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POTENT INHIBITORS OF HMG-COA REDUCTASE PHYTOCONSTITUENTS FROM *TERMINALIA ARJUNA* (ROXB. *EX* DC.) WIGHT AND ARN. —AN *IN SILICO* APPROACH THROUGH MOLECULAR DOCKING STUDIES

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ABSTRACT

Inhibition of cholesterol synthesis by targeting the enzyme hydroxymethylglutarate coenzyme A (HMG-CoA) reductase (HMGCR) a rate limiting enzyme in the melvonate pathway has been identified as a promising approach. The most commonly employed drugs for treatment of hyperlipidemia include HMGCR inhibitors, also called as statins. Statin users have been identified with some risk factor for muscle-related side effects.CYP450 enzymes, were associated with significantly increased muscle related side effects while on a statin, or even stopped statin. Even though the inhibitors of HMGCR is evidenced in earlier reports, but their site of metabolism is not clearly determined. So it is crucial to understand how these potential drugs are metabolized in the body. Terminalia arjuna stem bark derivatives have been found to possess anti hyperlipidemic activity, 23 compounds of stem bark extract have been used to build A five-featured 3D-pharmacophore model. pharmacophore consiste of three hydrogen bond acceptor site (A), and two hydrogen bond donor (D),The model AAADD was used as a query to find effective activators through database screening and AAADD was validated to check its reliability using enrichment calculations. The hypothesis was statistically significant with coefficient of correlation r^2 = 0.73 and cross validation correlation coefficient q^2= 0.55. External validation result displays significance of the model with r^2 (o) of 0.99 and r^2 (m) of 0.51. Quantum mechanical calculations were applied to top five screened compounds. The stability of the inhibitory reaction was illustrated by MDS studies. Computational methods has been used to predict the cytochrome P450 sites of metabolism of drug candidates, ADMET properties were predicted to confirm the safety profile of the identified virtual hits.

KEYWORDS: *Terminalia arjuna,* HMG-CoA reductase, phytoconstituents, Docking, quercetin.

INTRODUCTION

As the expectations for everyday comforts and way of life changed after some time, the predominance of metabolic disorders won and expanded at speedier pace. Specifically, instances of dyslipidemia and cardiovascular diseases expanded drastically and are treated with statins.

HMG-CoA reductase, a significant enzyme which rate-limiting the biosynthesis of cholesterol through a negative feedback system.[1] In normal mammalian cells, the degradation of low density lipoprotein (LDL) by the LDL receptor brings about the biosynthesis of cholesterol, which suppresses HMG-CoA reductase. The outflow of LDL receptors in the liver is up regulated by the competitive inhibitors of HMG-CoA reductase, which builds the breakdown rate of plasma LDL and results in lower levels of cholesterol in plasma. Low LDL-cholesterol ultimately leads to the atherosclerosis.[2]

Statins are typically favored for treating patients with coronary conduit ailments. Despite the facts that, statins treatment are useful in bringing down the serum low-density lipid levels, they regularly prompt unfavorable symptoms including liver harmfulness[3] and muscle-related side effects. Presently, health centres don't energize statins treatment in patients with prior liver infection. Dynamic liver illness or unexplained tenacious heights of serum transaminases are outright contraindications to statin utilize. The kidney clears statin metabolites; bringing about extreme renal impedance and that uplifts the danger of rhabdomyolysis.[4]

In general most statin metabolized by the cytochrome P450 (CYP450) 3A4 system were also co-administered a CYP450 3A4 inhibitor[5] Drugs that reduce statin metabolism by inhibiting CYP450 isozymes this can lead to increased systemic exposure of the statin and increase

risk of myopathy.[6] The uses of concomitant medication(s) that inhibit CYP450 isozymes, alone or in their combination would be associated with increased odds of new or worsening muscle pain while taking a statin or ever having stopped a statin because of muscle pain. Challenges associated with toxicity and CYP inhibition of potential inhibitors, remains to evade a positive therapy, therefore stimulating the hunt and development of highly active and effective inhibitors.

In recent years, there is a developing pattern to investigate plants for pharmacologically dynamic mixes and nutraceutical supplements; as plants are rich sources of compounds with a great deal of therapeutic esteem. In this specific situation, the Indian medication Ayurveda may offer a unique option in exploring the sources of medications for dyslipidemia and heart diseases. The stem bark of *Terminalia arjuna* (Roxb. *ex* DC.) Wight and Arn. of family Combretaceae is usually utilized by the specialists of Ayurveda for different cardiovascular sicknesses.[7] A few mixes of organic criticalness have been confined from the stem bark of *T. arjuna*, which incorporate (i) triterpenoids, for example, arjunolic corrosive, arjunic corrosive, arjunetin, arjunolitin (ii) tannins such as pentagalloyl glucose, hexadrox diphenyl galloyl glucose, tetragalloyl glucose, and ellagic acid (iii) flavonoids, for example, leucocyanidin and luteolin, and also minerals like magnesium, calcium, zinc and copper.[8,9] Numerous reports have detailed its antihypertensive, cancer prevention agent and hypocholesterolaemic impacts.[10,11,12] Every one of these impacts has remedial vastness in cardiovascular illnesses of people.

In the present study, *Terminalia arjuna* bioactive compounds were identified for from a detailed literature search. Bioinformatics studies provide vital clues to understand the mechanism of ligand binding to targets and also help to select the best ligands for further experimental validation.[13,14] Hence, we thought it would be wise to employ bioinformatics methods to analyze the efficiency of plant based compounds to bind and inhibit HMG-CoA reductase. Our results are will helpful to find promising and binding molecule and it could be further analyzed by experimental and clinical studies for development of an effective hypolipidemic drug.

MATERIALS AND METHODS

Protein Preparation

The X-ray crystal structure of human HMGCR was downloaded from Protein Data Bank (http://www.rcsb.org) (PDB ID: 1HW8). Both chains A and B comprising the binding site of HMGCR inhibitor were considered. The protein is prepared using the protein preparation wizard in Maestro v9.2 by adding H-atoms, correcting bond orders, removing water molecule, and then adding missing residues/side chains to the target protein using Prime module (Schrödinger LLC 2011). Finally, protein was minimized at a pH of 7.4±2.0 using OPLS 2005 force field.

Ligand selection and preparation

In the current study, 23 chemical constituents reported from stem bark of Terminalia arjuna[15] (Table 1) were retrieved from pubchem database, and drawn using chemdraw tool, and then processed using LigPrep wizard in Maestro v9.2 (Schrödinger, Inc) The ligands were prepared using the Optimized Potentials for Liquid Simulations (OPLS) 2005 force field at pH 7.0± 0.4 and resulted in 72 pose generation.

Docking-based virtual screening (DBVS)

For carrying out the docking-based virtual screening (DBVS), Glide extra precision (XP) protocol (Schrödinger LLC 2011). Implemented in Maestro v9.2 was used. For this purpose, the active site residues GLU 559A, SER565A, LYS735A, HIS752A, ASN755A, LEU853A, ALA856A, LEU859A, LEU862A, ARG590B,SER684B, ASP690B, LYS691B, LYS692B present in the target protein (1HW8)[16] was used to generate the grid box around the active site, with default parameters. The prepared ligands using Ligprep were docked to the active site using the Glide XP default parameters. Glide XP ranked the docked conformation of the ligands according to their Glide G-score. The top nine Glide G-scoring compounds were selected as hits for the target protein. ΔG binding free energy was calculated for these hits using Prime MM/GBSA method.

Database screening

The above resulted hypothesis was then used to screen the cocoa database containing 70, 00000 unique structure records, the obtained pharmocophoric features were then exported using find matches to hypotheses option in the 'Phase' tab. The unknown ligands with similar pharmacophoric features were identified and used for virtual screening.

Virtual screening

The structurally matched thousand ligands were then taken for the virtual screening. The Virtual Screening Workflow option is then performed which helps in prefiltering ligands. The virtual screening options for HTVS (High Throughput Virtual Screening), HTVS does primary screening and then secondary is the SP docking. The survivors of these preliminary screening would progress to Glide XP docking. Glide XP docking is to find hydrogen-bond interactions, electrostatic interaction, hydrophobic enclosure, and pi–pi stacking interactions and root mean square deviation (RMSD). The RMSD and fitness score of the best-scoring pose to the known ligand were reported. These hits were further given as an input to P450 SOM to check their site of metabolism, and further into Qickpro to check their drug like properties.

RESULTS

Table 1: List of phytoconstituents present in *Terimala Arjuna* stem bark.

S. No	Name	Phytochemicals
1	Arjungenin	Triterpenoids
2	Arjunic acid	Triterpenoids
3	Arjunin	Triterpenoids
4	Arjunolic acid	Triterpenoids
5	Terminic acid	Triterpenoids
6	Terminoltin	Triterpenoids
7	Qudranoside VIII	Ursane triterpenoids
8	2a,3b-dihydroyurs-12,18-oic acid 28-O-b-D-glucopyranosyl ester	Ursane triterpenoids
9	2a,3b,23-trihydroxyurs-12,18-dien-28-oic acid 28-O-b-glucopyranosyl ester	Ursane triterpenoids
10	Kajiichigoside F1	Ursane triterpenoids
11	2a,3b,23-trihydroxyurs-23-trihydroxyurs-12,19-dien-28-oic acid 28-O-b-D-glucopyranosyl ester	Ursane triterpenoids
12	Arjunetin	Glycosides
13	Terminarjunoside I	Glycosides
14	Terminarjunoside II	Glycosides
15	Arjunoside I	Glycosides
16	Arjunoside II	Glycosides
17	Arjunolone	Glycosides
18	Arjunolitin	Glycosides
19	Arjunaphthanoloside	Glycosides
20	Olean-3b, 22b-diol-12-en-28 b-D-glucopyranosie-oic acid	Glycosides
21	Terminoside A	Glycosides
22	Arjunglucoside IV	Glycosides
23	Arjunglucoside V	Glycosides
24	Arjunasides A-E	Glycosides
25	Termionic acid	Glycosides
26	Arjunone	Flavonoids and phenolics
27	Baicalein	Flavonoids and phenolics
28	Ethyl gallate	Flavonoids and phenolics
29	Gallic acid	Flavonoids and phenolics
30	Kempferol	Flavonoids and phenolics
31	Oligomeric proanthocyanidins	Flavonoids and phenolics
32	Luteolin	Flavonoids and phenolics
33	Pelargonidin	Flavonoids and phenolics
34	Quercetin	Flavonoids and phenolics
35	Catechin,	Flavonoids and phenolics
36	Gallocatechin	Flavonoids and phenolics
37	Epigallocatechin	Flavonoids and phenolics
38	Epicatechin	Flavonoids and phenolics
39	Ellagic acid	Flavonoids and phenolics
40	3-O-methyl-ellagic acid 4-O-b-D-xylopyranoside	Flavonoids and phenolics
41	3-O-methyl ellagic acid 40 -O-a-L-rhamnophranoside	Flavonoids and phenolics
42	3-O-methyl ellagic acid 3-O-rhamnoside	Flavonoids and phenolics
43	Punicalagin	Tannins
44	Punicallin	Tannins
45	Pyrocatechols	Tannins
46	Terchebulin	Tannins
47	Terflavin C	Tannins
48	Castalagin	Tannins
49	Casuariin	Tannins
50	Casuarinin	Tannins
51	b-Sitosterol A	others

Table 2: List of compounds taken from *Terimala Arjuna* stem bark (Table 1) based on the availability of the structural details.

S. No	Name	Phytochemicals	PDB & Marwin Structures
1	Arjungenin	Triterpenoids	12444386
2	Arjunic acid	Triterpenoids	15385516
3	Arjunin	Triterpenoids	102316370
4	Arjunolic acid	Triterpenoids	73641
5	Terminic acid	Triterpenoids	12314613
6	Luteolin	Flavonoids and phenolics	5280637
7	Ethyl gallate	Flavonoids and phenolics	13250
8	Arjunone	Flavonoids and phenolics	14034821
9	Baicalein	Flavonoids and phenolics	5281605
10	Catechin	Flavonoids and phenolics	9064
11	Epicatechin	Flavonoids and phenolics	72276
12	Epigallocatechin	Flavonoids and phenolics	72277
13	Gallic acid	Flavonoids and phenolics	370
14	Gallocatechin	Flavonoids and phenolics	65084
15	Kempferol	Flavonoids and phenolics	5280863
16	Quercetin	Flavonoids and phenolics	5280343
17	Ellagic acid	Flavonoids and phenolics	5281855
18	Pyrocatechols	Tannins	289
19	Qudranoside VIII	Ursane triterpenoids	10675744
20	B-Sitosterol A	others	222284
21	Terminoltin	Triterpenoids	
22	2α,3β-dihydroyurs-12,18-oic acid 28-O-β-d-glucopyranosyl ester	Ursane triterpenoids	
23	2α,3β,23-trihydroxyurs-12,18-dien-28-oic acid 28-O-β-glucopyranosyl ester	Ursane triterpenoids	
24	Kajiichigoside F1	Ursane triterpenoids	
25	2α,3β,23-trihydroxyurs-23-trihydroxyurs-12,19-dien-28-oic acid 28-O-β-d-glucopyranosyl ester	Ursane triterpenoids	
26	Arjunolone	Glycosides	
27	Terminoside A	Glycosides	
28	Arjunaphthanoloside	Glycosides	
29	Olean-3β, 22β-diol-12-en-28 β-D-glucopyranosie-oic acid	Glycosides	
30	3-O-methyl-ellagic acid 4-O-β-d-xylopyranoside	Flavonoids and phenolics	
31	3-O-methyl ellagic acid 4′-O-α-l-rhamnophranoside	Flavonoids and phenolics	
32	Casurinin	Tannins	
33	Casuriin	Tannins	
34	Castalagin	Tannins	
35	Terflavin	Tannins	
36	Terchebulin	Tannins	
37	Punicalin	Tannins	
38	Punicalagin	Tannins	

Chemical structures of the above components were constructed by the MarvinSketch then the structures were minimized through Macromodel[18] using Merck Molecular Force Field (MMFF). The structure constructed using the Marvin Sketch primarily given an unrefined molecular structure with bond angles and lengths distorted from their respective minima or with steric clashes between atoms, energy minimization process was used for correcting these flaws and to provide a stable confirmation.

In order to investigate the binding capacity of a few important bioactive compounds of *Terminalia arjuna* stem bark with anti-dysipidemic activity, on HMG-CoA reductase enzyme protein in humans, we docked each compound to the target proteins. Computational docking studies of *T. arjuna* stem bark compounds with HMG-CoA reductase showed binding interaction with key residues. (Figure 1).Our docking analysis revealed the four (quercetin, gallocatechin, luteolin, terminoside A) compounds from *T. arjuna* has potent inhibitory action against HMG-CoA reductase (Table 3).

Table 3: Top scoring compounds with its interaction analysis, and with the length.

S. No	Entry Name	Docking score	XP Score	Glide g - score	Glide energy	glide e - model	Interaction	H-Bond Length
1.	quercetin	-8.31958	-8.32488	-8.32488	-42.8855	-58.4799	0-H…O=CGLY(560A) NH_2(GLY(560A)…O=C 0-H…O=C Gly (765B) 0-H…O=C Gly (765B)	2.114 2.416 2.381 2.146
2.	gallocatechin	-7.56943	-7.57253	-7.57253	-47.1576	-58.2573	0-H…O=C Gly (765 B) 0-H…O=C Gly (765 B) 0-H…O-C Asp (767 B)	1.936 2.046 2.118
3.	luteoline	-7.43479	-7.44749	-7.44749	-44.5225	-59.6608	0-H…O=C Gly (765 B) 0-H…O=C Gly (765 B) 0-H…O=C GLY(560A) NH_2(GLY(560A)…O=C	2.152 2.373 2.079 2.481
4.	Terminoside A.	-7.37531	-7.37851	-7.37851	-45.9534	-41.2107	O-H….O=C GLY(560A) O-H….0-HGLH (559A) O-H….O=CLEU (862A)	1.838 1.961 1.889

Since docking studies showed promising results, the chemical descriptors for the pharmacokinetic properties were also calculated to check the compliance of *T. arjuna* stem bark with standard descriptors. The candidate compounds quercetin, gallocatechin, luteolin, and terminoside A, showed water soluble nature, moderate intestinal absorption, and binding to plasma protein. Besides, no predictive hepatotoxicity was observed for all compounds during ADME screening (Table 4A and Table4B). The predicted ADME results of *T. arjuna* stem bark compounds were found comparable to standard range. The drug likeness screening results showed that compounds showed Lipinski's rule of five within acceptable limit (Table 4A and Table4B).

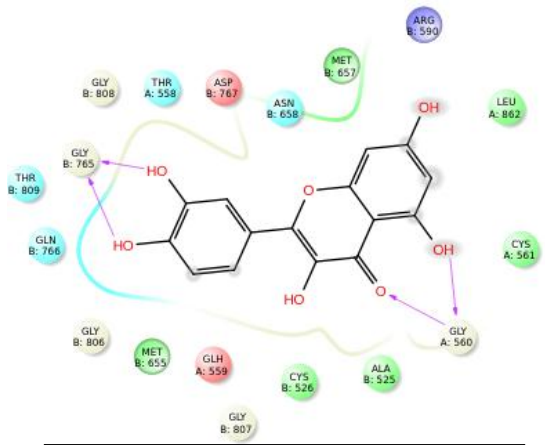

Fig 1: A- shows the interaction between HMG-CoA and Quercetin.

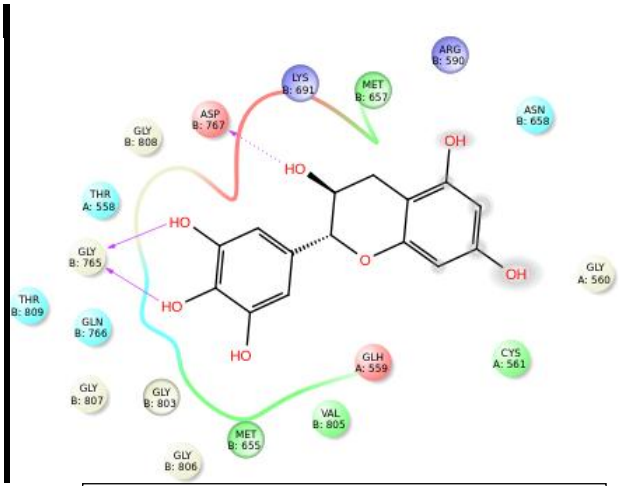

Fig 1: B- shows the interaction between HMG-CoA and gallocatechin.

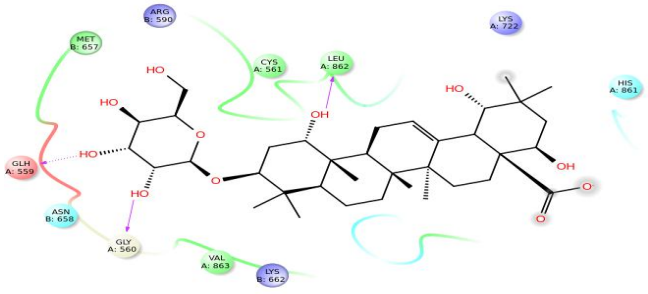

Fig 1: C- shows the interaction between HMG-CoA and Luteolin.

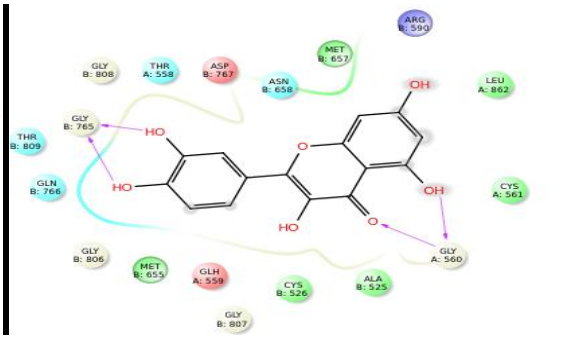

Fig 1: D- shows the interaction between HMG-CoA and Terminoside A.

Table 4A: Molecular weight, in Da (range for 95% of drugs: 130–725 Da).
Molecular weight of the volume.
Van der waals surface areas of polar nitrogen and oxygen atoms.
No: of Hydrogen bonds donated by the molecule (range for 95% of drugs: 0–6).
No: of Hydrogen bonds accepted by the molecule (range for 95% of drugs: 2–20).

Title	stars	mol MW	volume	PSA	donorHB	accptHB
Quercetin	0	302.24	861.437	140.06	4	5.25
gallocatechin	0	306.271	893.373	136.869	6	6.2
Luteolin	2	448.382	1246.231	199.959	6	13
Terminoside A	5	670.879	1851.248	183.69	9	18.7

Table4B: Predicted octanol /water partition co-efficient log P (acceptable range: −2.0 to 6.5).
Predicted aqueous solubility; S in mol /L (acceptable range: −6.5 to 0.5).
Apparent Caco-2 permeability (nm/s) (<25 poor, >500 great).
Log HERG, HERG K+channel blockage (concern below −5)
Apparent MDCK permeability (nm/s) (25 poor, >500 great).
Percentage of human oral absorption (<25% poor and >80% is high).

Title	QPlogPo/w	QPlogS	QPPCaco	QPlogHERG	QPPMDCK	Percent Human Oral Absorption
Quercetin	0.387	-2.804	21.058	-4.981	7.624	52.9
gallocatechin	-0.178	-2.383	19.275	-4.639	6.928	35.941
Luteolin	-0.923	-3.236	3.826	-5.927	1.207	6.053
Terminoside A	0.326	-3.963	17.466	-4.583	6.228	12.215

DISCUSSION

It is evaluated that few a huge number of human lives are lost every year because of cardiovascular maladies as a result of dyslipidemic reductase. People are for the most part considered at high danger of atherosclerosis because of sustenance propensities and hereditary components. Existing medications for lipid metabolism are costly and have reactions when utilized for delayed treatment. Plant based research has again demonstrated its significance over the customary statin medications and its utilization has been accounted for broadly.[19] Pharmacologically dynamic compounds from normal sources and specifically plants are picking up a considerable measure of consideration for conceivable improvement as medications against metabolic issue. HMG-CoA reductase is an imperative protein in the cholesterol biosynthesis and is thought to be a decent medication target.[18]

Compounds repressing HMG-CoA reductase and its possible interactions through docking examination have been already announced. Islam et al. reported 12 unique intensifies that can repress HMG-CoA reductase.[20] By *in-silico* docking studies, bioactives from *Ficus virens* bark; tomato juice and concentrates of *Centella asiatica*[21,22,23] have been reported as potential natural inhibitors and restrains the *in vitro* action of HMG-CoA reductase.

Keeping in mind the end goal to research the coupling limit of a couple of critical bioactive mixes announced in plants with hostile to dysipidemic action, on HMG-CoA reductase catalyst protein in people, we docked each compound to the objective proteins. The general outcomes demonstrated that HMG-CoA reductase indicated steady and solid H-bonding with *T. arjuna* compounds. It is vital to diminish the serum lipid levels to decrease the mortality related with cardiovascular ailments.

CONCLUSION

This study highlighted the potential property of *T. arjuna* bark compounds for its conceivable use in future to control lipid digestion through its communication with the key enzyme HMG-CoA reductase. The perceptions from our examination could be profitable and hence be utilized to accomplish huge advance on plant-based medicate disclosure for hypolipidemic activity.

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