints at their possible role in the regulation of cholesterol and triglyceride levels.

In vitro and in vivo verification of these findings and testing in clinical contexts remain to be determined.

4.9 Docking and interaction analysis:

We got 24 compounds which are not toxic and plays crucial role in lipid lowering. These compounds are docked with the 6 target proteins they are MAPK, AMPK, CYP2C19, ALOX12, PPARG, PPARA. So we got the docking energies. The highest docking energies and the compounds which is involved in binding with 6 different proteins has been depicted in table 1.

S No	*Proteins*	*Compound*	*Energies*	*Interactions*
1	PPARγ 	Apigenin-7-o-glucuronide 	-9.3	Van der Waals: LEU-325, LEU-326, LEU-309, LEU-433, LEU-436, PHE-439, PHE-346, TRP-305, HIS-435, VAL-265, VAL-342, VAL-349, ILE-345. Conventional Hydrogen Bond: ALA-327 Carbon Hydrogen Bond: GLN-275 Unfavorable Donor-Donor: ARG-316 Pi-Pi T-shaped: PHE-313 Amide-Pi Stacked: ALA-271 Pi-Alkyl: ALA-272, CYS-432, ILE-268
3	PPARγ 	Luteolin 	-8.6	Van der Waals: LEU-240, LEU-367, HIS-315, ILE-318, ALA-319 Conventional Hydrogen Bond: GLU-239, GLN-275 Carbon Hydrogen Bond: None Pi-Cation: ARG-316 Pi-Anion: GLU-243 Pi-Sigma: LYS-364 Pi Interactions Pi-Alkyl: PRO-244
6	PPAR A 	Apigenin-7-o-glucuronide 	-9.2	Van der Waals: LEU-240, LEU-367, HIS-315, ILE-318, ALA-319 Conventional Hydrogen Bond: GLU-239, GLN-275 Carbon Hydrogen Bond: None Pi-Cation: ARG-316 Pi-Anion: GLU-243 Pi-Sigma: LYS-364 Pi-Alkyl: PRO-244
8	PPARA 	Luteolin 	-8.9	Van der Waals: GLN-277, LEU-456, LEU-460, VAL-444, GLU-269, LEU-347, LEU-344, ILE-272 Conventional Hydrogen Bond: PHE-351 Pi-Donor Hydrogen Bond: HIS-440 Pi-Sulfur: MET-355 Pi Interactions Pi-Pi T-shaped: PHE-273, ILE-354 Pi-Alkyl: CYS-276, HIS-440, TYR-314, PHE-318

9	PPARA 	Quercetien 	-8.8	Van der Waals: ILE-317, LEU-344, LEU-347, LEU-456, LEU-460, VAL-444, GLU-269, ILE-272, PHE-351Conventional Hydrogen Bond: SER-280, CYS-276Pi-Donor Hydrogen Bond: HIS-440 Pi-Sulfur: MET-355 Pi-Pi T-shaped: PHE-273, ILE-354 Pi-Alkyl: HIS-440, TYR-314, PHE-318
11	MAPK 	Quercetien 	-9.5	Van der Waals: GLU-170, GLU-122, GLY-124, GLY-451, GLY-453, LEU-450, LEU-452 Conventional Hydrogen Bond: ASP-187, THR-186 Unfavorable Donor-Donor Interaction: ASP-187 Electrostatic Interactions Pi-Sulfur: MET-118, CYS-120 Pi-Alkyl: LEU-173, ALA-71, VAL-158
13	MAPK 	Luteolin 	-9.3	Van der Waals: GLU-170, GLU-122, GLY-124, GLY-51, GLY-53 Conventional Hydrogen Bond: LEU-52 Pi-Sulfur: MET-118, CYS-120 Pi-Alkyl: LEU-173, ALA-71, VAL-58
14	MAPK 	Apigenin-7-o-glucuronide 	-9.2	Van der Waals: GLU-170, GLY-51, GLY-52, GLY-123, GLY-124, LEU-452 Conventional Hydrogen Bond: VAL-49, GLN-48, GLU-122 Carbon Hydrogen Bond: GLY-124 Unfavorable Acceptor-Acceptor Interaction: ASP-187 Pi-Alkyl: LEU-173, LEU-50, VAL-58
16	CPY 	Apigenin-7-o-glucuronide 	-9.7	Van der Waals: LEU-131, LEU-178, LEU-362, LEU-440, GLN-356, LEU-294, LEU-445, THR-305, THR-302, GLY-444, GLY-437, ALA-287, ALA-436, ALA-441, PRO-427, VAL-213, VAL-436, PHE-320, ILE-112, ILE-254, ARG-124 Conventional Hydrogen Bond: GLY-298, GLN-356, THR-302 Carbon Hydrogen Bond: ALA-287, ALA-441 Electrostatic Interactions Pi-Sulfur: CYS-435 Pi-Sigma: GLY-298 Pi-Alkyl: ILE-254, ALA-287, ALA-441
18	CPY 	Quercetin 	-8.6	Van der Waals: LEU-362, LEU-366, LEU-391, LEU-294, SER-365, SER-429, PRO-427, THR-301, PHE-425, GLY-437, VAL-436, VAL-113 Conventional Hydrogen Bond: ARG-97 Pi-Donor Hydrogen Bond: ARG-433 Pi-Sulfur: CYS-435 Pi Interactions Pi-Sigma: CYS-435 Amide-Pi Stacked: ARG-124 Pi-Alkyl: ILE-112, VAL-113, VAL-436, ALA-287

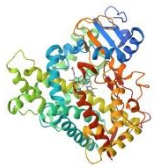
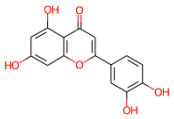
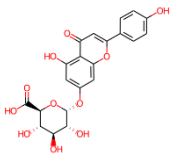
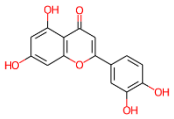
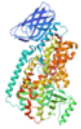
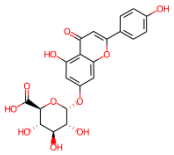
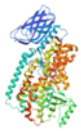
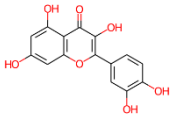
20	CPY 	Luteolin 	-8.5	Van der Waals: LEU-362, LEU-391, LEU-366, SER-429, SER-365, THR-301, PHE-425, PRO-427 Conventional Hydrogen Bond: TRP-120, ILE-112 Pi-Donor Hydrogen Bond: ARG-97 Pi-Cation: ARG-124Pi-Sigma: CYS-435 Amide-Pi Stacked: ALA-287 Pi-Alkyl: VAL-113, VAL-436
21	AMPK 	Apigenin-7-o-glucuronide 	-9.1	Van der Waals: LEU-22, VAL-24, TYR-95, VAL-96, SER-97, ALA-256 Conventional Hydrogen Bond: ASN-149, GLU-100, THR-26 Unfavorable Acceptor-Acceptor: ASP-157 Pi-Alkyl: LEU-146, VAL-30
23	AMPK 	Luteolin 	-8.4	Van der Waals: TYR-95, GLU-94, ILE-77, GLY-25, GLY-159, ASP-157, PHE-158 Conventional Hydrogen Bond: VAL-96 Pi-Donor Hydrogen Bond: TYR-95 Pi-Alkyl: LEU-22, LEU-146, VAL-30, ALA-43, ALA-156 Pi-Sulfur: MET-93
26	ALOX12 	Apigenin-7-o-glucuronide 	-7.5	Residues: TYR-395, GLU-1289, ALA-412, GLY-11, PHE-477, HIS-67, GLU-394 Conventional Hydrogen Bonds: GLU-394, GLU-1289, LYS-601 Carbon Hydrogen Bond: GLU-1289 Pi-Sigma: VAL-805 Pi-Alkyl: ARG-600, PRO-806 Pi-Anion: ASP-803Unfavorable Acceptor-Acceptor: HIS-608 Unfavorable Donor-Donor: HIS-608
29	ALOX12 	Quercetin 	-6.8	Residues: ILE-390, MET-614, ASN-163, ARG-165, TYR-395, ASP-603, HIS-167, ARG-394, PHE-477 Conventional Hydrogen Bonds: TYR-416, GLU-169, ASP-603 Carbon Hydrogen Bond: ARG-394 Pi-Anion: GLU-612 Unfavorable Acceptor-Acceptor Interactions Pi-Sigma: PHE-477 Pi-Pi Stacked & Pi-Pi T-Shaped: TYR-416, ARG-394 Pi-Alkyl Interactions

Table 1 Shows the Docking Energies of top 3 Compounds with 6 Protein along with the Binding Interactions

Molecular docking study identified three major bioactive molecules of Ocimum sanctum with multi-target interactions, which suggest their utility in cholesterol control and cardiovascular health. These are:

- Apigenin-7-O-glucuronide: Highly binds to PPARγ, PPARα, CYP enzymes, and AMPK, which suggests it may help with metabolism, energy balance, and drug metabolism.
- Quercetin: Interacts with MAPK (anti-inflammatory), PPARα (metabolism), and CYP (drug metabolism), suggesting anti-inflammatory and metabolic regulation activities.
- Luteolin: Interacts moderately with PPARα, MAPK (anti-inflammatory), CYP, and AMPK, favoring lipid metabolism and energy homeostasis.

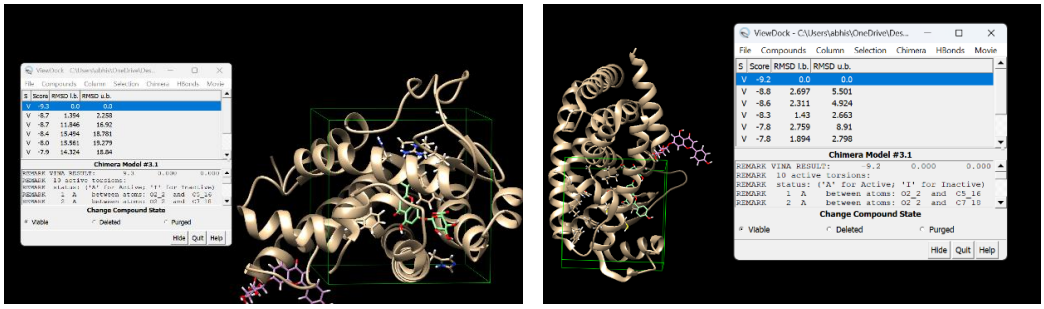


Figure 4 Molecular docking of with Apigenin-7-o-glucuronide Shows High affinity with PPARγ, PPARα

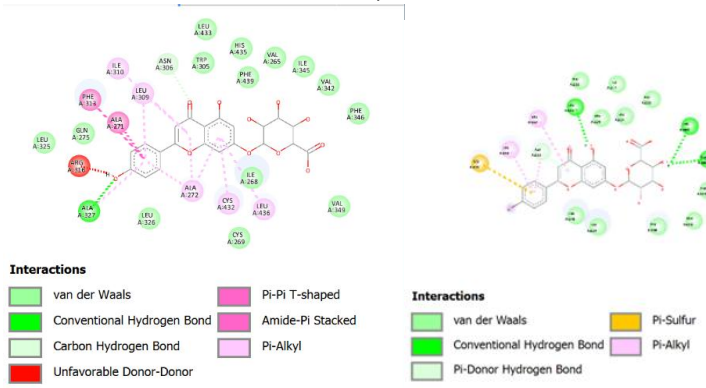


Figure 3 Receptor Ligand Interactions with Apigenin-7-o-Glucuronide PPARγ, PPARα

These multi-target agents imply a synergistic action in cholesterol metabolism, inflammation regulation, and lipid management.To guarantee their efficacy, in-vitro studies on cell lines and enzymatic assays are required.Experimental confirmation will establish their therapeutic merit in hypercholesterolemia and justify their application as natural hypocholesteremic drugs.

V. Conclusion:

The metabolic effects on lipids by Ocimum sanctum are analyzed through network pharmacology and molecular docking. It provides significant new information regarding potential therapy of hypercholestromelia . It is possible that Ocimum sanctum controls lipid

metabolism because of the phytochemicals interactions with important metabolic proteins (AMPK, MAPK, CYP2C9, ALOX12, PPARα, and PPARγ). Docking studies show a strong binding between phytochemical compounds and proteins, which supports their potential efficacy. This study establishes the foundation for additional experimental verification invivo and invitro has to be done.

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