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In Silico Study of *Syzygium Cumini* Components with HMG-CoA Reductase for Potential Anti-Obesity Effects

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***Abstract*— *Syzygium cumini* (Jamun), a tropical fruit renowned for its rich nutritional and medicinal properties, has been widely studied for its potential therapeutic applications. This in silico study investigates the bioactive phytochemicals of *Syzygium cumini* for their anticholesterol activity by analyzing their interactions with the target protein HMG-CoA reductase. Structures of selected phytochemicals, including flavonoids, anthocyanins, tannins, and essential oils, were retrieved from the PubChem database, prepared as ligands, and evaluated for their pharmacokinetic properties and Lipinski's Rule of Five.**

Nine compounds, including Simvastatin (positive control), Dihydroquercetin, Gallic Acid, Ellagic Acid, Kaempferol, Quercetin, Mycaminose, and Tetradecanoic Acid, were identified as ligand candidates. Docking analysis revealed that Dihydroquercetin (-8.7), Kaempferol (-7.9), Ellagic Acid (-8.6), and Quercetin (-8.4) exhibited stronger binding affinities with HMG-CoA reductase than Simvastatin (-7.7), indicating their higher potency as anticholesterol agents.

These findings emphasize the therapeutic potential of Syzygium cumini phytochemicals, particularly for cholesterol management. Future in vitro and clinical studies are necessary to further validate these effects. It holds promise as an alternative plant-based medicine for obesity and related diseases.

***Index Terms*— Molecular Docking, Drug discovery, Syzygiumcumini, HMG-CoA and Anti-Cholesterol.**

I. INTRODUCTION

Obesity is a condition characterized by excessive body fat accumulation, typically indicated by a BMI of 30 or higher. It significantly raises the risk of serious health issues such as diabetes, heart disease, and certain cancers. Contributing factors include poor diet, lack of physical activity, hormonal imbalances, and genetics. Treatment often involves lifestyle changes, including regular exercise, a healthier diet, and, in some cases, medication or surgery [1].

Another global health concern is hyperlipidemia, which is characterized by high blood lipid levels and is strongly associated with metabolic syndromes and cardiovascular diseases [2]. A genetic disorder of lipoprotein metabolism, causes high plasma cholesterol and an elevated risk of cardiovascular disorders such as myocardial infarction are largely caused by atherosclerosis, which is fueled by high cholesterol. This condition is linked to obesity, diabetes, and cancer and is primarily caused by elevated levels of triglycerides and low-density lipoprotein (LDL) [3,4].

A key enzyme in the biosynthesis of cholesterol is HMG-CoA reductase, which transforms HMG-CoA into mevalonate. Sterol regulatory element-binding protein-2 (SREBP-2) is activated when this enzyme is inhibited, resulting in an increase in HMG-CoA reductase and LDL receptor expression and a decrease in cholesterol levels.

Syzygium cumini (Jamun), a plant in the Myrtaceae family, is well known for its medicinal qualities. Jamun has anti-inflammatory, antibacterial, wound-healing, Antioxidants and dietary fiber. It's used in both Ayurvedic and Unani medicine

[6]. In this study, the phytochemicals from Syzygium cumini binding interactions with HMG-CoA Reductase was identified and evaluated. It also compares the phytochemicals' docking results with those of simvastatin, the positive control, to find possible compounds with anti-cholesterol activity.

II. MATERIALS AND METHOD

In this, In Silico study we used phytochemical components of Syzygium cumini [7] as ligands and it was docked with HMG COA Reductase (Target protein) to find anticholesterol activity. This was compared with the positive control simvastatin.

A. Identification of Phytochemical Structures:

From the PubChem database, we obtained the 2D and 3D structures of 32 phytochemicals of Syzygium cumini (Jamun) [7], and looked for infractions. For docking, eleven compounds with zero violations were chosen as ligands. Together with simvastatin, these compounds' structures and PubChem IDs were verified and recorded (https://pubchem.ncbi.nlm.nih.gov).

B. Lipinski's Rule of Five:

Simvastatin and the chosen phytochemicals were evaluated for drug-likeness using Lipinski's Rule of Five. We used the Molinspiration tool (https://www.molinspiration.com/) to examine the molecules' hydrogen bond donors, acceptors, and logP values after obtaining their canonical SMILES using PubChem.

C. Pharmacokinetic Study:

To assess the bioavailability of the phytochemicals and simvastatin, pharmacokinetic characteristics including GI Absorption, BBB Permeability, ESOL Class, and Bioavailability were examined using the Swiss ADME tool (http:/www.swissadime.ch/).

D. Ligand Preparation:

Lipinski's Rule was followed in order to prepare the ligands. The Cactus NCI tool was used to convert PubChem structural data to PDB format. CB Dock software was used to visualize the resultant ligands.

E. Preparing the Target Protein:

HMG-CoA Reductase was chosen as the target protein. Its structure was retrieved from the PDB database (https://www.rcsb.org/), and a docking template was created using sequence information.

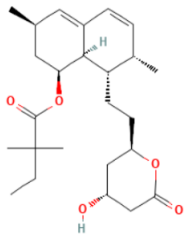
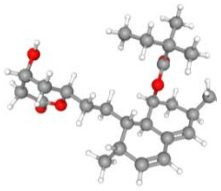
F. Docking:

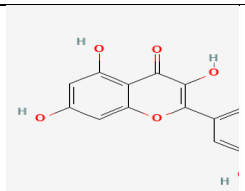
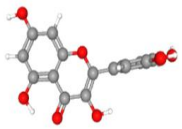
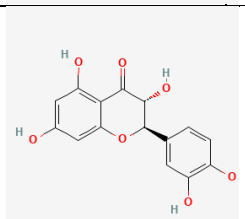
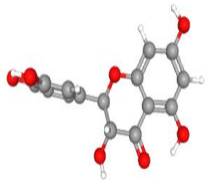
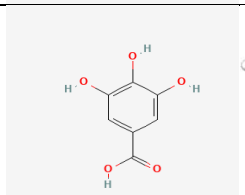
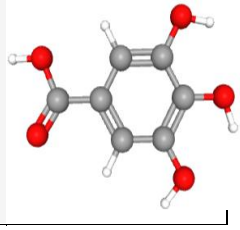
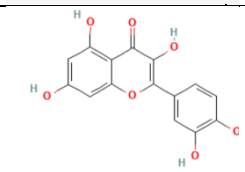
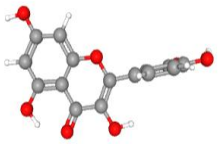
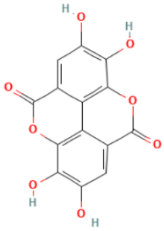
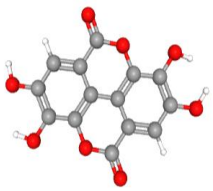
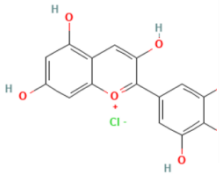
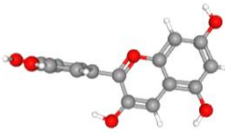
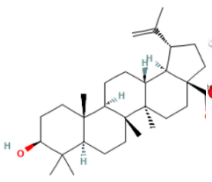
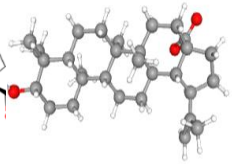
By uploading the PDB files of the target protein and ligands, docking studies were carried out using the CB Dock software (http://clab.labshare.cn/cb-dock/php/index.php). The binding score was used to determine which protein-ligand complex was the best. To find possible substances with anticholesterol action, the docking results of the phytochemicals were contrasted with the effectiveness of simvastatin.

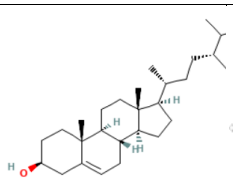
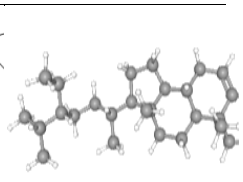
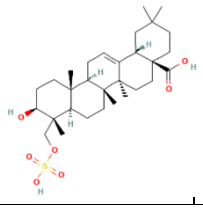
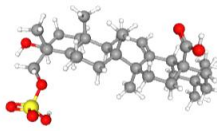
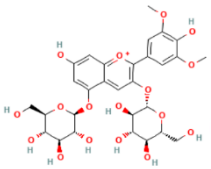
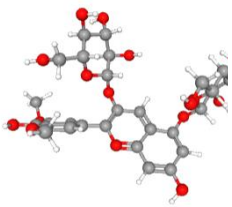
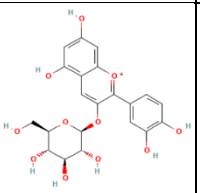
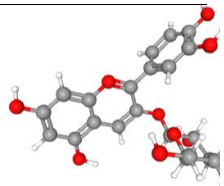
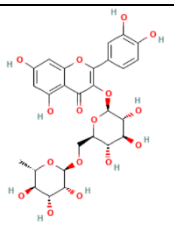
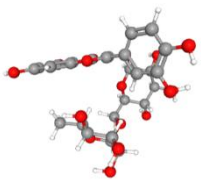
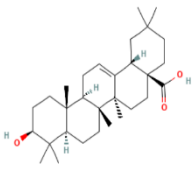
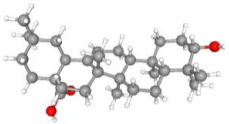
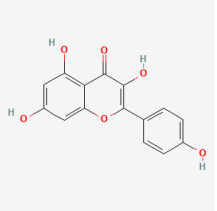
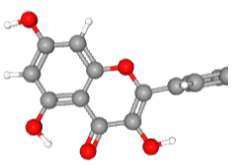
III. RESULT AND DISCUSSION:

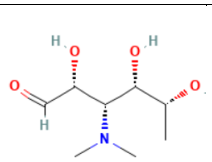
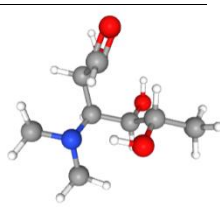
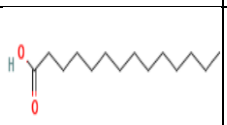
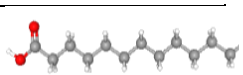
Phytochemicals from *Syzygium cumini* were chosen for this in silico investigation due to their possible anticholesterol properties. Following the retrieval of these compounds 'structures from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Table 1 shows the smile and structure of the phytochemical components of ***S cumini* .** Based on this, ligand preparation was carried out.

Table1: Structure of phytochemical components of *S cumini* and Simvastatin

Sr no	Compound name	Pubchem id	SMILES	2D Structure	3D Structure
1	Simvastatin(positive control)	54454	CCC(C)(C)C(=O)O[C@H]1C[C@H](C=C2[C@H]1[C@H]([C@H](C=C2)C)CC[C@@H]3C[C@H](CC(=O)O3)O)C		

2	Myricetin	5281672	C1=C(C=C(C(=C1O)O)O)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O		
3	Dihydroquercetin	439533	C1=CC(=C(C=C1[C@@H]2[C@H](C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O		
4	Gallic acid	370	C1=C(C=C(C(=C1O)O)O)C(=O)O		
5	quercetin	5280343	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O		
6	Ellagic acid	5281855	C1=C2C3=C(C(=C1O)O)OC(=O)C4=CC(=C(C(=C43)OC2=O)O)O		
7	Delphidin	68245	C1=C(C=C(C(=C1O)O)O)C2=[O+]C3=CC(=CC(=C3C=C2O)O)O.[Cl-]		
8	Betulinic acid	64971	CC(=C)[C@@H]1CC[C@]2([C@H]1[C@H]3CC[C@@H]4[C@]5(CC[C@@H](C([C@@H]5CC[C@]4([C@@]3(CC2)C)C)(C)C)O)C)C(=O)O		

9	β-sitosterol	222284	CC[C@H](CC[C@@H](C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C)C(C)C		
10	Triterpenoid	451674	C[C@]12CC[C@@H]([C@@]([C@@H]1CC[C@@]3([C@@H]2CC=C4[C@]3(CC[C@@]5([C@H]4CC(CC5)(C)C)C(=O)O)C)C)(C)COS(=O)(=O)O)O		
11	Malvidin-3,5-diglucoside	441765	COC1=CC(=CC(=C1O)OC)C2=C(C=C3C(=CC(=CC3=[O+]2)O)O[C@H]4[C@@H]([C@H]([C@@H]([C@H](O4)CO)O)O)O)O[C@H]5[C@@H]([C@H]([C@@H]([C@H](O5)CO)O)O)O		
12	cyanidin 3-glucoside	441667	C1=CC(=C(C=C1C2=[O+]C3=CC(=CC(=C3C=C2O[C@H]4[C@@H]([C@H]([C@@H]([C@H](O4)CO)O)O)O)O)O)O)O		
13	quercetin 3-rutinoside	5280805	C[C@H]1[C@@H]([C@H]([C@H]([C@@H](O1)OC[C@@H]2[C@H]([C@@H]([C@H]([C@@H](O2)OC3=C(OC4=CC(=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)O)O)O)O)O)O)O		
14	Oleanolic acid	10494	C[C@]12CC[C@@H](C([C@@H]1CC[C@@]3([C@@H]2CC=C4[C@]3(CC[C@@]5([C@H]4CC(CC5)(C)C)C(=O)O)C)C)(C)C)O		
15	Kaempferol	5280863	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O		

16	Mycaminose	160504	C[C@H]([C@H]([C@@H]([C@H](C=O)O)N(C)C)O)O		
17	Tetradecanoic acid	11005	CCCCCCCCCCCCCC(=O)O		

Lipinski's rule of five, which predicts a compound's oral bioavailability, was applied to the chosen phytochemicals. In accordance with the rule, a drug must have a molecular mass of less than 500 Daltons, fewer than 10 hydrogen bond donors and acceptors, a LogP of no more than 5, and no violations in the number of rotatable bonds in order to be considered orally active. The compounds that met these requirements, such as Dihydroquercetin, Gallic Acid, Ellagic Acid, Kaempferol, Quercetin, Mycaminose, and Tetradecanoic Acid (Table 2), were taken into consideration for future investigations.

Table 2 : Lipinski rule of five of *S cumini* and simvastatin

Compound Name	M.W	H Bond Donor	H Bond Acceptor	Log P	Violation
Simvastatin (positive control)	418.57 g/mol	1	5	3.77	0
Dihydroquercetin	304.25	5	7	0.64	0
Gallic Acid	170.12	4	5	0.16	0
Kaempferol	286.24G/Mol	4	6	0.03	0
quercetin	302.24	5	7	0.56	0
Ellagic Acid	302.19 g/mol	4	8	0.14	0
Betulinic acid	456.70 g/mol	2	3	5.82	1
Myricetin	464.38 g/mol	8	12	2.32	2
β-sitosterol	414.71 g/mol	1	1	6.73	1
Triterpenoid	552.76 g/mol	3	7	4.37	2
Delphidin	587.36 g/mol	2	6	5.36	2
Malvidin-3,5-diglucoside	655.58 g/mol	10	17	3.88	3
cyanidin 3-glucoside	449.38 g/mol	8	11	1.76	2
quercetin 3-rutinoside	610.52 g/mol	10	16	3.89	3
Oleanolic acid	456.70 g/mol	2	3	5.82	1
Mycaminose	191.22 g/mol	3	5	1.41	0
Tetradecanoic acid	228.37 g/mol	1	2	3.69	0

The pharmacokinetic characteristics of simvastatin (positive control) and phytochemicals were computed using the Swiss ADME database. It offers information on drug absorption, distribution, metabolism, and elimination, and was also used to assess the pharmacokinetic characteristics of these substances and simvastatin. The pharmacokinetic properties of the ligand molecule of phytochemicals and positive control Simvastatin are listed below in the Table -3.

Table - 3: pharmacokinetic properties of phytochemicals of *S cumini* and Simvastatin

y	Elog S	Class	GI	BBB	Bioavailability Score
Simvastatin (positive control)	4.92	Moderately soluble	Absorption	No	0.55
myricetin	3.01	soluble	High	no	0.55
Dihydroquercetin	2.66	soluble	low	no	0.55
Gallic acid	1.64	soluble	high	no	0.56
Kaempferol	3.31	soluble	high	No	0.55
quercetin	3.16	Soluble	High	No	0.55
Ellagic acid	2.94	soluble	High	No	0.55
Delphidin	3.16	Soluble	High	No	0.55
Betulinic acid	7.71	Poorly soluble	High	No	0.85
β-sitosterol	7.90	Poorly soluble	low	No	0.55
triterpenoid	6.71	Poorly soluble	Low	No	0.56
Malvidin-3,5-diglucoside	1.97	Very soluble	Low	No	0.17
cyanidin 3-glucoside	2.82	Soluble	Low	No	0.17
quercetin 3-rutinoside	3.30	Soluble	Low	No	0.17
Oleanolic acid	7.32	Poorly soluble	Low	No	0.85
Mycaminose	0.35	Highly soluble	Low	No	0.55
Tetradecanoic acid	4.31	Moderately soluble	High	Yes	0.85

According to the findings, substances with high gastrointestinal absorption included simvastatin, dihydroquercetin, gallic acid, kaempferol, quercetin, and others. The majority of substances did not penetrate the blood-brain barrier, guaranteeing the brain's safety. The range of bioavailability scores was 0.17 for diglucoside, malvidin, and 0.85 for betulinic acid, oleanolic acid, and tetradecanoic acid. For oral drug activity, a bioavailability score of 0.55 or greater is ideal.

A. Target protein:

The target protein, HMG-CoA reductase (PDB ID: 1HW8), was obtained from the PDB database. The protein structure was modeled using the Swiss model database, with a Z-score, GMQE value of 0.90, QMEAN value of -0.32, solvation value of 0.67, and torsion value of -0.59, indicating good structural quality.

B. Molecular docking

Gallic acid, Dihydroquercetin, Kaempferol, Quercetin, Ellagic acid, Mycaminose, Tetradecanoic acid and Simvastatin were among the phytochemicals that were subjected to molecular docking using the CB-Dock software tool (http://clab.labshare.cn/cb-dock/php/index.php) against the target protein HMG-CoA reductase (Table 4).

Table 4 - Docking scores and docked amino acid residues of phytochemicals with HMG-COA reductase

COMPOUND NAME	VINA SCORE	CAVITY SIZE	CENTRE			SIZE			AMINOACID
			X	Y	Z	X	Y	Z	
Simvastatin	-7.7	2743	29	-11	-10	28	22	22	G344, G385, M234, T383, A233, M238, N237, T388, T270, G345
Gallic acid	-6.3	3647	21	10	0	26	29	17	P377, S284, G280, E279, I278, K185, H214, E189, T215, K283,I217,L163, N276, E279
Dihydro-quercetin	-8.7	2225	22	-27	9	21	27	21	E140, T136, E138, D269, R169, K314, S144, T145,

									L432, A330, G139, K270, S261, M236, L141
Kaempferol	-7.9	3647	21	10	0	21	29	21	P377, S284, G280, E279, T168, N169, G227, H331, A330, M234,G235,I278,H214, Y185,E189,T215,N315, K314
Ellagic acid	-8.6	2310	21	23	27	19	29	19	M234,M236,Q349, N350,K270,D346,A331,N334, G385,T388,I381,
Tetradecanoic acid	-5.6	2225	22	-27	9	22	22	22	T136, E138, T137, G387, G344, T341, Q345, T337, V349, Q346
Mycaminose	-5.5	2310	21	23	27	24	29	23	V384, G382, N237, G385, V237, G394, N169, G139
Quecertin	-8.4	3647	21	10	0	21	29	21	S144, L432, V142, C140, L436, R164, B263, N336,A330

The enzyme HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis. Statins, also known as HMG-CoA reductase inhibitors, reduce cholesterol by blocking this enzyme. Statins inhibit the enzyme's activity by firmly attaching to its active site, which stops the liver from producing cholesterol [8].This raises HDL while dramatically lowering LDL, triglycerides, and total cholesterol. Statins are useful in treating hypercholesterolemia because the majority of cholesterol is produced internally [9]

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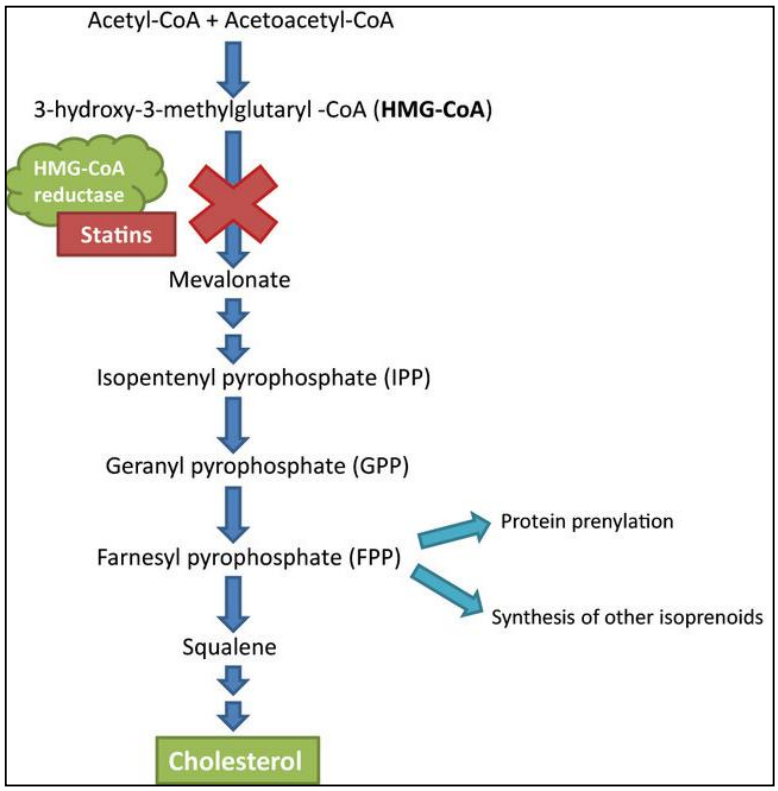

Fig 1. Mechanism of HMG CoA reductase in Cholesterol biosynthesis (Jaime I. Sainz de Medrano Sainz and Mercè Brunet Serra, 2023).

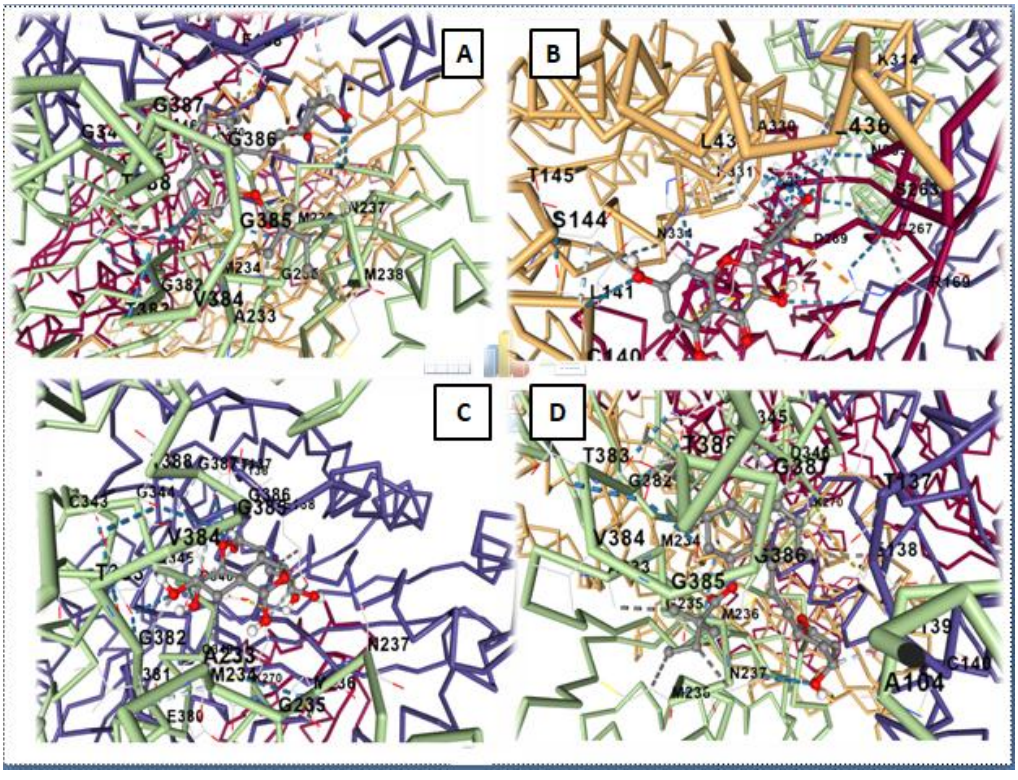

Fig 2 – Docking ligands with HMG-COA reductase
A) Simavstin B) Dihydroquercetin, C) Ellagic acid D) Quercetin

The binding scores were computed after identifying the active site and docked amino acid residues. On the basis of the binding affinity, the best-docked complexes were selected. As compared to Simvastatin (-7.7), the results showed that Dihydroquercetin, Ellagic acid, Quercetin and Kaempferol had higher docking scores (-8.7, -8.6, -8.4, -7.9), indicating their greater potency against HMG-CoA reductase (Fig2).

IV. Conclusion:

Dihydroquercetin, gallic acid, ellagic acid, kaempferol, and quercetin are among the important phytochemicals that have been shown through molecular docking studies to have strong binding affinities for HMG-CoA reductase, an enzyme that is essential for the synthesis of cholesterol. These substances showed higher docking scores than the positive control, simvastatin, indicating that they might be effective inhibitors of HMG-CoA reductase. Furthermore, these substances showed optimal bioavailability and gastrointestinal absorption without passing through the blood-brain barrier, lowering the risk of central nervous system toxicity. They also satisfied Lipinski's rule of five, which indicates favorable bioavailability and solubility.

As natural remedies for controlling hypercholesterolemia and improving cardiovascular health, Syzygium cumini extracts, especially those derived from seeds and leaves, show a great deal of promise. **Dihydroquercetin,** Ellagic acid**, and kaempferol** in particular are among the bioactive compounds that have been identified as promising candidates for the development of novel therapeutic approaches for the management of cholesterol. Further in vivo research is necessary to validate these results and evaluate Syzygium cumini's clinical suitability for treating hypercholesterolemia.

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