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In *silico* drug-likeness /ADMET prediction and molecular docking studies on key chemical constituents of *Crataegus Azarolus L.* for preventing cardiovascular disease

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A B S T R A C T

Introduction: Elevated plasma LDL cholesterol levels play a crucial role in cardiovascular disease development. Squalene synthase (SQS), a regulatory enzyme in cholesterol biosynthesis, is a target for controlling hypercholesterolemia. Traditional medicine recommends *Crataegus Azarolus L.* for heart-related conditions, including high blood pressure, irregular heartbeat, and arteriosclerosis. Our research focuses on drug-likeness/ADMET prediction and molecular docking studies of C. azarolus constituents for cardiovascular disease prevention.

Materials & Methods: Chemical constituents of *C. azarolus L.* were selected based on the squalene synthase co-crystal molecule (3ASX). After energy optimization with Hyperchem, Auto Dock Vina facilitated ligand docking into the SQS active site, providing data on binding methods and compound binding energy. SwissADME and SCF Bio IITD webserver were used for in silico drug-likeness/ADME predictions.

Results: Auto Dock Vina results and pharmacokinetic (PK) studies revealed that 2,4-Di-tert-butylphenol exhibited the highest alignment with the synthetic co-crystal molecule concerning position, binding energy, and pharmacokinetic properties among herbal compounds.

Conclusion: Overall, 2,4-Di-tert-butylphenol demonstrated significant affinity for squalene synthase, suggesting its potential to occupy the enzyme's active site. This compound holds promise as a viable substitute for the synthetic co-crystal molecule, pending laboratory confirmation.

Keywords: Squalene synthase, Drug-likeness, ADMET prediction, *C. azarolus*, Docking study

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Introduction

The cardiovascular system, comprising the heart and blood vessels, is integral to human physiology. Unfortunately, a spectrum of issues may afflict this system, with cardiovascular diseases (CVDs) emerging as a leading cause of global morbidity and mortality, affecting both developed and developing nations. Identified risk factors for CVDs include high blood pressure, smoking, elevated cholesterol levels, diabetes, physical inactivity, obesity, family history, and ethnic background (1-3).

Elevated plasma cholesterol concentration stands out as a fundamental risk factor for cardiovascular diseases. The body's cholesterol levels are influenced by both diet and biosynthesis processes (4, 5). Squalene, a crucial precursor in the cholesterol biosynthetic pathway, is produced by squalene synthase (SQS, EC.2.5.1.21). SQS, a regulatory enzyme located in the microsomal membrane, catalyzes the conversion of two farnesyl pyrophosphate (FPP) molecules into squalene. Given its pivotal role, SQS has become a target for addressing hypercholesterolemia, emphasizing the use of inhibitors to modulate cholesterol metabolism (6-8).

Plant-derived prescription drugs, known for their safety, constitute over 25% of medicinal compounds. Despite this, only a small fraction of traditional herbal medicines has undergone scientific evaluation. Therefore, comprehensive investigations, including in silico, in vitro, and in vivo studies, are crucial to validating the medicinal efficacy of phytochemicals (9, 10). Crataegus azarolus L., a member of the Rosaceae family, is prevalent in North America, Asia, and Europe. Historically, its fruits have been consumed as food and employed in traditional medicine for treating cardiovascular ailments (11,12).

Molecular docking, a theoretical method, is employed to predict binding energy and interactions between macromolecules and small molecules. In this study, a molecular docking was utilized to elucidate the interactions and binding modes of C. azarolus's main chemical constituents with squalene synthase, presenting them as potential inhibitory drugs. Furthermore, the drug-likeness prediction and ADME properties of all investigated compounds are thoroughly examined (13-16).

Materials and Methods

Main Chemical Constituents selection and preparation

The selection of main chemical constituents from C. azarolus L. was based on prior research findings (11, 17, 18). Compounds were chosen according to the scaffold of the squalene synthase co-crystal molecule in 3ASX. The structures of selected compounds were drawn using ChemDraw Pro 8.0 software and subsequently optimized for energy using HyperChem Professional 8.

Target selection and preparation

Squalene synthase, a crucial enzyme in cholesterol biosynthesis inhibition (4, 7), was designated as the target macromolecule. The enzyme, sourced from the protein data bank (PDB) with properties including Accession code: 3ASX (19), Organism: Homo sapiens, Mutation: No, Resolution: 2.00 Å, Sequence Length: 340, underwent preparation by removing phosphate ion (PO4400),1-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]pheny

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l}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (co-crystal molecule), and all water molecules using Accelrys Discovery Studio 3.5.

In silico docking protocol validation

Validation of the docking protocol was conducted to ascertain the accuracy of docking results, involving comparison of the molecular interactions of the co-crystal compound before and after docking. Auto Dock Vina facilitated the investigation of the ligand's binding mode with the squalene synthase active site, and the resulting docked complexes were compared with 3ASX in the PDB site.

Molecular docking studies

Molecular docking studies, crucial for modeling ligand interactions with target receptors (20, 21), followed the validation stage. Ligands, previously optimized for energy, underwent Auto Dock Vina. The PDBQT format was initially created for ligands, wherein partial charges (Q) and atom types (T) were determined. The most suitable docking pose, determined through the analysis of output files and different conformations, exhibited the lowest binding energy (ΔGbind) and root mean square deviation (RMSD) (22).

ADME properties

The investigation of absorption, distribution, metabolism, and excretion (ADME) properties is vital for pharmacodynamic analysis. Ligands demonstrating favorable docking results were subjected to ADME property studies using SwissADME (23).

Drug-likeness screening

Drug-likeness screening, employing Lipinski's Rule of Five (RO5), assessed key criteria for oral drug administration. The online tool in SCF Bio IITD webserver was utilized for this purpose, with Isomeric SMILES as the input sequence (24). The screening criteria included: the number of hydrogen bond donors < 5, molecular weight < 500 g/mol, number of hydrogen bond acceptors < 10, calculated logP < 5, and Mol. Refractivity between 40 - 130.

Results

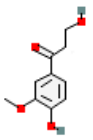
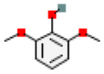
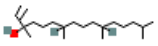
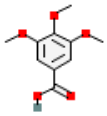
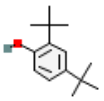
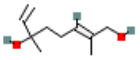
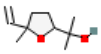
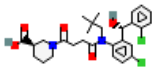
Main Chemical Constituents selection and preparation

In accordance with the highly potent squalene synthase inhibitor co-crystal molecule structure (19), featuring two cyclohexatriene moieties, tert-butyl, and a hydroxyl group, compounds with a higher concentration of these moieties in the extract of C. azarolus L. leaves were selected and optimized as ligands. The name, molecular formula, and chemical structure of the selected compounds are presented in Table 1.

Table 1. Details of selected compounds in the present study - name, molecular formula, compound CID, and chemical structure

Number	Name	Molecular formula	Compound CID*	Chemical structure

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1	beta-Hydroxypropiovanillone	$C_{10}H_{12}O_4$	75142	
2	4-Oxo-beta-isodamascol	$C_{13}H_{20}O_2$	597350	
3	Syringol	$C_8H_{10}O_3$	7041	
4	Isophytol	$C_{20}H_{40}O$	10453	
5	3,4,5-Trimethoxybenzoic acid	$C_{10}H_{12}O_5$	8357	
6	2,4-Di-tert-butylphenol	$C_{14}H_{22}O$	7311	
7	8-Hydroxylinalool	$C_{10}H_{18}O_2$	5280678	
8	Epoxylinalool	$C_{10}H_{18}O_2$	22310	
10	cocrystal molecule	$C_{28}H_{34}Cl_2N_2O_5$	54669582	

*CID: Compound Identifier, a unique identifier assigned to chemical compounds in the PubChem database.

Color code: Red, gray, and green square represent oxygen, hydrogen, and chlorine atom respectively.

Target selection and preparation

The crystallized squalene synthase enzyme (3ASX), as reported by Ichikawa and colleagues (19), was retrieved from the protein data bank. The sequence length of this crystal structure comprised 340 amino acids

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in a single chain. Utilizing Discovery software, the enzyme was visualized, and unnecessary segments were removed to facilitate and expedite docking calculations. The final structure of squalene synthase is depicted in Figure 1.

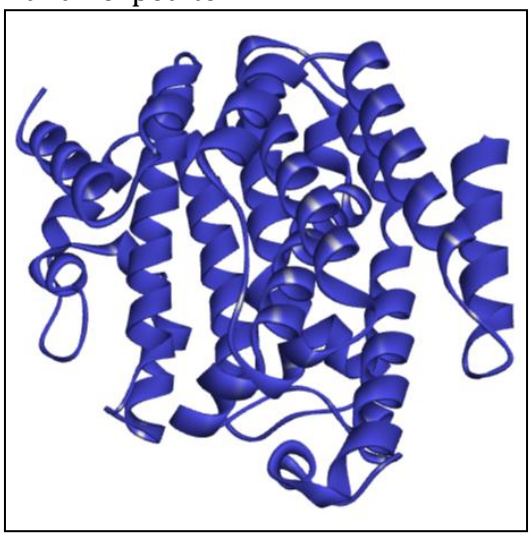


Figure 1. The final 3d structure of squalene synthase post-preparation. the protein chain is uniquely composed of multiple alpha helices.

In silico docking protocol validation

Following scrutiny of the enzyme's active site, the optimal grid center was chosen with coordinates X = 17.711, Y = -4.411, and Grid size: X = 13.47, Y = 13.6, Z = 12.41. Re-docking results demonstrated an overlap of the co-crystal molecule in two states, both before and after docking. The conformation of the co-crystal molecule in these two states within the active site of squalene synthase is illustrated in Figure 2.

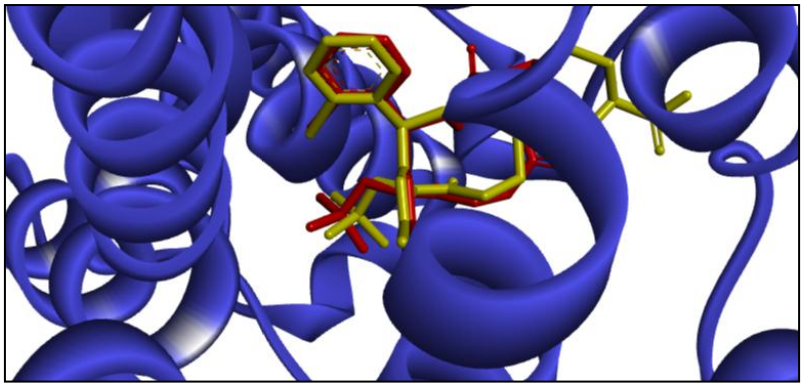


Figure 2. Conformation of the co-crystal molecule in two states—before (yellow) and after (red) docking—in the active site of squalene synthase.

Molecular docking studies

Post-protocol validation, a molecular docking study was conducted to ascertain the binding energy and orientation of C. azarolus's main compounds in the active site of squalene synthase. Auto Dock Vina, utilizing a Grid space of 0.375, was employed for this purpose, given its efficiency in accurately performing docking between small molecules and

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macromolecules. The ligands' affinity to the receptor, based on binding energy, is detailed in Table 2. The Discovery Studio Visualizer software facilitated the exploration of interaction types, including hydrogen bonds, pi, and hydrophobic interactions between compounds and squalene synthase (Table 2).

Table 2. Affinity, hydrogen-bonding residues, and hydrophobic interactions following docking of selected compounds.

Compounds	Affinity (kcal/mol)	Amino acids in h-bind	Amino acids in hydrophobic interactions
1	-5.89	Gly180	Val179,Leu183,Leu211,Tyr276,Met207
2	-6.55	Gly180	Val179,Leu183,Leu211,Phe54,Phe288,Pro292,Gln293,Cys289,Met207
3	-5.01	-	Cys286,Val179,Leu183,Leu211,Tyr276,Met207
4	-6.71	Gly208	Phe54,Leu76,Tyr73,Phe72,Gln293,Pro292,Val69,Phe288,Val179,Leu183,Leu211,Gly180
5	-5.28		Ile58,Val179,Leu183, Phe288,Phe72,Leu76
6	-7.02	Gly180, Gly208	Ala176,Val179,Leu183, Phe54,Phe288,Pro292, Cys289,Met207,Leu211
7	-5.47	Gln293, Gly208	Val179,Leu183,Leu211, Phe288,Pro292,Gly180
8	-5.63	-	Cys289, Leu183,Leu211, Met207, Gly180,Pro292, Phe288
10	-8.13	Arg77	Phe54,Leu76, Pro292,Val179,Phe288, Leu183,Leu211,Ala176,Val175

ADME properties and Drug-likeness screening

Table 3 outlines the ADME properties of all ligands. Compounds with a Total Polar Surface Area (TPSA) less than 140 $Å^2$ exhibit favorable membrane permeability. Orally administered drugs should have a LogP value of less than 5 for high gastrointestinal absorption. The impact of ligands on cytochromes significantly influences drug absorption and efficacy. Non-inhibition of cytochrome indicates oral consumption viability. Lipinski's Rule of 5, evaluating hydrogen bond donors, molecular weight, hydrogen bond acceptors, logP, and molar refraction, confirms the acceptable medicinal properties of the selected compounds, as outlined in Table 3.

Table 3. ADME properties and drug-likeness screening for selected compounds.

CN	MW	TPSA	LogP	GI Absorption	HBD	HBA	CYP inhibitor					Water Solubility	Molar refraction
							1A2	2C19	2C9	2D6	3A4		
1	196.202	66.76	1.71	High	2	4	No	No	No	No	No	Very soluble	50.692
2	208.30	37.30	2.28	High	1	2	No	No	No	No	No	Soluble	61.543

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	1												
3	154.165	38.69	1.15	High	1	3	No	No	No	No	No	Very soluble	41.211
4	296.539	20.23	4.88	Low	1	1	No	No	Yes	No	No	Moderately soluble	95.540
5	212.20	64.99	1.45	High	1	4	No	No	No	No	No	Soluble	53.057
6	206.329	20.23	3.08	High	1	1	No	No	No	Yes	No	Moderately soluble	65.50
7	170.252	40.46	1.72	High	2	2	No	No	No	No	No	Very soluble	50.898
8	170.252	29.46	2.43	High	1	2	No	No	No	No	No	Soluble	49.007
10	515	98.15	4.46	High	0	7	No	No	No	Yes	Yes	Poorly soluble	111.89

CN: Chemical Number, MW: Molecular Weight (g/mol), TPSA: Topological polar surface area, logP: lipophilicity factor, GI absorption: Gastrointestinal absorption, HBD: Hydrogen Bond Donor, HBA: Hydrogen Bond Acceptor, CYP inhibitor: cytochrome P450 inhibitor, Molar refraction: corresponds to the overall polarity of a molecule.

Discussion

Cardiovascular diseases pose a significant public health challenge, with elevated blood cholesterol identified as a key risk factor (25, 26). The relationship between total cholesterol and cardiovascular events underscores the importance of strategies targeting LDL cholesterol reduction, resulting in a substantial decrease in cardiovascular mortality (27). Given the pivotal role of squalene synthase in cholesterol synthesis and the consequential impact on cholesterol levels, this study explored the inhibitory effects of *Crataegus azarolus L.*'s main chemical constituents on squalene synthase through an *in silico* approach.

The rising popularity of herbal medicine, attributed to its minimal side effects, has led to an increased use of phytochemicals as alternatives to conventional treatments. Crataegus sp. has been extensively studied, revealing its antioxidant properties, anti-diabetic effects, endothelial protection, anti-obesity impact, anti-inflammatory activity, and cardiovascular disease prevention potential. Previous research by Rashidi et al. indicated that Crataegus supplements reduced cardiovascular disease risk factors in heart failure patients (28). Wang et al. demonstrated the beneficial effects of Crataegus leaf extract in reducing blood sugar levels in male rats (29). Another study in 2015 illustrated Crataegus's ability to reduce triglyceride accumulation (29).

In alignment with Crataegus's benefits, the main chemical constituents were selected based on their similarity to the co-crystal molecule, and in silico drug-likeness, ADMET prediction, and molecular docking studies were conducted. All selected compounds shared similarities with the co-crystal molecule, featuring oxygen atoms in ketone or hydroxyl groups. Specifically, compounds like beta-Hydroxypropiovanillone, Syringol, 3,4,5-Trimethoxybenzoic acid, and 2,4-Di-tert-butylphenol exhibited a cyclohexatriene moiety akin to the co-crystal molecule.

The docking results revealed binding energy values ranging from -5.01 to -

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7.02, with compound 6 exhibiting the most negative energy level and highest affinity, mirroring the structural resemblance to the co-crystalized ligand. The tert-butyl group in compound 6 enhanced its hydrophobicity, contributing to interactions with key amino acids in squalene synthase. Notably, interactions with amino acids such as Phe54, Pro292, Val179, Fhe288, Leu183, Leu211, Ala176, and Val175 were consistent with the co-crystal molecule.

Comparisons with previous research by Xiaoqian et al. (30) emphasized similar interactions in squalene synthase, reinforcing the validity of our results. Pharmacokinetic assessments using SwissADME and adherence to Lipinski's rule indicated that all compounds were suitable for oral consumption.

Conclusion

The study highlights the exceptional overlap of 2,4-Di-tert-butylphenol with the co-crystal molecule, emphasizing its potential as an effective inhibitor. Herbal medicines, with their fewer side effects, represent valuable alternatives to synthetic drugs. Given the herbal origin and promising results of compound 6, further laboratory investigations are warranted to validate its potential as a therapeutic agent.

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Conflict of Interests

The authors declare that they have no conflicts of interest.

Authors' Contributions

AA originated the research idea, formulated the theory, and oversaw project administration. AA conducted computational analysis. AA, MA, and FM collaborated on data collection, manuscript writing, and editing. All authors have reviewed and endorsed the final manuscript.

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