



**IN-SILICO MOLECULAR DOCKING STUDY ON PHYTOCHEMICAL
COMPONENTS OF *RHODODENDRON ARBOREUM* LINN AGAINST ENZYME
TRANSPORT PROTEIN**

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ABSTRACT

To analyze the cholesterol absorption inhibitory activity of phytoconstituent present in *Rhododendron arboretum* Linn using *in silico* docking study. The software Molegro Virtual Docker and tools were used for molecular docking v 6.0 along with Graphical User Interface, calculate dock score and evaluate conformers. Molegro virtual docker is a discriminatory programme to predict ligand interactions. The presence of four phytochemical constituents from ethyl acetate extract and nine phytochemical constituents from ethanolic extract were identified by GC-MS. These components undergone *insilico* molecular docking studies using enzyme transport protein. The lead compounds were selected through the docking score. The compounds of ethyl acetate extract such as Dibutyl phthalate (-114.342); 1,2-Bis(trimethylsilyl)benzene (-86.8186); 2-(Heptyloxycarbonyl) benzoic acid (-73.179) and the compounds of ethanolic extract like Arsenous acid, tris (trimethylsilyl) ester (-90.6775); Methyltris (trimethylsiloxy) silane (-89.5094); Propiophenone, 2'-(trimethylsiloxy)- (-88.7413). Each extract has been shown three lead compounds from *in-silico* molecular docking using standard atorvastatin (-104.402). Further investigations on the above phytochemical constituents and *insilico* molecular docking study are necessary to develop potential chemical entities for the prevention and treatment of anti-hyper cholesterolemia.

Keywords: Anti-hypercholesterolemia, Atorvastatin, Molecular docking, *Rhododendron arboretum* Linn, 3QNT

INTRODUCTION

Atherosclerosis generally starts when a person is young and worsens with age. Almost all people are affected to some degree by the age of 65. It is the number one cause of death and disability in the developed world. Though it was first described in 1575, there is evidence that the condition occurred in people more than 5,000 years ago. Arteriosclerosis is a general term describing any hardening (and loss of elasticity) of medium or large arteries [from Greek *arteria*, meaning 'artery', and *sklerosis*, meaning 'hardening']; arteriosclerosis is any hardening of arterioles (small arteries); atherosclerosis is a hardening of an artery specifically due to an atheromatous plaque.

Low-density lipoprotein (LDL) particles in blood plasma invade the endothelium and become oxidized, creating risk of cardiovascular disease. A complex set of biochemical reactions regulates the oxidation of LDL, involving enzymes (such as Lp-LpA2) and free radicals in the endothelium. Cholesterol is delivered into the vessel wall by cholesterol-containing low-density lipoprotein (LDL) particles. To attract and stimulate macrophages, the cholesterol must be released from the LDL particles and oxidized, a key step in the ongoing inflammatory process.

Rhododendron arboreum Linn is an evergreen shrub or small tree with a showy

display of bright red flowers. The name 'RHODODENDRON' is derived from the Greek word 'RHODO' means rose & 'DENDRON' means tree. Rhododendron is the national flower of Nepal & is known as (Laligurans) & the state tree of Uttarakhand. It is called 'Burans, Bras, Buras or Barahke-phool' in local dialect. It is widely popular for the processed juice of its flowers which have gained market popularity as rhodojuice / sharbat. The plant is found in the Himalayas from Kashmir eastwards to Nagaland. Various parts of the plant exhibited medicinal properties & it is used for the treatment of various ailments.

Rhododendron arboreum Linn plant belongs to genus *Rhododendron* and family *Ericaceae*. Commonly it is known as "Billi" and "Buransh" in hindi. The flowers of *R. arboreum* range in color from a deep scarlet, to red with white markings, pink to white. Bearing up to twenty blossoms in a single truss this rhododendron is a spectacular sight when in full bloom. It is reported that the bright red forms of this rhododendron are generally found at the lower elevations [1]. Flowers are showy, red in dense globose cymes [2]. Calyx- fine cleft, Corolla-tube spotted funnel shaped, Stamens-hypozygous declining, Filaments filiform, Anthers-ovate, Style-capitate [3].

It is one of the most traditional system of medicine in Ayurvedic and Siddha.

Sub species

- *Rhododendron arboreum* spp. Arboreum (red or rose red flowers) found in Western Himalayas.
- *Rhododendron arboreum* spp. Cinnamomeum (white, pink or red flowers) found in Central Himalayas.
- *Rhododendron arboreum* spp. Delavayii (red flowers) found in Eastern Himalayas.
- *Rhododendron arboreum* spp. Nilagiricum (red flowers) found in Nilgiri.
- *Rhododendron arboreum* spp. Zeylancium (orange red flowers) found in Sri Lanka.

MATERIALS AND METHODS

1. MOLECULAR MODELING STUDIES

Molecular docking was performed using the software Molegro Virtual Docker (MVD) v 6.0 (www.molegr.com) along with Graphical User Interface (GUI), Molegro Virtual Docker tools was utilized to generate grid, calculate dock score and evaluate conformers. Molegro virtual docker is a discriminatory programme for predicting-ligand interactions [4-11].

2. LIGAND PREPARATION

The ligands used in this research were prepared using the chemical structure

of phytochemical compounds was obtained from PubChem compound database. It was prepared by Chems sketch and MOL SDF format of this ligand was converted to 3D structure of ligand [12-15].

3. PROTEIN PREPARATION

The three-dimensional (3D) structure of transport protein (PDB-ID: 3QNT) was transformed from the RCSB protein Data Bank. Inhibition or depletion of NPC₁L₁ reduces intestinal cholesterol absorption, resulting in reduction of plasma cholesterol levels. If the reduction of plasma cholesterol level Niemann Pick C₁ Like₁ protein (NPC₁L₁). This protein is an established molecular target for the cholesterol lowering drug atorvastatin [16-20].

4. STRUCTURE BASED

Structure based drug design relies on knowledge of the 3D structure of the biological target obtained through methods such as X-ray crystallography or NMR spectroscopy. If an experimental structure of a target is not available, it may be possible to create homology model of the target based on the experimental structure of a related protein. Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may designed using interactive graphics and the intuition of a medicinal chemist. Alternatively, various automated computational procedure may be

used to suggest new drug candidates [21-23].

RESULTS AND DISCUSSION

The molecular docking analysis were done with the targeted enzyme transport protein (PDB-ID: 3QND) was selected. The standard drug atorvastatin (cholesterol lowering drug) was used. This analysis of ethyl acetate extract contains 4 phytochemical compounds are Butanedioic acid, hydroxyl-, diethyl ester, (+/-)-; Dibutyl phthalate; 1,2-Bis(trimethylsilyl)benzene and 2-(Heptyloxycarbonyl)benzoic acid. Then ethanolic extract contains 9 phytochemical compounds are Butanedioic acid, hydroxyl-, diethyl ester, (+/-)-; Cyclobarbital; Trimethyl [4-(2-methyl-4-oxo-2-pentyl)phenoxy]silane; Methyltris(trimethylsiloxy) silane; 1,4-Bis(trimethylsilyl)benzene; 2-Ethylacridine; Arsenous acid, tris(trimethylsilyl) ester; Propiophenone, 2'-(trimethylsiloxy)- and 1,2-

Bis(trimethylsilyl)benzene. Then the molecular docking score are best three phytochemical compounds of *Rhododendron arboreum* Linn flower of ethyl acetate extract such as Dibutyl phthalate (-114.342); 1,2-Bis(trimethylsilyl)benzene (-86.8186); 2-(Heptyloxycarbonyl) benzoic acid (-73.179) and the compounds of ethanolic extract like Arsenous acid, tris(trimethylsilyl) ester (-90.6775); Methyltris(trimethylsiloxy) silane (-89.5094); Propiophenone, 2'-(trimethylsiloxy)- (-88.7413). This docking score for all phytochemical compounds were compared with standard drug atorvastatin. From the results, we may observe that for successful docking, intermolecular hydrogen bonding and lipophilic interactions between the ligand and the receptor are very important.

Table 1: Docking Scores of ethyl acetate extract of *Rhododendron arboreum* flower of Ligands in Cavity 1 of 3QNT

S. No	Phytochemical compound names	Mol. Dock Score	Rerank Score	H Bond
1	Butanedioic acid, hydroxyl-, diethyl ester, (+/-)-.	-66.6959	-58.4584	-10.4165
2	Dibutyl phthalate.	-114.342	-92.4153	-4.28243
3	1,2-Bis(trimethylsilyl)benzene	-86.8186	-78.3749	-5.87699
4	2-(Heptyloxycarbonyl)benzoic acid	-73.179	-16.872	0

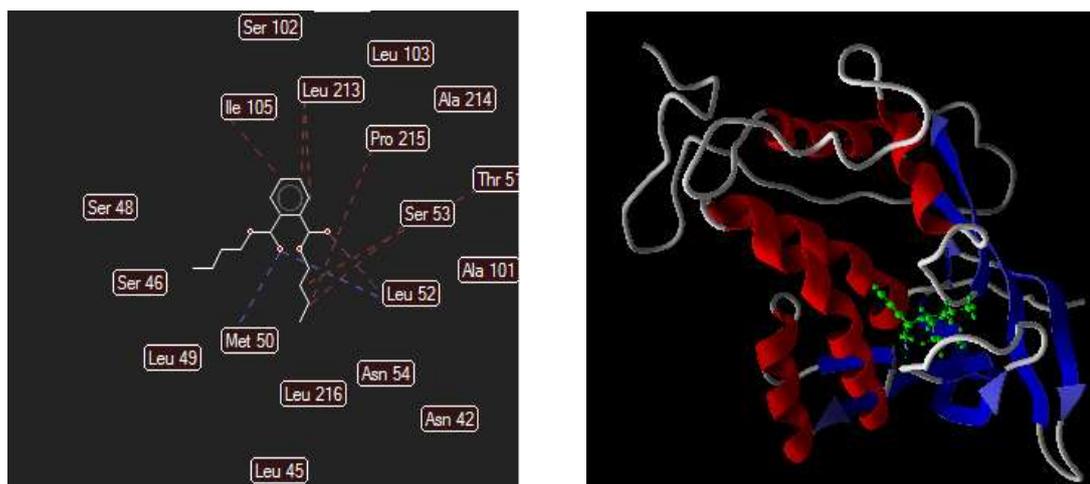


Figure 1: Stearic interaction and docking pose of Dibutyl phthalate

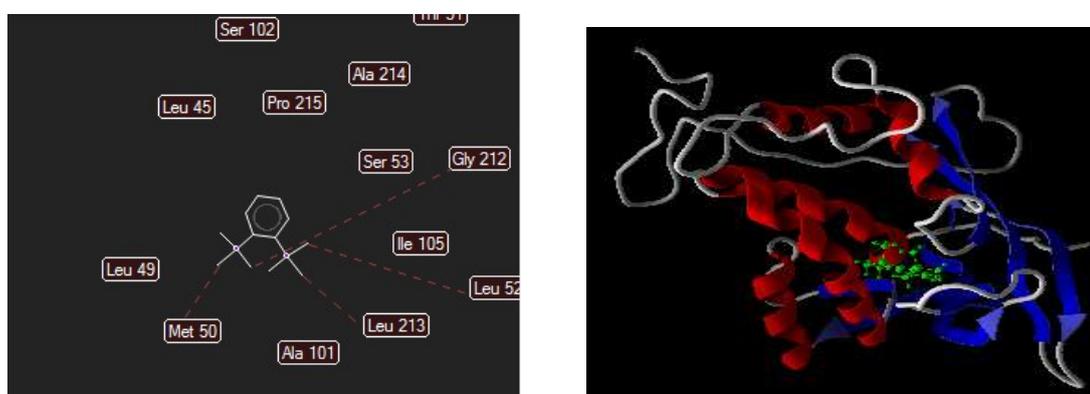


Figure 2: Stearic interaction and docking pose of 1,2-Bis(trimethylsilyl)benzene

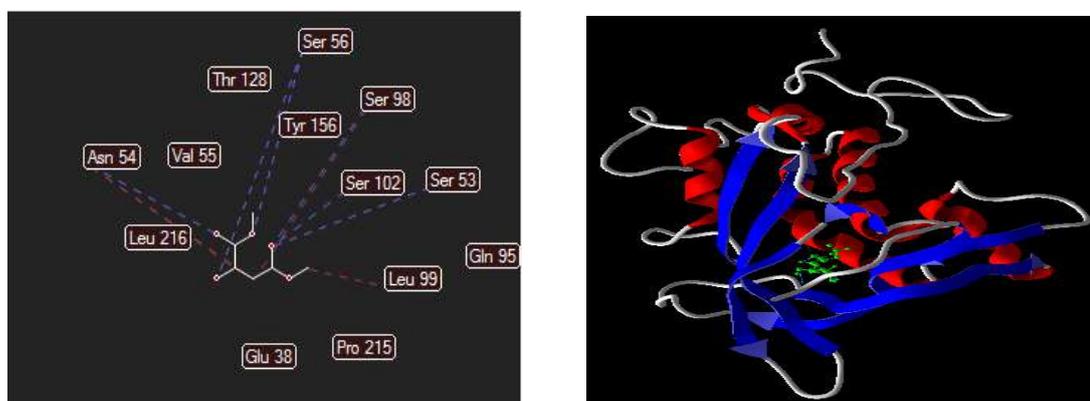


Figure 3: Stearic interaction and docking pose of 2-(Heptyloxycarbonyl) benzoic acid

Table 2: Docking scores of ethanolic extract of *Rhododendron arboreum* flower of ligands in cavity 1 of 3QNT

S. No	Phytochemical compound names	Mol. Dock Score	Rerank Score	H Bond
1	Butanedioic acid, hydroxyl-, diethyl ester, (+/-)	-66.6959	-58.4584	-10.4165
2	Cyclobarbitol	-72.977	-58.4834	-2.8445
3	Trimethyl [4-(2-methyl-4-oxo-2-pentyl)phenoxy]silane	-82.4172	-62.549	-0.563043
4	Methyltris (trimethylsiloxy) silane	-89.5094	-22.7408	-2.4501
5	1,4-Bis(trimethylsilyl)benzene	-77.844	-30.7064	0
6	2-Ethylacridine	-81.7722	-68.528	0
7	Arsenous acid, tris (trimethylsilyl) ester	-90.6775	-61.4785	-2.5
8	Propiophenone, 2'-(trimethylsiloxy)-	-88.7413	-67.027	-2.5
9	1,2-Bis(trimethylsilyl)benzene	-86.8186	-78.3749	-5.87699

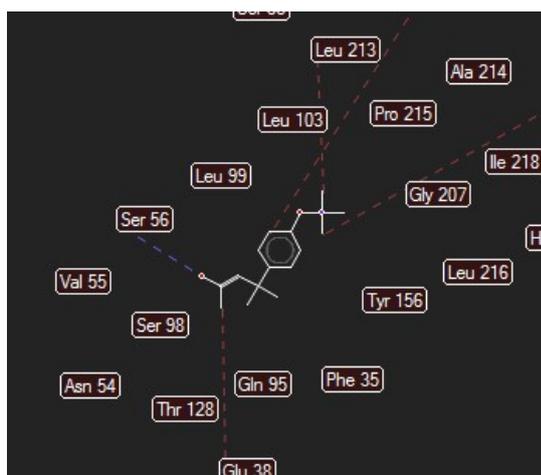


Figure 4: Stearic interaction and docking pose of Arsenous acid, tris(trimethylsilyl) ester

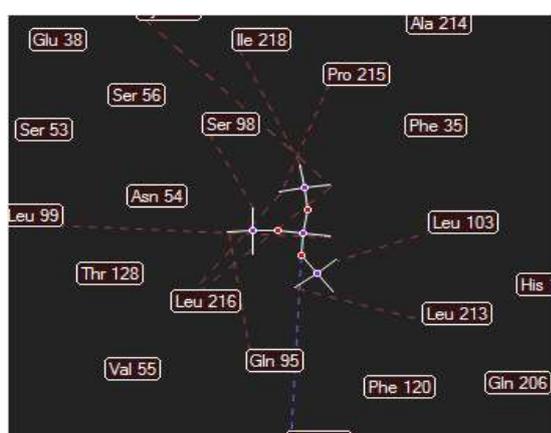
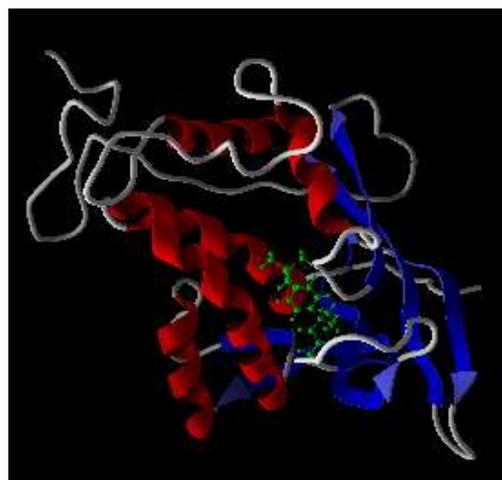


Figure 5: Stearic interaction and docking pose of Methyltris(trimethylsiloxy) silane

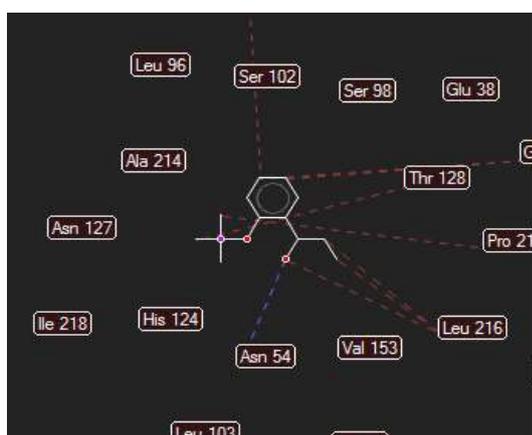


Figure 6: Stearic interaction and docking pose of Propiophenone, 2'-(trimethylsiloxy)-

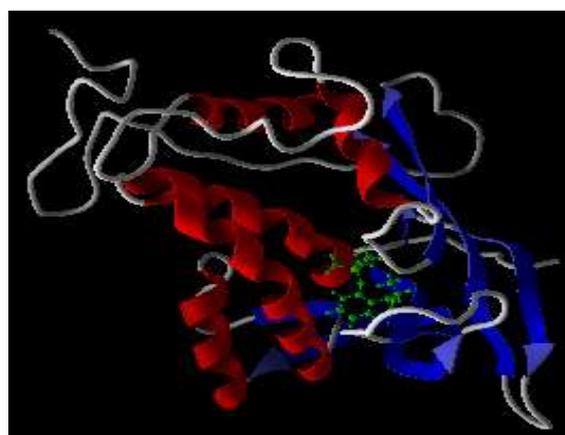


Table 3: Molecular docking score of standard drug atorvastatin

Standard drug	Mol. Dock Score	Rerank Score	H Bond
Atorvastatin	-104.402	-555.041	-8.45232

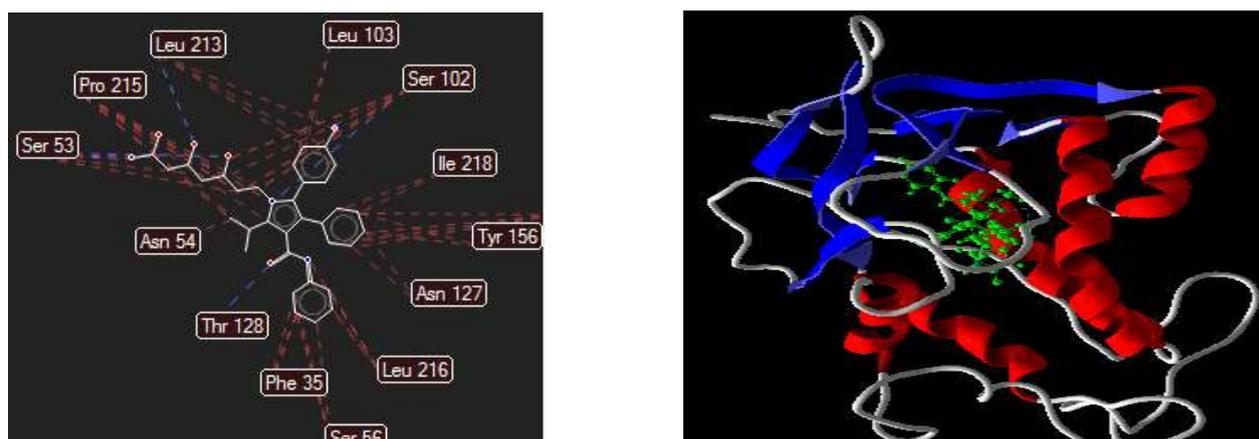


Figure 7: Stearic interaction and docking pose of standard drug atorvastatin

CONCLUSION

The research of result present in four phytochemical constituents from ethyl acetate extract and nine phytochemical constituents from ethanolic extract were identified by GC-MS. These components undergone *in-silico* molecular docking studies using enzyme transport protein. The lead compounds were selected through the docking score. The compounds of ethyl acetate extract such as Dibutyl phthalate (-114.342); 1,2-Bis(trimethylsilyl)benzene (-86.8186); 2-(Heptyloxycarbonyl) benzoic acid (-73.179) and the compounds of ethanolic extract like Arsenous acid, tris (trimethylsilyl) ester (-90.6775); Methyltris (trimethylsiloxy) silane (-89.5094); Propiophenone, 2'-(trimethylsiloxy)- (-88.7413ss). Each extract has been shown three lead compounds from *insilico* molecular docking using standard atorvastatin (-104.402). In the excellent binding sites and interactions with transport protein compared to the standard drug.

Further investigations on the above phytochemical compounds in *insilico* molecular docking studies are necessary to develop potential chemical entities for the prevention and treatment of atherogenic activity.

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