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Computational Identification of Natural Compounds as Potential Inhibitors for HMGCoA Reductase

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Abstract

Elevated cholesterol levels in the body contribute significantly to cardiovascular diseases by narrowing the arteries and impeding blood flow. Although statins are currently effective in treating this condition, they can have adverse effects with prolonged use. As a result, there is a growing interest in finding natural compounds as alternatives to statins. To explore this, we conducted a virtual screening of compounds from various edible foods to identify those that can bind effectively to HMG CoA reductase, the key enzyme in cholesterol synthesis. Our screening identified 22 natural compounds and 6 existing drugs that exhibit strong binding to HMG CoA reductase. We analyzed the binding site to determine the precise region of interaction, similar to that of statins. Additionally, we assessed the compounds' pharmacokinetic properties and concluded that commonly consumed foods have the potential to offer alternative options to medication. Future studies will focus on evaluating enzyme inhibition in vitro to confirm their activity, and experimental verification will follow in due course.

Keywords: Cholesterol, HMG CoA reductase, Statin, Natural products, Virtual Screening

Introduction

One of the most significant and ubiquitous biomolecules with crucial functions in humans is cholesterol. It serves important functions like maintaining the fluidity and integrity of cell membranes and acts as a precursor to producing some vital substances like steroid hormones, vitamin D, and bile acids. (1) This makes its metabolism very significant and highly regulated, with the main location being the liver. In humans, the limited ability for catabolizing cholesterol along with the rapid changes in lifestyle and environment lead to cholesterol accumulation, referred to as hypercholesterolemia, which eventually is the cause of many devastating health disorders. Elevated cholesterol levels are one of the prime causes of atherosclerosis, though other reasons are evident; this hypercholesterolemia is the permissive factor that lets other factors operate. (2) These lipoprotein disorders are clinically significant as they contribute to atherogenesis and the associated risk of atherosclerotic cardiovascular disease (ASCVD). Cholesterol-lowering in such cases led to a steady decline in cardiovascular mortality and cardiovascular events. (3)

Understanding the synthesis mechanism of cholesterol is deemed necessary for reducing cholesterol levels. The mevalonate pathway through which cholesterol is synthesized is a highly regulated cascade of enzymatic reactions involving a crucial rate-limiting step in which Hydroxyl-Methyl Glutaryl-Coenzyme A (HMG-CoA) is converted into mevalonate catalyzed by the enzyme 3-hydroxy-3-methylglu-

taryl-coenzyme A reductase (HMGR), making HMGR a potential therapeutic target. HGMR inhibitors, also referred to as statins," are a class of lipid-lowering drugs used in coordination with diet and exercise and are considered to be the most frequent medication for lowering cholesterol. (4) Statins lower total cholesterol, low-density lipoprotein cholesterol, and triglycerides and increase high-density lipoprotein cholesterol concentrations. Statins are generally indicated in the management of atherosclerotic cardiovascular disease. They share similarities in structure with HMG CoA and competitively bind to HMGR and inhibit its activity. Statins proved to be beneficial in lowering lipid levels and additionally induced a pleiotropic effect by hampering other downstream products of the mevalonate pathway, improving endothelial function, inducing an anti-inflammatory effect, immunomodulatory properties, and, along with other factors, an anti-thrombotic effect. (5) Despite the various positive effects of statins, there are certain concerns with respect to their use. Studies have shown that they may cause either self-limited myotoxicity or an autoimmune myopathy. (6) It was revealed that certain patients on statin administration showed an increased risk of developing diabetes mellitus during large randomized clinical trials, with the risk proportional to the dose. Also, some patients exhibited an enhanced risk of hemorrhagic stroke. (5, 7)

To minimize the side effects of any chemical drug, the research community is persistent in discovering novel natural compounds from various sources that can be of therapeutic benefit. Natural products have been used for therapeutic purposes since time immemorial by humans. The active principles in medicinal plants are generally the secondary metabolites, which are called Natural Products (NPs), which are basically small molecules that are encoded genetically, usually from plants, microbes, and animals. Their pharmaceutical activity is attributed to their structural diversity, which enables them to effectively interact with target proteins. Owing to the expensive experimental studies involved in NP analysis, *In-silico* predictions have come in handy in recent times to decode their interactions with targets prior to experiments, thus making this approach time-saving and cost-effective. (8)

Therefore, this study aimed to identify NPs from various edible sources and screen them for their efficiency in binding to HMGR through computational methods, as this would provide cues for experimental validations.

Materials and Methods

Selection of targets and retrieval of structural information

The target protein was identified based on the mechanism of cholesterol synthesis and a literature study and has been verified as a WHO-approved drug target. Target molecule structure and sequence were retrieved from the PDB (Protein Data Bank), which is also a freely available online structure database.

Ligand identification

The primary clause to select ligands was to look out for natural, edible plant compounds, and hence the PhytoHub database was used, which is a repository of all dietary phytochemicals and their human and animal metabolites. The basic information on the selected compounds was obtained from Phytohub, which includes monoisotopic mass, molecular formula, family, and class. Ligands were also obtained through virtual screening to explore all possible small molecules that could effectively bind to the target. MTiOpenScreen, an online virtual screening tool, was used to identify compounds that could interact with the target.

Toxicity analysis of selected compounds

The screened compounds were initially checked for their toxicity, as any candidate lead molecule should be biologically safe. This was carried out using Osiris, which gives information regarding toxicity, mutagenicity, irritant effect, and reproductive effect. The result will be in the

form of colors ranging from green (safe to use), yellow (may have a harmful effect), and red (harmful). Apart from toxicity, Osiris also gives information regarding log-p value, drug score, and drug likeliness.

Pharmacokinetics assessment

ADME properties for the given ligands were analyzed using SWISSADME, which enables them to calculate physicochemical properties along with ADME and pharmacokinetic properties, drug likeliness, and biochemical friendliness to assist drug discovery. SwissADME gives various information regarding the ligand, such as the log-p value, number of hydrogen donors and hydrogen acceptors, relative molecular mass, consensus value, Lipinski's rule of 5, etc.

Identification of binding sites and Interaction studies

The binding sites within the target were predicted to understand the locations where the ligands can bind and analyze the possible effects of that interaction. Primary details of binding sites would be collected based on structural information available in the PDB database. Docking was performed using Biovia Discovery Studio, and the interactions are visualized in 2D and 3D formats.

Results and Discussion

Target selection

Cholesterol is one of the most pressing problems of the current generation due to changes in the food habits, physical activities etc. Hypercholesterolemia is a condition that has been treated successfully for 15 years, using statin family of drugs that target HMG-CoA reductase (HMGR) which is a rate-limiting enzyme in the mevalonate pathway. HMGR catalyzes the conversion of HMG-CoA to mevalonic acid, a very important step in the biosynthesis of cholesterol. Statins competitively bind to the catalytic domain of 3-hydroxy-3-methylglutaryl coenzyme A reductase and block the conversion of HMG-CoA to mevalonate. (9) Statins are found to reduce plasma low-density lipoprotein cholesterol levels and also impair the progression of atherosclerosis and coronary artery disease (10). Therefore, HMGR is used as a target to identify natural compounds that can bind to it and inhibit its activity. The preliminary data related to HMGR is identified from UniProt and the structural information is obtained from PDB (PDB ID: 1HW8) which is a complex between HMGR and mevastatin and the structure is given in Fig 1.

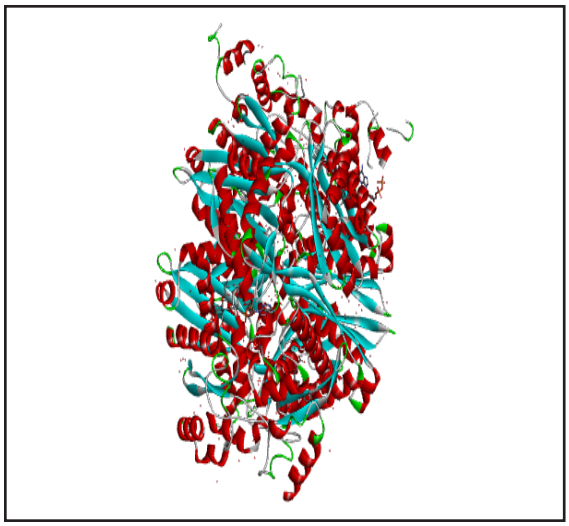

Figure 1. Complex of the catalytic portion of human HMG-COA reductase with compactin (also known as mevastatin)

Ligand identification

Edible plants and foods in natural form are a source of many phyto components that are known to show great potential in treating various medical conditions. Also, they are the primary cue to development of drugs. Therefore, this study focused on identifying edible foods with such phytochemicals that can effectively interact with the selected target and inhibit its effect. Based on the literature and newly evolving theories of food-based management, the following foods were selected as a phytochemical source. The foods include spices, edible plants, and cit-

rus fruits which in the recent past have become most prominent in weight management.

The various phytocompounds are retrieved from the database Phyto Hub which is the first online database to inventory all phytochemicals present in food commonly consumed. (11) It compiles data scattered in more than 20 databases as well as data manually extracted by experts from the literature, or experimentally obtained in collaborative platforms. A total of 45 edible foods were used for the study from Phytohub with a total of 558 compounds. Additionally, virtual screening was performed for the target HMGR to identify the possible small molecules that can bind using MTI OpenScreen. MTI OpenScreen houses five different small molecule libraries namely a diverse chemical compound collection (Diverse-lib) and a focused chemical compound collection (iPPI-lib) to target protein-protein interactions (PPI), a collection of purchasable approved drugs (Drugs-lib), a food constituent compound collection (FOOD-lib) and a natural product compound collection (NP-lib) from which screening for the target is being carried out based on docking shows binding. (12) The results of virtual screening presented a total of 183 compounds that can potentially bind to HMGR via MTI Openscreen. Therefore, a total of 741 compounds were initially identified as possible ligands that can bind to the target and they were further assessed for other properties like toxicity, drug likeness to recognize the best possible compounds. The list of spices and edible foods considered for the study included black Cumin, Cumin, Fennel, Cardamom, Ginseng, Peppermint, Lemon Grass, Coriander, Cinnamon, Fenugreek, Ginger, Pepper, Rosemary, Cloves, Mint, Parsley, Sweet Bay, Cucumber, Celery Stalks, Bitter Guard, Olive Green, Basil, Almond, Broccoli, Cauliflower, Flaxseeds, Green Tea, Watermelon, Cocoa, Oat, Kale, Walnut, Tomato, Apple, Banana, Grapefruit, Lemon, Lime, Mandarin Orange, Mikan, Sour Orange, Sweet Orange and Pummelo as in the current times, food-based approaches to weight management has gained enormous interest.

Toxicity analysis and drug-likeness

One of the key steps in drug development is understanding the absorption, distribution, metabolism, excretion, and toxicity of the candidate drug molecule. Most of the experimental failures in the drug discovery process are attributed to ADME issues. Sub-significant results for ADME and toxicity could eventually lead to failures leading to unfruitful investment of money and time. (13) Toxicity analysis was carried out using the Osiris software tool, to find out whether the compounds that were retrieved were mutagenic, toxic, and irritant or have a reproductive effect. OSIRIS tries to generate data with more reliability and that which minimizes the need for animal testing. The compounds selected from Phytohub and Virtual screening are analyzed using OSIRIS to ensure the non-toxic nature of these compounds and the results predicted 114 compounds to be safe based on all negative results for mutagenicity, toxicity, irritant nature and reproductive effect. These compounds were further analyzed for their pharmacokinetic properties to understand their drug like properties

ADME and drug likeness properties were assessed using SWISSADME which will calculate the physicochemical descriptors and predict ADME parameters, pharmacokinetic properties, drug-like nature, and medicinal chemistry friendliness. As natural products are a valuable source of drug candidates, their ADME profiling is crucial in obtaining critical data. The plant-based compounds and those selected after the initial virtual screening were analyzed for their toxicity and pharmacokinetic properties using OSIRIS and SWISSADME. Based on the values obtained for molecular weight, drug-likeness, H-bond acceptors, H-bond donors, TPSA value, log-p value, Lipinski's violation, Veber rule, GI absorption a total of compounds were finalized as they displayed no violation for drug-likeness (Table 1)

Table 1.Toxicity and druglikeness results of the selected compounds

S.No	Compound	Pharmacokinetic properties based on SWISSADME								Toxicity based on Osiris	
		Molecular weight	TPSA value	H-Bond acceptor	H-Bond donor	Rotatable bond	Lipinski violation	Solubility	Log P	Drug like liness	Drug score
1	Rishitin	222.32	40.46	2	2	1	0	Soluble	2.31	-19.15	0.45
2	Farnesol	222.37	20.23	1	1	7	0	Moderately soluble	4.32	-3.38	0.32
3	Phloretin	274.27	97.99	5	4	4	0	Soluble	1.93	-0.56	0.62
4	Luteolin	286.24	111.13	6	4	1	0	Soluble	1.73	1.9	0.84
5	(-)-Epicatechin	290.27	110.38	6	5	1	0	Soluble	0.85	1.92	0.87
6	(+)-Catechin	290.27	110.38	6	5	1	0	Soluble	0.83	1.92	0.87
7	Caffeoyl aspartic acid	279.25	123.93	6	4	7	0	Very soluble	0.39	-8.94	0.47
8	Hesperetin	302.28	96.22	6	3	2	0	Soluble	1.91	1.68	0.82
9	(+)-Pinoresinol	358.39	77.38	6	2	4	0	Soluble	2.37	0.18	0.67
10	(+)-Matairesinol	358.39	85.22	6	2	6	0	Moderately soluble	2.75	1.7	0.77
11	(+)-Lariciresinol	360.4	88.38	6	3	6	0	Soluble	2.39	0.96	0.74
12	Secoisolariciresinol	362.42	99.38	6	4	9	0	Soluble	2.46	-2.37	0.46
13	Curcumin	368.38	93.06	6	2	8	0	Soluble	3.03	-3.95	0.4
14	Delequamine	350.48	58.23	5	0	2	0	Soluble	1.97	4.5	0.86
15	Balaglitazone	395.43	115.59	5	1	5	0	Moderately soluble	2.37	7.58	0.78
16	Gevotroline	309.38	31.92	3	1	4	0	Moderately soluble	3.48	2.45	0.8
17	Difemetorex	295.42	23.47	2	1	5	0	Moderately soluble	3.57	2	0.74
18	Triclazate	325.4	49.77	4	1	6	0	Soluble	2.74	11.86	0.89
19	Exepanol	193.24	41.49	3	2	1	0	Very soluble	1.21	2.68	0.93
20	Azepindole	186.25	16.96	1	1	0	0	Soluble	1.87	3.7	0.93

21	Disopyramide	339.47	59.22	3	1	8	0	Soluble	3	10.82	0.88	
22	Deracoxib	397.37	95.59	8	1	5	0	Moderately soluble	3.11	2.38	0.71	
23	Sdx-101	287.35	62.32	3	2	4	0	Soluble	2.95	2.12	0.78	
24	Leucocianidol	306.27	130.61	7	6	1	1	Very soluble	0.07	1.28	0.84	
25	Nestifylline	298.38	112.42	3	0	2	0	Soluble	0.95	0.19	0.72	
26	Sinitrodil	238.2	84.59	5	0	4	0	Soluble	0.54	1.87	0.87	
27	Nicoclonate	289.76	39.19	3	0	5	0	Moderately soluble	3.71	4.86	0.79	
28	Perbufylline	441.5	82.13	6	0	7	0	Soluble	2.52	8	0.73	
29	Niaprazine	356.44	48.47	4	1	7	0	Soluble	2.62	9.45	0.86	
30	Articaine	284.37	95.67	4	2	8	0	Soluble	2.34	4.53	0.89	
31	Meptazinol	233.35	23.47	2	1	2	0	Soluble	2.99	2.52	0.85	
32	Trocimine	307.38	48	4	0	5	0	Soluble	2.78	5.62	0.84	
33	(S)-1-(4-(1H-Pyrazol-4-yl)phenyl)-2-amino-1-(4-chlorophenyl) ethanol	313.78	74.93	3	3	4	0	Soluble	2.5	4.5	0.82	
34	Texacromil	310.32	122.27	6	2	6	0	Soluble	1.51			
35	Bimethoxycaine	313.43	30.49	3	1	8	0	Moderately soluble	4.04	4.1	0.73	
36	Methyl (1S,14R,15E,18R)--15-ethylidene-18-(hydroxymethyl)-17-methyl-12-oxo-10,17-diazatetracyclo[12.3.1.03,11.04,9] octadeca-3(11),4,6,-8-tetraene-18-carboxylate	382.45	82.63	5	2	3	0	Soluble	2.17	2.58	0.8	

37	MolPort-039-338-824	368.47	54.56	4	1	4	0	Moderately soluble	3.3	2.47	0.73	
38	Antirhine	296.41	39.26	2	2	3	0	Soluble	2.9	1.29	0.75	
39	Isoquinoline, 1,2,3,4-tetrahydro-5,6-dimethoxy-	193.24	30.49	3	1	2	0	Soluble	1.57	1.4	0.86	
40	Episyringaresinol	418.44	95.84	8	2	6	0	Soluble	2.33	1.09	0.71	
41	2-(2-Oxopiperidin-1-yl)-N-[(3R)-1-(2-phenylethyl)piperidin-3-yl]acetamide	343.46	52.65	3	1	7	0	Soluble	2.13	2.01	0.84	
42	Hyoscyamine	289.37	49.77	4	1	5	0	Soluble	2.06	5.82	0.9	
43	n-(2-Carboxyethyl) aspartic acid	205.17	123.93	7	4	7	0	Highly soluble	-1.88	-0.01	0.74	
44	(2S,8As)-1,2,3,5,6,7,8,8a-octahydroindolizin-2-ol	141.21	23.47	2	1	0	0	Very soluble	0.9	1.89	0.91	
45	L-Arabinaric acid	180.11	135.29	7	5	4	0	Highly soluble	-2.44	1.59	0.9	
46	3'-O-Methylguanosine	297.27	148.51	7	4	3	0	Very soluble	-1.63	1.09	0.82	
47	Fargesin	370.4	55.38	6	0	4	0	Soluble	2.92	1.58	0.7	
48	1-Methylguanosine	297.27	148.65	7	4	2	0	Very soluble	-1.95	2.65	0.92	
49	Primapterin	237.22	138.01	6	4	2	0	Very soluble	-1.29	0.99	0.84	
50	Trigonelline	137.14	44.01	2	0	1	0	Very soluble	-0.61	-1.68	0.57	
51	3'-Hydroxytyrosol	154.16	60.69	3	3	2	0	Very soluble	0.56	-1.3	0.59	
52	4'-Hydroxyphenylacetic acid	152.15	57.53	3	2	2	0	Very soluble	0.95	-1.78	0.56	

53	Coumaric acid (m-)	164.16	57.53	3	2	2	0	Soluble	1.36	0.52	0.78
54	Coumaric acid (o-)	164.16	57.53	3	2	2	0	Soluble	1.4	0.51	0.78
55	Dihydrocaffeic acid	182.17	77.76	4	3	3	0	Very soluble	0.63	-.0.45	0.67
56	Homovanillic acid	182.17	66.76	4	2	3	0	Very soluble	0.88	0.17	0.75
57	Homovanillyl alcohol	168.19	49.69	3	2	3	0	Very soluble	1.14	-1.96	0.54
58	Phloretic acid	166.17	57.53	3	2	3	0	Very soluble	1.31	-1.56	0.57
59	Rosmaquinone B	358.43	69.67	5	0	2	0	Soluble	2.8	-6.75	0.42
60	Camphor	152.23	17.07	1	0	0	0	Soluble	1.95	-3.71	0.48
61	Rotundone	218.33	17.07	1	0	1	0	Soluble	3.56	-20.66	0.39
62	Menthol	156.27	20.23	1	1	1	0	Soluble	2.59	-10.42	0.46
63	Menthone	154.25	17.07	1	0	1	0	Soluble	2.61	-11.8	0.37
64	Menthyl acetate	198.3	26.3	2	0	3	0	Soluble	3	-21.93	0.35
65	Epiisorosmanol	346.42	86.99	5	3	1	0	Moderately soluble	2.94	-3.52	0.41
66	Epirosmanol	346.42	86.99	5	3	1	0	Moderately soluble	2.88	-3.52	0.41
67	Methoxy carnosol	346.46	66.76	4	2	3	0	Moderately soluble	4.18	-5.22	0.33
68	Rosmadiphenol	316.43	57.53	3	2	1	0	Moderately soluble	4.37	-4.27	0.3
69	Rosmanol	330.42	66.76	4	2	1	0	Moderately soluble	3.67	-3.83	0.37
70	Rosmaquinone A	358.43	69.67	5	0	2	0	Soluble	2.74	-6.75	0.42
71	Carnosic Acid	332.43	77.76	4	3	2	0	Moderately soluble	3.82	-5.43	0.35
72	Carnosol	330.42	66.76	4	2	1	0	Moderately soluble	3.72	-3.83	0.37
73	Methyl carnosate	346.46	66.76	4	2	3	0	Moderately soluble	3.93	-6.23	0.33

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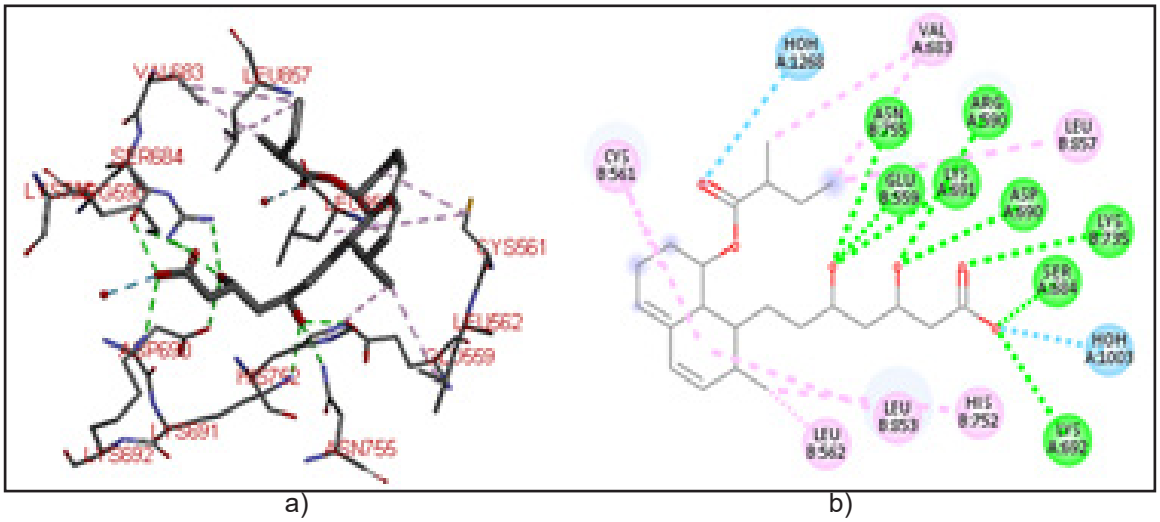
Of the 73 compounds, 46 compounds are of natural origin while 27 compounds were found to be chemical compounds (CCs) obtained via MTI Openscreen virtual screening. Despite being chemical compounds, they displayed the required drug-like properties and hence they were also analyzed for their interactions. The values for the natural compounds clearly indicate the possibility that these can be potential bioactive candidates and hence these were further used for docking studies to comprehend the nature of interactions with HMGR. The results are provided as a table with the interaction parameters and figures which contain the 2D images of the interaction clearly specifying the list of amino acids involved in the interaction.

Binding site analysis and Interaction studies

The effectiveness of the ligands in inducing an inhibitory effect depends on the site of interaction and hence a detailed study was carried out to understand the active site of HMG CoA reductase and nature of interactions between statins with that of HMG CoA reductase (Fig 2). The active site of HMGR includes the following amino acids in the pocket region: Cys 561, Ser 565, Ser 661, Leu 562, Leu 853, Asn 755, Glu 559, Val 683, Met 657, Lys 691, Ala 751, Arg 590, Asp 690, Leu 857, Lys 735, Ser 684, His 752, Lys 692, Asn 686, His 861. Statins-HMG CoA reductase interactions involve hydrogen bonds between four oxygen atoms of statin and Asn 755, Glu 559, Lys 691, Arg 590, Asp 690, Lys 735, Ser 684, Lys 692 while two water hydrogen bonds are formed with HOH 1268 and HOH 1003. Moreover, non-covalent interactions were observed between statin and Cys 561, Leu 562, Leu 853, His 752, Val 683, Leu 857. (14)



a) b)

Figure 2. Statins-HMG CoA reductase interactions a) 3D image b) 2Dimage - Blue - water hydrogen bonds, Green - conventional hydrogen bonds, Pink - non-covalent bonds (alkyl, alkyl pi bonds)

Interaction analysis

The present investigation tried to identify natural compounds that could effectively interact with HMG CoA reductase in the active site by using the Libdock software of Discovery studio after removing the ligands. Analysis of the docking results was based on the number of interactions and hydrogen bonds formed between the ligand and the protein. Dock score was used to evaluate the efficiency of docking. A comparison was made between drug-protein interaction and ligand-protein interactions to understand the nature of binding and the results were provided in Table 2.

Table 2. Interaction between HMG CoA reductase and natural compounds

Compounds	2D Structure	Libdock score	Relative energy	Absolute energy	Number of hydrogen bonds	Residues involved in H-bonding	Number of non-covalent bonds and interacting residues	Number of carbon hydrogen bond and interacting amino acids residues	Unfavourable bonds and aminoacid residues
Rishitin		76.5587	3.72001	20	4	OH-ASP -690 O-LYS -735 OH-SER -684 O-LYS -692	5- MET -657 LEU -857 LEU -853	2- ALA -751, ASP -690	1- O-Lys 692
Farnesol		86.018	9.36349	33.6964	1	O-Lys 692	6- HIS -752 LEU -853	2- SER -684, ASP -690	1- OH-Lys 735
Phloretin		96.8003	2.70468	38.1885	6	OH-CYS 561, O-LYS 735, O-LYS 692, OH-SER 684, O-LYS691, O-ASN 755	5- ASP 690, ARG 590, LEU 853, CYS 561		
Luteolin		97.7662	0.0431269	34.4952	4	O-ASN 755, O-HIS 752, OH-ALA 851, O-SER 684	6- GLU 559, CYS561, LEU 853, ASP 690,		1- OH-LYS 692
(-)-Epicatechin		110.505	0	31.4772	6	O-SER 684, OH-LYS 692, OH-ASN 686, OH-ALA 751, O-ASN 755,	6- ASP 690, ARG 590, LEU 853,, GLU 559	2- SER 565, LEU 562	2- O-GLU 560, OH- LYS 692
(+)-Catechin		104.775	0.50572	30.9713	5	O-LYS 735, O-SER 684, OH-LYS 692, OH-ASN 686, OH-ALA 751	8- ASP 690, ARG 590, LEU 853, LEU 562, SER 565, GLU 559	1- HIS 752	2- O-GLU 560, OH- LYS 692

Caffeoyl aspartic acid		107.517	2.42765	33.7339	5	O-HIS 752, O-ASN 755, O-SER 684, OH-ASN 686, OH-GLU 559	3- ASP 690, ARG 590, LEU 853	1- O-HIS 752	1- OH-LYS 692
Hesperetin		102.156	9.87844	52.3241	4	O-ASN 755, O-LYS 691, O-LYS 692, OH-GLY 560	4- ASP690, LYS 69, LEU 853, HIS 752	3- OH-GLU 559, ASN 755, OH--SER 565	
(+)-Pinoresinol		119.533	11.83	70.4661	4	O-ARG 568, O-ASN 755, O-HIS 752, O-LYS 692	9- ALA 856, LEU 853, HIS 752, ASP 690, LYS 691, CYS 561	2- SER 565, CYS 561	
(+)-Matairesinol		115.965	1.37393	50.4396	6	O-LYS 692, OH-SER 684, O-LYS 735, O-ARG 590, O-SER 661	5- LEU 853, HIS 752, MET 657		1- OH-LYS 735
(+)-Lariciresinol		113.749	16.1743	67.1105	4	O-LYS 692, OH-GLU 559, O-SER852, O-ARG 568	6- HIS 752, LYS 691, ASP 690, LEU 853, ALA 856	1- SER 565	
Secoisolariciresinol		111.911	17.6315	70.6231	4	O-LYS 692, OH-SER 684, OH-ASP 690, OH-GLU 559	5- ASP 690, LYS 691, LEU 853, ALA 856	1- H-HIS 861	1- OH-ARG 590
Curcumin		118.849	4.95466	63.1066	6	O-SER 661, O-ASN 755, O-LYS 692, OH-SER 684, O-LYS 735	5- MET 657, LYS 691, LEU 853, ARG 590, ASP 690		
Delequamine		92.8782	0.992849	37.3091	2	O-HIS 752, O-ASN 755	8- LEU 853,LEU 857, ALA 856, ARG 590, ASP 690	1- H-SER 684	

Balaglitazone	108.751	0.348557	52.489	4	O-LYS 735, O-LYS 692, O-SER 684, O-ARG 590	4- ALA 654, GLU 559, MET 657, HIS 752	2- ASN 658	
Gevotroline	101.757	3.80404	100.363	2	F-THR 558, N-ASN 755	5- LYS 691, ASP 690,MET 657, MET 655	3- H-GLU 559	
Difemetorex	95.9715	14.3325	56.0746	1	OH-GLU 558	2- ASP 767, MET 655	2- GLY 560, GLY 808	
Triclazate	99.5985	9.55216	60.7662	2	O-LYS 691, O-ASN 755	6- LEU 562, LEU 853, ARG 590, ASP 690, MET 657, CYS 561	1- H-GLY 560	1- OH-ASN 755
Azepindole	70.2141	2.84741	82.5149	2	NH-ASP 690, NH-ALA 751	4- ARG 590, LEU 853, LEU 857	3- H-ASP 690, ALA 751	
Disopyramide	92.8185	7.33853	95.2949	1	NH-ASP 690	11- LYS 691, LEU A57, LEU 853, HIS 752, LEU 562, CYS,561, ARG 590, ASP 690		

Deracoxib	96.6676	0	61.4089	6	NH-ASP 690, NH-ALA 751, O-LYS 735, O-LYS 692, O-SER 684, O-ARG 590	8- LEU 853, ARG 590, LEU 857, VAL 683	2- F-HIS 861
Sdx-101	96.213	13.4752	101.991	2	0-ARG 590, O-LYS 735	6- LYS 691, GLU 559, LEU 853, LEU 562, HIS 752	3- H-HIS 752, OH-LYS 692, O-ASP 690
Leucocianidol	105.07	0.794073	34.482	6	O-LYS 735, O-SER 684, O-LYS 692, OH-ASN 686, OH-ALA 751	6- ARG 590, ASP 690, LEU 853, LEU 562, GLU 559	2- O-SER 565, O-LEU 562 1- OH-LYS 692
Exepanol	71.417	3.19043	28.5283	3	N-ARG 590, O-LYS 735, OH-SER 684	3- ASP 690, LYS 691, HIS 752	1- OH-LYS 692
Nestifylline	90.6039	1.28417	31.6057	2	O-LYS 692, O-ASN 755	12- ARG 590, ASP 690, LYS 691, LEU 562, HIS 752, LEU 853, LEU 857,	4- H-ASP 690, H-SER 684, H-GLU 559
Sinitrodil	88.1225	5.44847	41.6101	4	O-LYS 735, O-SER 684, O-ASN 755, O-HIS 752	6- GLU 559, LEU 562, LYS 692, LYS 735, ARG 590, ASP 690	1- H-ASP 690 1- N-LYS 735
Nicoclonate	84.5486	16.4841	48.9033	3	O-LYS 692, O-SER 684, O-ASN 755	6- ASP 690, MET 657, CYS 561, LEU 853, LYS 691	1- N-SER 565

Perbufylline		132.392	5.79118	49.5263	4	O-LYS 692, O-LYS 735, F-GLY 808, F-THR 558	8- ASP 767, MET 657, LYS 691, LEU 853, ARG 590, LEU 857,ASP 767	6- H-GLU 559, H-ASP 690, H-ALA 751	
Niaprazine		105.134	12.4473	57.7664	5	F-GLY 808, F-THR 558, N-ARG 590, O-ASN 755, O-HIS 52	3- ASP 690, LYS 691,LEU 853	6- H-GLU 559, H-560	
Articaine		78.1423	7.9042	29.7971	2	O-LYS 735, O-SER 684	9- CYS 688, ALA 856, LEU 857, LEU 853, HIS 752, LYS 691, ASP 690	2- H-ASN 686, H-SER 684	
Meptazinol		79.0091	5.8383	41.8371	2	OH-ASP 767, O-GLN 770	4- GLU 559, MET 657, MET 655	1- H-GLY 765	
Trocimine		85.8418	9.88189	72.807	4	O-LYS 692, O-HIS 752, O-ASN 755, O-ARG 590	3- LEU 853, ASP 690, CYS 561	5- H-ALA 751, H-ASP 690, H-SER 684, O-SER 684	
(S)-1-(4-(1H-Pyrazol-4-yl) phenyl)-2-amino-1-(4-chlorophenyl) ethanol		96.706	1.28872	67.1541	3	NH-ASP 690, NH-GLU 559, NH-GLY 560	8- LEU 853, LYS 691,ASP 690, ALA 856, CYS 561, GLU 559	2- H-SER 565, H-GLY 560	

Texacromil		101.486	5.06556	28.3847	6	O-ARG 590, O-SER 684, OH-ASP 690, O-HIS 752, O-ASN 755, OH-GLY 560	6- ASP 690, LEU 853, HIS 752,	
Bimethoxy caine		96.6389	17.1293	65.0658	1	O-SER 684	6- VAL 683, ALA 856, LEU 857, LEU 853, LYS 691, ASP 690	4- H-GLU 665, H-ASP 690, H-SER 684
Methyl (1S,14R,15E,18R)-15-ethylidene-18-(hydroxymethyl)--17-methyl-12-oxo-10,17-diazatetracyclo[12.3.1.03,11.04,9]octadeca-3(11),4,6,8-tetraene-18-carboxylate		92.4014	8.83949	158.852	3	H-GLY 560, O-ASN 658,O-ASN 658	4- CYS 561,GLU 559, METH 657	1- H-ASP 767
MolPort-039-338-824		96.906	19.6431	131.998	2	O-ASN 755, O-ARG 590	11- LEU 853, HIS 752, CYS 561, ALA 856, LEU 562, GLU 559, ASP 690	2- H-ASN 690, H-SER 684
Antirhine		90.1955	4.83322	100.254	3	H-GLU 559, O-LYS 735, O-SER 684	6- LYS 691, HIS 752, LEU 853, MET 657	1- H-ALA 751
								1- H-ASN 755, H-HIS 752
								1- OH-LYS 692

Isoquinoline, 1,2,3,4-tetra-hydro-5,6-di-methoxy-		60.0337	0.803637	34.1321	2	NH-ALA 751, NH-ASP 690	2- LEU 853, ARG 590	2- H-ALA 751	
Episyringares-inol		106.582	17.5463	95.1524	2	OH-ALA 751, O-LYS 692	3- ARG 590, ASP 690, MET 657	5- H-THR 558, H-GLU 559, H- ASP 690, O-SER 682	
2-(2-Oxopi-peridin-1-yl)--N-[(3R)-1-(-2-phenylethyl) piperidin-3-yl] acetamide		111.623	8.62476	30.4251	2	NH-GLU 559, NH-ASP 767	3- MET 657, LYS 691, ASP 690	5- O-GLY 807, H-ASP 690, H-GLU 559,	
Hyoscyamine		109.083	20.1188	52.8993	2	O-LYS 691, O-HIS 752	7- ARG 590, LEU 853, HIS 752, LEU 562	3- H-GLU 559, H-GLY 560, H-ASP 690	
n-(2-Car-boxyethyl) aspartic acid		86.1863	4.39729	13.9503	7	O-LYS 692, OH-SER 684, OH-ASN 686, OH-ASP 690, OH-ALA 751, O-ASN 755			1- OH-LYS 735
(2S,8As)-1,2,3,5,6,7,8,8 a-octahydroin dolizin-2-ol		60.882	0	9.0621	2	OH-SER 684, O-LYS 692	3- HIS 752, LEU 853, LYS 691	3- H-ASP 690	1- OH-LYS 735
L-Arabinaric acid		82.249	7.30076	17.8228	6	O-ARG 590, OH-ALA 751, O-LYS 735, OH-ASP 690, O-HIS 752, O-ASN 755			3- OH-ARG 590, OH-LYS 692

3'-O-Methyl-guanosine		101.847	0	42.7511	6	OH-GLU 559, O-LYS 735, O-SER 684, N-LYS 692, O-HIS 752	5- HIS 752, LYS 691, ASP 690,ARG 590, LEU 853	1- H-GLU 559	1- NH-LYS 735
Fargesin		105.089	0	102.183	2	O-SER 565, O-VAL 683	8- ALA 856, LEU 853, LEU 857, GLY 860, GLU 665, VAL 683		
1-Methylgua-nosine		101.344	17.429	62.8616	5	NH-ALA 751, NH-ASP 690, O-ARG 590, O-ASN 755, O-HIS 752	3- ASP 690,LEU 853	2- H-ASP 690, H-GLU 559	
Primapterin		92.3171	12.9624	41.9452	5	N-HIS 752, N-ASN 755, NH-ASP 690, O-ARG 590	4- LYS 691, GLU 559, LEU 853,		
Trigonelline		57.9849	0	13.7899	3	O-LYS 62, O-SER 684, O-LYS 735	8- LEU 853, HIS 752, ASP 690, LYS 691, LYS 735, LYS 692, ARG 590	2- H-ASP 690, H-ALA 751	
3'-Hydroxyty-rosol		70.6664	1.02116	14.1821	5	O-LYS 692,OH--ALA 751, O-LYS 735, OH-GLU 559, O-ASN 755	3- ARG 590, LEU 853, ASP 690		1- OH-LYS 692
4'-Hydroxy-phenylacetic acid		65.6592	1.00176	14.1627	3	O-LYS 692, OH-SER 684, O-HIS 752	2- LEU 853, ARG 590		3- O-GLU 559, OH-LYS 691, OH-ASN 755

Computational identification of natural compounds as potential inhibitors for hmgcoa reductase

Coumaric acid (m-)		69.4907	0.264771	23.3664	2	O-ASN 755, OH-ALA 751	2- ASP 690, LEU 853	1- O-ASP 690
Coumaric acid (o-)		63.7732	0.225625	25.0122			1- LEU 853	
Dihydrocaffeic acid		80.4904	0.334075	15.4545	5	O-ASN 755, OH-ALA 751, O-LYS 692, OH-ALA 751, O-SER 684	3- ARG 590, ASP 690, LEU 853	1- OH-LYS 692
Homovanillic acid		79.0653	2.52435	24.3043	4	O-LYS 735, O-LYS 692, OH-SER 684,O-HIS 752	2- ARG 590, LEU 853	4- OH-LYS 735, O-GLU 559, OH-ASN 755, OH-LYS 691
Homovanillyl alcohol		73.3287	6.79834	27.8417	5	OH-SER 684, O-LYS 692, O-LYS 735, OH-GLU 559, O-ASN 755	3- ASP 690, ARG 590, LEU 853	
Phloretic acid		71.8841	2.22105	16.4541	5	O-LYS 692, OH-SER 684, OH-GLU 559, O-HIS 752, O-ASN 755	3- LEU 853, ARG 590, ASP 690	
Rosmaqui-none B		89.0551	7.48477	38.9008	3	O-ASN 755, O-HIS 752, O-ARG 590	8- LYS 691,HIS 752, LEU 853, GLU 559, CYS 561	

Camphor		52.6872	0	24.2354	1	O-ARG 590	5- HIS 752,LEU 853, MET 657, LYS 691		
Rotundone		76.6043	7.07798	26.128	1	O-LYS 692	LYS 691, LEU 562, LEU 853, HIS 752		
Menthol		60.8933	8.88262	16.1852	2	O-LYS 735, OH-ALA 751	6- LEU 857, VAL 683, LEU 853, HIS 752, LYS 691	1- OH-LYS 692	
Menthone		62.1228	1.69336	7.27444	3	O-LYS 735, O-SER 684, O-LYS 692	4- LEU 853, LEU 857, LYS 691		
Menthyl ac- etate		61.0479	7.98587	24.6597	4	O-LYS 692, O-SER 684, O-ARG 590	5- VAL 683, LEU 857, LYS 691, LEU 853		
Epiisorosma- nol		89.2467	3.14444	72.885	5	O-ARG 590, O-SER 661, OH-ASP 690, O-ASN 755	6-0 S 752, LEU 853, MET 657, MET 655	1- H-GLU 559	
Epirosmanol		83.1667	0.135898	45.3237	3	O-ARG 590, O-LYS 691, OH-ASP 690	11- VAL 683, ARG 590, MET 657, GLU 559,MET 655, LEU 857, LEU 853		

Methoxy carnosol		78.9409	18.6268	66.4566	3	OH-GLU 559, O-HIS 752, O-LYS 691	9- ALA 856, CYS 561, LEU 853, ASN 755, LYS 691		
Rosmaridiphenol		91.8029	10.4367	54.4079	2	OH-ALA 751, O-ASN 755	10- CYS 561, LEU 853, ASP 690, ALA 751, HIS 752, LEU 562		1- OH-ASN 755
Rosmanol		93.8702	13.3331	58.5523	3	OH-ASP 690, O-ASN 755, O-SER 661	5- MET 657, ARG 590, LYS 691, LEU 853	1- H-GLU 559	
Rosmaquinone A		94.5584	0.462107	31.2082	2	O-HIS 752, O-ASN 755	8- LYS 691,HIS 752, LEU 853, ALA 856, CYS 561		
Carnosic Acid		80.0866	5.31861	50.8901	2	O-LYS 691, OH-GLU 559,	9- LYS 691,CYS 561, HIS 752, LEU 853, MET 657		
Carnosol		84.5675	4.61242	63.0326	2	O-ARG 590, OH-GLU 559	9- ALA 75, LEU 853, HIS 752, CYS 561, LEU 562, LYS 691		1- O-ASN 755
Methyl carnosate		86.1311	0.902494	43.4143	2	OH-GLU 559, O-LYS 691	8- LYS 691,MET 657, HIS 752, LEU 853, CYS 561	1- H-GLU 559	

The compounds that effectively bound to HMGR were selected based on LibDock score as high Libdock score indicates a higher chance of ligand binding with the protein, along with number of hydrogen bonds and binding energy in the interaction. These results may provide information at the molecular level to understand the probable mode of action for the best compounds. (15) Moreover, understanding the presence of unfavourable bonds in interactions is equally important as they are known to disturb the stability and activity of the drug as these may cause a repulsive force between the two molecules. (16) This may not be the case always but considering these would provide an idea regarding the efficiency of interactions.

Six compounds namely Farnesol, Camphor, Rotundone, Difemetorx, Disopyramide and Bimethyoxycaine were found to dock with HMGR with 1 hydrogen bond involving the aminoacids LYS 692, GLU 559, ASP 690, SER 684, ARG 590 and LYS 692 which are located in the binding site and crucial for interaction with Orlistat as well. Also, they showed good number of noncovalent interactions that could play a role in stabilizing the interaction. Of these Difemetorx, Disopyramide and Bimethyoxycaine are drugs whithatd a higher dock score in the range of 92 while the other three NCs are Farnesol, Camphor, Rotundone were having a dock score of 82, 56 and 76 respectively. Twenty-two compounds were found to interact with the target with two hydrogen bonds and non-covalent interactions of which 10 compounds were NCs while 12 were chemical compounds. Of these, 3 CC and 4 NCs showed unfavourable bonds with the main amino acids directly involved in interactions. Remaining compounds namely Delequamine, Gevotroline, Azepindole, Nestifylline, Articaine, Meptazinol, Episyringaresinol, 2-(2-Oxopiperidin-1-yl)-N-[(3R)-1-(2-phenylethyl) piperidin-3-yl] acetamide are CCs while Hyoscyamine, Fargesin, Rosmaquinone A, Carnosic Acid, Methyl carnosate are NCs. All these compounds mostly interacted with ASP 690, Lys 691, LYS 692, Ser 684, ASN 755, ARG 590 and GLU 559 indicating the ability of these compounds to bind in the exact Orlistat site thereby possibly inducing the same inhibitory effect which could be confirmed by experimental studies. The dock score was higher for Episyringaresinol, Hyoscyamine, Fargesin and Rosmaquinone A which was 106, 109, 105 and 94 indicating a stronger binding with the target.

Twelve compounds bound to the target with three hydrogen bonds along with non-covalent bonds of which 8 are NCs while 4 are CCs. Only 3 compounds had unfavorable interaction of which 2 are chemical compounds and one natural compound. The NCs formed bonds with the target in its active site involving the key amino acids namely ASP 690, LYS 692, SER 684, ASN 755, ARG 590 and GLU 559. Rosmanol, Rosmaquinone B, Epirosmanol and Methoxy carnosol showed good dock scores with values 93, 89, 83 and 78 respectively. Though Antirhine β-carbolines which is an indole alkaloid isolated from *Antirhea putaminosa* (17) and also from the root bark of *Strychnos angolensis* (18), showed one unfavorable bond, the dock score was high with hydrogen bonds with key amino acids and hence can be considered as a potent binder with the target. Twelve compounds formed 4 hydrogen bonds with the target of which 8 are NCs while 4 are CCs. Of these, 4 CCs and 1 NCs were found to have unfavorable bonds. Two chemical compounds namely Balaglitazone and Sinitrodil are in the clinical trials stage. Balaglitazone and Perbufylline showed good dock score compared to other chemicals but the interactions of Balaglitazone were more relevant in terms of amino acids involved which include LYS 735, LYS 692, SER 684, ARG 590 with a dock score of 108. With respect to NCs, Homovanillic acid had 4 unfavorable bonds despite interacting with the main amino acids and hence was not considered. Of the other NCs, Hesperetin, (+)-Pinoresinol, (+)-Lariciresinol and Secoisolariciresinol showed a high dock score of 102.156, 119.533, 113.749, and 111.911 respectively. The interactions of these ligands with the target involved

LYS 692 GLU 559 SER 684 ASN 755 and SER 684 though Secoisolariciresinol showed one unfavorable interaction.

10 compounds (9 natural compounds and 1 chemical compound) were able to form 5 hydrogen bonds with the target of which a total of 5 compounds (+)-Catechin, Caffeoyl aspartic acid, Niaprazine, 1-Methylguanosine and Primapterin showed higher dock score of 104.775, 107.517, 105.134, 101.344, 92.3171 respectively interacting mainly with SER 684, ASN 755, ARG 590, ASP 690 and ARG 590. (+)-Catechin, Caffeoyl aspartic acid showed one unfavorable bond but slight modifications to the structure could possibly avoid this interaction and lead to the formation of a more stable complex with good dock score. Nine compounds (5 NCs and 4 CCs) were able to form 6 hydrogen bonds with the target of which 5 compounds showed one and more unfavorable bonds though the dock score was high. Phloretin and Curcumin were two natural compounds that docked with a good score of 96 and 118 respectively while Deracoxib and Texacromil (CCs) docked with 96 and 101 score.

The final list of compounds that effectively bound to the target included 6 drugs namely Difemetorx, Texacromil, Disopyramide, Niaprazine, Bimethyoxycaine, Deracoxib and 22 NCs which are Farnesol, Camphor, Rotundone, Episyringaresinol, Hyoscyamine, Fargesin, Rosmaquinone A, Rosmanol, Rosmaquinone B, Epirosmanol, Methoxy carnosol, Antirhine, Hesperetin, (+)-Pinoresinol, (+)-Lariciresinol, Secoisolariciresinol, (+)-Catechin, Caffeoyl aspartic acid, 1-Methylguanosine, Primapterin, Phloretin, and Curcumin

We support the potential of these compounds by performing a through literature search highlighting the role of these compounds in various bioactivities. Farnesol is available in apple, plums, blueberries, apricots, raspberries, peaches, tomatoes, and strawberries, and herbs like lemon grass and chamomile. Studies reported the efficacy of Farnesol as an antimicrobial agent especially an antifungal agent for candida infection. (19) Another study reported the efficacy of Farnesol in the treatment of *Enterococcus faecalis* in endodontic infections via photodynamic inactivation confirmed by electron microscopy (20). The ability of Farnesol against oral candidiasis was further enhanced by developing a novel gel-based formulation using niosomes loaded with farnesol making it an efficient alternative to conventional treatment strategies. (21) Farnesol is also proven to inhibit the biofilm formation in ultra-filtration membranes in the beverage industry in combination with natamycin (22). Recent studies have also pointed out that farnesol can ameliorate cardiac hypertrophy in rats. (23)

Fargesin is another phytocompound belonging to the lignans isolated from *Magnolia* plants and is known to be used in the treatment of inflammation, sinusitis, rhinitis, and headache. Studies have shown that fargesin displays potential anti-inflammatory and cardioprotective effects. (24-26) Interestingly another study revealed that fargesin showed antihypertensive effect in rats by reducing oxidative stress and stimulating nitric oxide release. (27) The role of fargesin in osteoartritis management was also demonstrated when it was found to alter the phenotypes of M1 and M2 phenotypes which subsequently prohibited cartilage degeneration by regulating P38/MAPK and p65/NF-κB signaling pathways (28). Additionally, fargesin was also found to inhibit the growth of colon cancer cells through G1/S cell cycle transition inhibition. (29) One report also examined the role of fargesin in obesity management where it was found to improve dyslipidemia and hyperglycemia in high fat induced mice by activating Akt and AMPK in WAT. (30)

Rosmarinus officinalis L commonly called as Rosemary, houses a lot of metabolites that offers great potential in pharmacological studies. Rosmaquinone A and Rosmaquinone B, abietane-type diterpenoid o-quinones, isolated from *Rosmarinus officinalis* L aerial parts through spectroscopic analysis were found to

possess antitrypanosomal activities against *Trypanosoma brucei rhodesiense* isolated from *Salvia officinalis* L. (31, 32) Though not much research on the therapeutic ability of these compounds is carried out, this study suggests the potential they are offering as natural cholesterol reducing agents. Rosmanol and epiromanol are also frequently used names in pharmacological studies. Diterpenes were found to possess significant antioxidant activities along with oxidation of LDL. (33) Rosemary leaves and oil has been officially approved as therapeutic supplement in treatment of high blood pressure, dyspepsia, and rheumatism. (34) Carnosol and its derivatives, phenolic diterpenes, has gained interest in recent past due to its anti-oxidant, anti-inflammatory, neuroprotective and anti-cancer properties. (35)

Rotundone is a sesquiterpene derived from the precursor, α-guaiene, through oxidation followed by biosynthetic transformation. (36-39) basically associated with strong spicy black pepper aroma. Till date pharmacological studies on rotundone exclusively, plants containing these compounds were found to show certain medical properties. For instance *Cyperus rotundus* Linn a medicinal plant showed anti-inflammatory properties. (40) Our study has provided an insight into the plausible use of this compound as an agent to inhibit the activity of HMGR based on *In-silico* studies and therefore can be experimentally studied.

Camphor from *Cinnamomum camphora* is probably one the most common substance used in medicine since ages as antiseptic, analgesic, anti-infective, antipruritic,anti-inflammatory, antispasmodic, expectorant and nasal decongestant in ayurvedic medicine, unani and modern medical science. (41) Its effectiveness via external and internal administration has been well documented. Our study further explains the mechanism through which this can bind to HMGR which could inhibit its activity. But some animal studies have shown that camphor in higher doses can cause toxicity. (42) Camphor being lipid soluble can cross the blood brain barrier and can act as neurotoxin. It can irritate the skin and mucosa and therefore ingesting large quantities can lead to vomiting and diarrhea. (43) Therefore determining the appropriate concentrations for administration via experimental studies is mandatory.

Episyringaresinol, (+)-Pinoresinol, (+)-Lariciresinol, Secoisolariciresinol are lignan compounds found in edible plants like *Synsepalum dulcificum* or Miracle berry plant, seeds like flax, pumpkin etc., whole grains etc. These lignans are found to be popular for anticancer activity besides other positive health effects like antioxidant, and anti-estrogenic effects. (44) Specifically, lignans show extraordinary antioxidant efficacy and can be used in therapeutics. (45) Studies have shown that lignan secoisolariciresinol diglucoside from flax seeds were shown to prevent certain diseases like diabetis and hypercholesterolaemic atherosclerosis by inducing adipopectin expression by enhancing PPARgamma DNA binding activity. (46) Secoisolariciresinol diglucoside was also found to improve glycaemic control partially by enhancing insulin signaling. (47) Another study revealed an association between high lignan diet to reduced obesity in Spanish children (48) though a clear mechanism of action has not been suggested.

Catechins and polyphenols are a major constituent in green tea and well known for its high antioxidant activity due to the presence of hydroxyl groups. (49) The role of catechins in obesity management has been reported in recent times. Research stated the role of the catechin (−)-epigallocatechin-3-gallate (EGCG) showed highest biological activity among green tea catechins (GTCs) including antiobesity activity by suppressing the expression of transcription factors and enzymes involved in lipogenesis and adipogenesis. (50) Many medicinal plants were also found to show antiobesity activity in which catechin was one of the phytoconstituents along with quercetin-3-rhamnoside, catechin, kaempherol, quercetin, quercetin-3-glucoside, 1-caffeyolquinic acid etc. (51)

Catechins are also known to possess significant antimicrobial activity, anti-allergenic and anti-inflammatory activities, anti-viral and anti-cancer activities. (52) Despite the bioactive potential possessed by catechins, bioavailability of these compounds is a major concern. This problem is addressed by the research community using certain functional foods as carriers, structural modifications, and nanoparticles. (53)

Another phenol, Phloretin found in apple tree leaves was found to effectively interact with HMGR in this study. Studies reported that Phloretin substantially diminished excessive lipid accumulation, suppressed the activity of transcription factors of lipogenesis and fatty acid synthase and enhanced lipolysis and fatty acid β-oxidation in mice. (54) Guansine and its derivatives were found to show anticancer activity in certain studies. A study reported that of the thioguanosine (sulfinosine) displayed anticancer effect by inducing apoptosis and autophagy in glioma cells. (55) Another derivative Isoguanosine gel showed anticancer activity with dual-functions as anticancer compound and delivery system. (56) Though reports for antiobesity activity for caffeoyl aspartic acid are unavailable currently, Caffeoyl acid derivatives like caffeoylquinic acid derivatives are known to display a lot of antioxidant properties with catechol moiety being crucial for radical scavenging activity. (57)

Curcumin, also known as diferuloylmethane, is a bioactive polyphenol component found in the rhizomes of turmeric that is used as a food additive, spice, and has been used for centuries

in traditional Asian therapy to treat wide range of illnesses. (58) When compared to the commonly used drug atorvastatin, the active pharmaceutical ingredient in curcumin exhibits a large amount of binding energy, which allows it to interact with the HMG-CoA reductase target protein. (59) Numerous studies in both the pre-clinical and clinical stages have demonstrated that curcumin has bioactivities that lower blood total cholesterol, fatty acids, and inhibit the accumulation of triglycerides, aids in weight loss, improved percentage reduction of body fat, enhanced hip circumference reduction, increased waistline reduction, and increased Phosphatidylserine reduction. (60-62) Curcumin can disrupt or limit numerous phases of adipocyte development. This compound can modify the adipocyte life cycle by suppressing preadipocyte proliferation and mitogenesis, inhibiting adipogenesis, and inducing mature adipocyte apoptosis. (63)

Though not many reports exist on the bioactive potential of primapterin, it is used as a marker in childhood asthma and inherited metabolic conditions (https://www.bocsci.com/primapterin-and-impurities-list-1747.html) (64) A study reported primapterin to display antagonistic activity against *Escherichia coli* and *Pseudomonas aeruginosa* (65) and can be further used to evaluate other biological activities.

Similar approach has been utilized by other scientific community as this methodology would help in the identification of possible lead compounds that show effective binding and required pharmacokinetic properties. Suganya *et al* (2017), Lin *et al* (2015) has carried out the same protocol and were able to identify certain compounds from some foods and medicinal plants. Our work adds to the list of possible compounds that can act as possible lead compounds, especially from edible foods suggesting a natural way of managing the condition. Further experimental analyses would positively bring out a candidate lead compound that can be later evolved into therapeutics. (66, 67) Therefore these results demonstrate the fact that the food that is consumed on a regular basis has potential to treat and manage several human disorders and can therefore be experimentally verified to develop a lead molecule that in due course of time can be used as a drug.

Conclusion

The inhibition of HMG CoA reductase using statins is the line of treatment for hyper-

cholesterolemia. But owing to the resource of compounds present in our edible foods, an attempt has been made to identify natural compounds that can effectively bind to HMG CoA reductase through computational studies. This study demonstrated that many natural compounds were effectively binding to the target in the precise location like that of the drug Statin and could possibly bring similar inhibitory effect. This report provides a cue to experimental studies which are currently deliberate by us thereby suggesting that the foods available in house can hold promise in providing remedy to certain health conditions.

Conflict of interests

The authors have declared that no conflict of interest exists

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