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MOLECULAR DOCKING STUDIES OF PHYTOCONSTITUENTS IDENTIFIED IN *CINNAMOMUM VERUM* AND *CORIANDRUM SATIVUM* ON HMG CoA REDUCATSE – AN ENZYME TARGET FOR ANTIHYPERLIPIDEMIC ACTIVITY

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ABSTRACT: Obesity refers to abnormal or excessive fat accumulation in the human body which results in health risk. The aim and objective of the present study is to perform *in-silico* docking analysis of the phytoconstituents identified in two medicinal plants namely *Cinnamomum verum* (cinnamaldehyde, eugenol, cinnamyl acetate, caryophyllene and cinnamic acid) and *Coriandrum sativum* (nerolidol, geranyl acetate, decanol and linalool) on HMG CoA reductase an eznynme target for antihyperlipidemic activity. The phytoconstituents of the medicinal plants were retrieved from pubchem chemical database. The target for docking study is selected as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA reductase). The 3D protein structure of the enzyme HMG CoA Reductase is obtained from Protein Data Bank [PDB ID: 3CCT]. *In-silico* docking analysis was performed by using Molegro virtual docker (MVD). The parameter used for docking analysis are MolDock score, Rerank score and hydrogen bond interactions. The docking score and the binding pattern of the phytoconstituents are compared against the standard drugs. The MolDock score of standard drugs atorvastatin, pitavastatin and simvastatin was found to be 182.685, -145.191 and -124.657 respectively. The MolDock score of phytoconstituents e – nerolidol, geranyal acetate, cinnamyl acetate and eugenol was found to be -90.2398, -88.2053, -81.3754 and -79.4759 respectively. It was found that the investigated phytoconstituents showed potent inhibiting activity as compared to that of the standard drugs as MolDock score directly reflects potential binding to the enzyme. The studied phytoconstituents show promise as antihyperlipidaemic leads and justify antiobesity claims of their source plants *Cinnamomum verum* and *Coriandrum sativum*.

INTRODUCTION: Obesity is commonly defined in adults as a body mass index [BMI > 30kg/m^2] [1]. Weight gain and obesity are major risk factors for conditions and diseases ranging from insulin resistance and type - 2 diabetic mellitus, cardiovascular diseases, and non-alcoholic fatty liver diseases, and with an increased risk of disability [2].

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Obesity is associated with a modestly increased risk of all-cause mortality [3]. Docking studies play an important role in the designing of new chemical entities for treatment of various ailments [4].

The present study aims to perform a reverse pharmacological evaluation of selected phytoconstituents of medicinal plants indicated in folklore medicine for their antiobesity effect. *Cinnamomum verum* (Family - Lauraceae) widely used as a spice, flavouring agent, used in preparation of chocolates and alcoholic flavourings[5]. Essential oil composition of petiole of *Cinnamomum verum* Bercht and Presl was studied by Rajeswara Rao *et al.*, [6].

The phytoconstituents identified from this plant for the study were cinnamaldehyde, eugenol,, cinnamyl acetate, caryophyllene and cinnamic acid. Traditionally it is used to treat bowel complaints such as dyspepsia, flatulency, diarrhea and vomiting, digestive disturbances / digestive complaints such as mild spasms/cramps of the gastrointestinal tract/gastrointestinal colic, feeling of repletion/bloating, and flatulence/carminative [7]. It has been evaluated for analgesic, antioxidant, anti diabetic, anthelmintic, anti tuberculosis activities and also used as chemotherapeutic agent [8 - 12].

Coriander (*C. sativum* L.) belonging to the family Umbelliferae/ Apiaceae is a glabrous aromatic, herbaceous annual plant, which has a long history as a culinary herb being the source of aroma compounds and essential oils with biologically active components possessing antibacterial, antifungal and antioxidant activities, and thus *C. sativum* is useful in food preparation (as a flavouring agent and adjuvant) and preservation as well in preventing food borne diseases and food spoilage. *Coriandrum sativum* is mainly cultivated from its seeds throughout the year. Phytoconstituents include linoleic acid, alpha-tocopherol, vitamin-k, nerolidol, geranyl acetate, decanol and linalool. It has been evaluated for anti-oxidant, anti-diabetic, anti-mutagenic, antihyper lipidemic, anti-spasmodic activity [13-17].

The lipid lowering effect of Cinnamomum species on experimentally induced hypercholesterolemic rats was studied by Rahman *et al* [18]. Previous study has been carried out to evaluate the hypolipidemic effect of coriander for triton-induced hyper lipidaemia (biphasic model) in Wistar rats by Lal *et al*., [19]. Further in Ayurvedic literature, the regular use of the decoction of the seeds of coriander is considered to be effective in lowering blood lipid levels [20].

The plant species showed potent anti-hyperlipidemic activity in *in-vivo* experiments and the present study is aimed to evaluate the effect of phytoconstituents using docking studies. The target for docking studies was selected as 3-hydroxy-3-methylglutaryl-coenzymeA (HMG CoA reductase). Hence it was planned to investigate effect of various phytoconstituents on HMG CoA reductase enzyme as a target protein using Molegro virtual docker (MVD). These docking score of the phytoconstituents are compared with the standard drugs *i.e*., atorvastatin, pitavastatin, simvastatin which are obtained from drug data bank.

MATERIALS AND METHODS:

Preparation of ligand: The phytoconstituents were identified from the selected medicinal plants namely *Cinnamomum verum* (Cinnamyl acetate, eugenol, caryophyllene, cinnamic acid and cinnamaldehyde and *Coriandrum sativum* (e–nerolidol, geranyal acetate, decanol and L–linalool) respectively and the 3D structures of the phytoconstituents were retrieved either from PubChem chemical databases [21]. The ligands were imported to the workspace of the MVD software and preparation was done. The docking scores of the phytoconstituents were compared against the standard drugs (Atorvastatin, Pitavastatin and Simvastatin) obtained from drug bank in .mol format [22].

Preparation of Enzyme: The target for docking studies was selected as 3-hydroxy-3-methylglutaryl coenzyme A reductase, an enzyme target responsible for anti hyperlipidemic activity. Docking analysis was done by initially selecting the target for the disease and followed by obtaining the 3D structure of HMG CoA reductase (3CCT) from protein data bank in .pdb format [23, 24]. It is well known that PDB files often have poor or missing assignments of explicit hydrogen and the PDB file format cannot accommodate bond order information. Therefore, proper bonds, bond orders, hybridization and charges were assigned using the MVD. The potential binding sites of both the targets were calculated using the built-in cavity detection algorithm implemented in MVD. The search space of the simulation exploited in the docking studies was studied as a subset region of 25.0 Angstroms around the active side cleft. The water molecules are also taken in to consideration and the replaceable water molecules were given a score of 0.50.

Parameters for Scoring Function:

Mol Dock Score: The MolDock scoring function (MolDock Score) used by MVD is derived from the PLP (piecewise linear potential) scoring functions originally proposed by Gehlhaar *et al*., and later

extended by Yang *et al*., [25-28]. The MolDock scoring function further improves these scoring functions with a new hydrogen bonding term and new charge schemes. The docking scoring function, E_{score}, is defined by the following energy terms:

$E_{score} = E_{inter} + E_{intra}$

Where E_{inter} is the ligand-protein interaction energy, E_{intra} is the internal energy of the ligand

Re rank score: The re ranking score function used was computationally more expensive than the scoring function used during the docking simulation but it is generally better than the docking score function at determining the best pose among several poses originating from the same ligand. While the rerank score in MVD provides an estimate of the strength of the interaction, it is not calibrated in chemical units and it does not take complex contributions (such as entropy) into account. Even though the rerank score might be successful in ranking different poses of the same ligand, it might be less successful in ranking poses of different ligands.

Software and Hardware: Molegro Virtual Docker (MVD - 2010, 4.2.0) trial windows version was downloaded from CLC drug discovery work bench, Drug Likeness Tool (DruLiTo 1) software is an open source virtual screening tool. Dell Studio 1555 with Intel Core 2 Duo Processor 2.2GHz 4GB DDR2 RAM, 320GB Hard Drive, Windows 8.1 served as the platform for performing docking study.

RESULTS: The ability of the phytoconstituents to bind with the targets is given in terms of MolDock Score. The MolDock Score is used as the parameter for analysing the docking results. The phyto constituents are ranked according to their MolDock Score, rerank score and hydrogen bond interaction. The pose of the ligand which has least MolDcok score shows a strong affinity towards its enzyme target.

In-silico docking analysis of phytoconstituents identified from *Cinnamomum verum* and *Coriandrum sativum* on HMG CoA reductase (PDB ID: 3CCT) ranking based on MolDock Score is represented in **Table 1**, H Bond is represented in **Table 2** and Rerank score is represented in **Table 3**. The binding patterns of the poses are captured using ligand energy inspector tool of MVD. The pose is represented in ball and stick model along with the molecular weight and the amino acids in protein are represented in stick frame model with the residue numbers.

TABLE 1: RANKING OF LIGAND AND POSES BASED ON MOLDOCK SCORE

Name	Ligand	MolDock Score	Rerank Score	H Bond
[00]Atorvastatin	Atorvastatin	-182.685	-112.553	-6.21252
[00]Pitavastatin	Pitavastatin	-145.191	-100.003	-3.39191
[00]Simvastatin	Simvastatin	-124.657	-67.759	-0.0785037
[00]e – nerolidol	e – nerolidol	-90.2398	-70.3728	-2.5
[00]Geranyl acetate	Geranyl acetate	-88.2053	-73.8683	-1.487
[00]Cinnamyl acetate	Cinnamyl acetate	-81.3754	-66.443	-0.850935
[00]Eugenol	Eugenol	-79.4759	-67.0701	-3.68009
[00]Decanol	Decanol	-76.716	-62.531	-2.5
[00]Caryophyllene	Caryophyllene	-76.0595	-54.2424	0
[00]Cinnamic acid	Cinnamic acid	-71.3106	-51.361	-4.77986
[00]L – Linalool	L – Linalool	-71.0934	-60.7538	-2.5
[00]Cinnamaldehyde	Cinnamaldehyde	-70.9645	-60.07	0

TABLE 2: RANKING OF LIGAND AND POSES BASED ON H-BOND

Name	Ligand	MolDock Score	Rerank Score	H Bond
[00]Atorvastatin	Atorvastatin	-182.685	-112.553	-6.21252
[00]Cinnamic acid	Cinnamic acid	-71.3106	-51.361	-4.77986
[00]Eugenol	Eugenol	-79.4759	-67.0701	-3.68009
[00]Pitavastatin	Pitavastatin	-145.191	-100.003	-3.39191
[00]e – nerolidol	e – nerolidol	-90.2398	-70.3728	-2.5
[00]Decanol	Decanol	-76.716	-62.531	-2.5

[00]L – Linalool	L – Linalool	-71.0934	-60.7538	-2.5
[00]Geranyl acetate	Geranyl acetate	-88.2053	-73.8683	-1.487
[00]Cinnamyl acetate	Cinnamyl acetate	-81.3754	-66.443	-0.850935
[00]Simvastatin	Simvastatin	-124.657	-67.759	-0.0785037
[00]Caryophyllene	Caryophyllene	-76.0595	-54.2424	0
[00]Cinnamaldehyde	Cinnamaldehyde	-70.9645	-60.07	0

TABLE 3: RANKING OF LIGAND AND POSES BASED ON RERANK SCORE

Name	Ligand	MolDock Score	Rerank Score	H Bond
[00]Atorvastatin	Atorvastatin	-182.685	-112.553	-6.21252
[00]Pitavastatin	Pitavastatin	-145.191	-100.003	-3.39191
[00]Geranyl acetate	Geranyl acetate	-88.2053	-73.8683	-1.487
[00]e - nerolidol	e - nerolidol	-90.2398	-70.3728	-2.5
[00]Simvastatin	Simvastatin	-124.657	-67.759	-0.0785037
[00]Eugenol	Eugenol	-79.4759	-67.0701	-3.68009
[00]Cinnamyl acetate	Cinnamyl acetate	-81.3754	-66.443	-0.850935
[00]Decanol	Decanol	-76.716	-62.531	-2.5
[00]L - Linalool	L - Linalool	-71.0934	-60.7538	-2.5
[00]Cinnamaldehyde	Cinnamaldehyde	-70.9645	-60.07	0
[00]Caryophyllene	Caryophyllene	-76.0595	-54.2424	0
[00]Cinnamic acid	Cinnamic acid	-71.3106	-51.361	-4.77986

In-silico docking results were supplemented with comparative graph in **Fig. 1** to illustrate relative scoring of phytoconstituents and standard drugs.

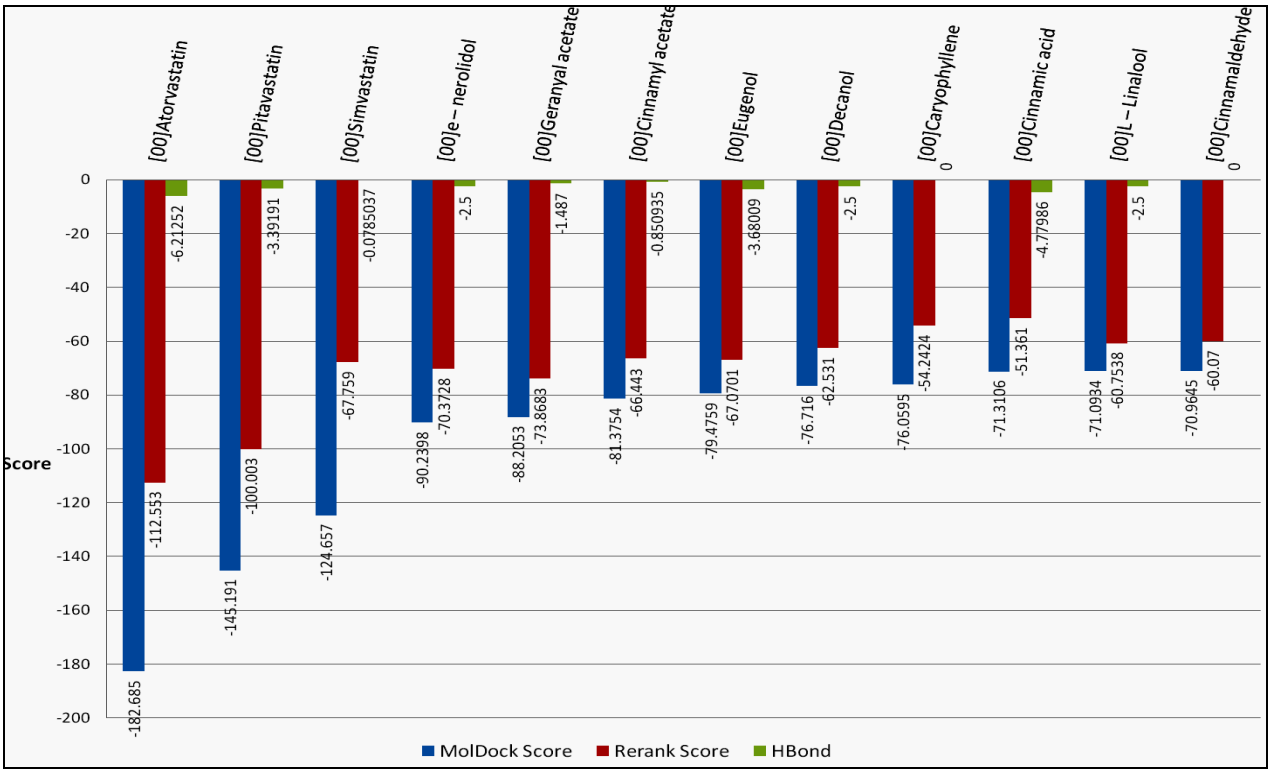

FIG. 1: *IN – SILICO* DOCKING ANALYSIS OF PHYTOCONTITUENTS IDENTIFIED FROM *CINNAMOMUM VERUM* AND *CORIANDRUM SATIVUM*

The **Fig. 2 - 5** corresponds to the docking pose of atorvostatin, pitavastatin, e-nerodilol and geranyl acetate respectively, evaluated and captured by the ligand energy inspector tool in Molegro virtual docker.

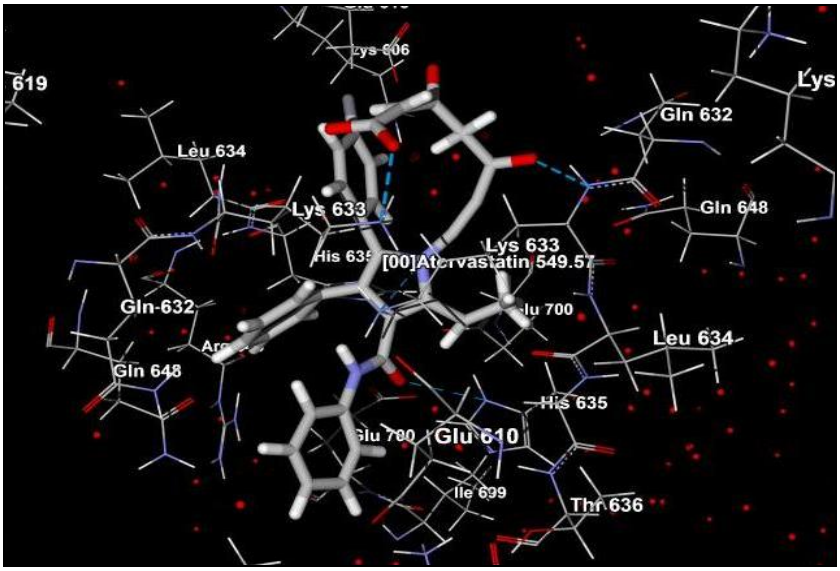

FIG. 2: DOCKED VIEW OF [00] ATORVASTATIN USING LIGAND ENERGY INSPECTOR

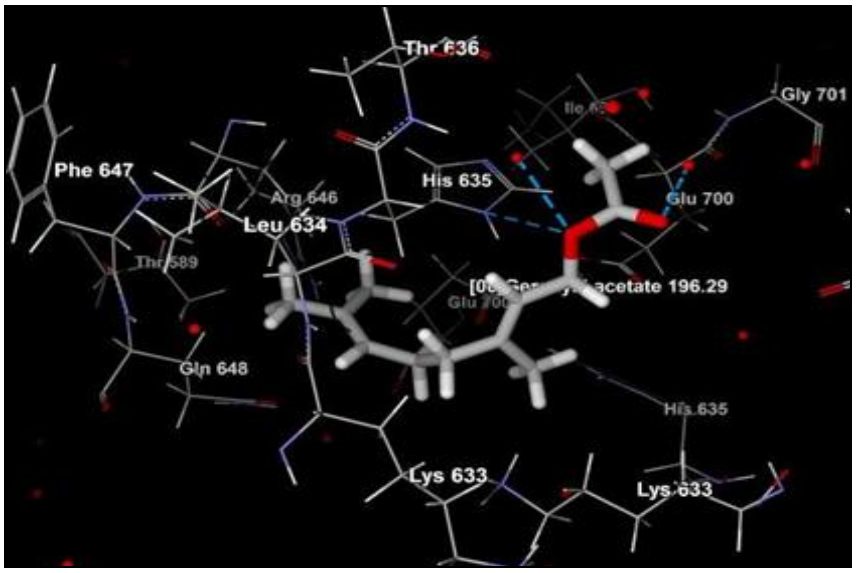

FIG. 3: DOCKED VIEW OF [00] PITAVASTATIN USING LIGAND ENERGY INSPECTOR

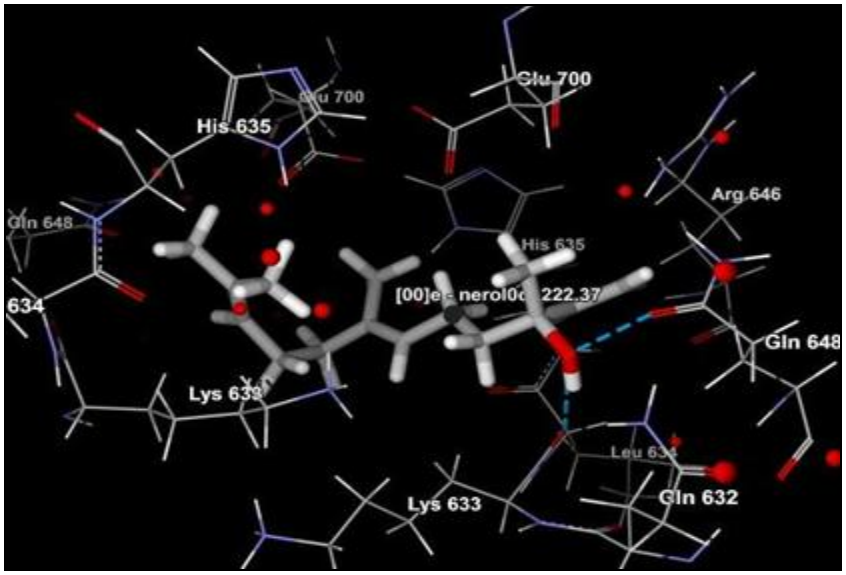

FIG. 4: DOCKED VIEW OF [00] E-NERODILOL USING LIGAND ENERGY INSPECTOR

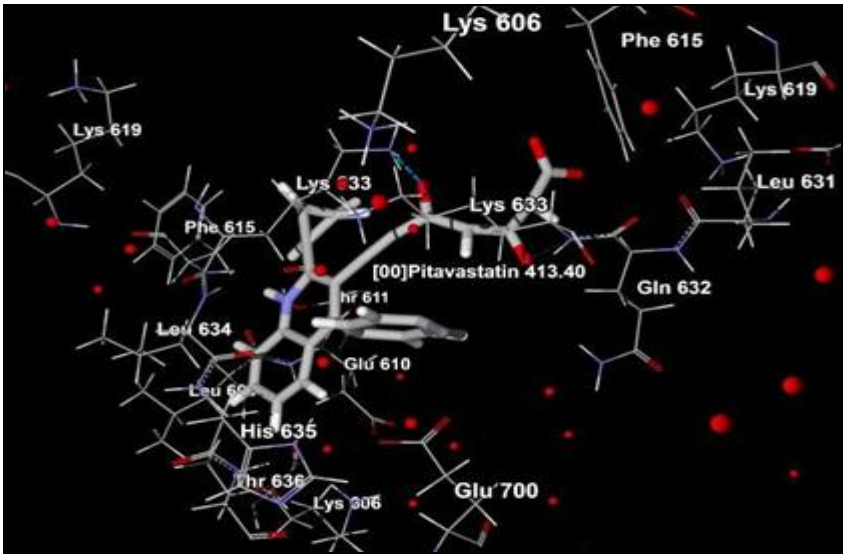

FIG. 5: DOCKED VIEW OF [00] GERANYL ACETATE USING LIGAND ENERGY INSPECTOR

The MolDock score of the ligands atorvastatin, pitavastatin, simvastatin, e – nerolidol, geranyl acetate, cinnamyl acetate, eugenol, decanol, caryophyllene, cinnamic acid, l – linalool, cinnamaldehyde was found to be -182.685, -145.191, -124.657, -90.2398, -88.2053, -81.3754, -79.4759, -76.716, -76.0595, -71.3106, -71.0934 and -70.9645 respectively using the software.

The Rerank score of the ligands atorvastatin, pitavastatin, simvastatin, e – nerolidol, geranyl acetate, cinnamyl acetate, eugenol, decanol, caryophyllene, cinnamic acid, l – linalool, cinnamaldehyde was found to be -112.553, -100.003, -67.759, -70.3728, -73.8683, -66.443, -67.0701, -62.531, -54.2424, -51.361, -60.7538 and -60.07 respectively using the software.

The Hydrogen bond interactions of the ligands atorvastatin, pitavastatin, simvastatin, e – nerolidol, geranyl acetate, cinnamyl acetate, eugenol, decanol, caryophyllene, cinnamic acid, l – linalool, cinnamaldehyde was found to be - 6.21252, - 3.39191, - 0.0785037, - 2.5, -1.487, - 0.850935, - 3.68009, - 2.5, 0, - 4.77986 , -2.5 and 0 respectively using the software. The lipinski rule of 5 was evaluated for the phytoconstituents using DruLito software and the results are represented in **Table 4**.

TABLE 4: MOLECULAR DESCRIPTOR PARAMETERS OF THE PHYTO-CONSTITUENTS EVALUATED USING DRULITO SOFTWARE FOR DRUG LIKENESS PROPERTY

Name of the ligand	Molecular Weight	Log P	Hydrogen Bond Acceptors	Hydrogen Bond Donors
Caryophyllene*	204.19	6.044*	0	0
Cinnamaldehyde	132.06	1.968	1	0
Cinnamic acid	148.05	1.887	2	1
Cinnamyl acetate	176.08	2.531	2	0
Decanol	158.17	4.265	1	1
e-nerolidol	222.2	4.29	1	1
Eugenol	164.08	2.223	2	1
Geranyl acetate	196.15	3.264	2	0
L-linalool	154.14	2.468	1	1

* Fails the Lipinski rule of 5 as log P value was greater than 5

It is evident from the study that the phytoconstituents evaluated in the study posses drug likeness property except caryophyllen which posess a Lop value greater than 5.

DISCUSSION: Statins are evident to produce a variety of adverse effects such as cognitive loss, neuropathy, pancreatic, hepatic and sexual dysfunction and diabetes which is supported by evidence from many Randomized Controlled Trials [29, 30]. This promotes the development of medicines from herbals in the alternative system of medicine suggesting the use of these herbs in day today life

preventing the life style modifying diseases like obesity.

The phytoconstituent Geranyl Acetate has been patented for homeopathic composition comprising *Hypericum perforatum* extract and essential oils for the treatment of neuropathic Pain (Patent ID US2015374773). Geranyl acetate was identified as a volatile compound found in fresh, tree-ripened apricots and plumcots at concentrations of 4 and 3 ug/kg of fresh fruit tissue, respectively [31]. It is a component of Balkan pine, *Pinus peuce*, twig oil from Greece at 0.7% [32]. Geranyl acetate is a component of essential oils and occurs in varying amounts; up to 60% in oils from Callitris and Eucalyptus species, and up to 14% in palmarosa oil. A smaller amount occurs in, for example, geranium, citronella, petitgrain, and lavender oils [33]. Moreover the chemical composition of essential oil from *Blumea eriantha* DC consists of both geraniol and nerolidol which is proved to possess antioxidant activity. Antioxidant capacity is correlated with atherosclerotic index and lipoprotein lipase activity [34, 35].

Thus the phytoconstituent responsible for maximum MolDock score namely geranyl acetate and nerodilol as compared to the standard drugs may possess free radical scavenging mechanism for exhibiting anti hyperlipidemic activity.

Total number of phytoconstituents filtered using the DruLiTo software is 9 and the total number of phytoconstituent violated the rule is 1 *i.e*., caryophyllen which had a Log P value of 6.044.

The medicinal property of phytoconstituents present in *Cinnamomum verum* and *Coriandrum sativum* may be due to inhibitory effect on HMG CoA enzyme. The phytoconstituents such as eugenol, cinnamaldehyde, caryophyllene, cinnamyl acetate, e-nerodiol, linalool, decanol were docked with HMG CoA reductase enzyme. The docking score of these phytoconstituents showed less inhibitory effect with the standard drugs as evident from the docking score. Further all the phytoconstituents analysed by DruLiTo software proved all of them has drug likenees property except caryophyllene as it has a log P value greater than 5 and therefore these compounds may act as potent source to treat obesity.

CONCLUSION: In conclusion, our results strongly favour the therapeutic use of phytoconstituents from *Cinnamomum verum* and *Coriandrum sativum* as a potential herb which can be consumed in our day today life for preventing hyperlipidaemia over the currently prescribed pitavastatin and atorvastatin, where these phytocontituents are free from any side/adverse effects. According to the terminology coined by Hippocrates, the father of western medicine "Food is medicine" the concept of taking these medicinal plants as food in day today life may prevent hyperlipidemic profile. Further research may be carried out to identify the exact mechanism of action through which the medicinal plants exhibited antihyperlipidemic activity.

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CONFLICT OF INTEREST: The authors declare that they have no conflict of interest.

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