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**Original Research Article**

# *In-silico* studies of HMG-Co A reductase inhibitors present in fruits of *Withania coagulans* Dunal (Solanaceae)

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## *Abstract*

***Purpose:*** *To evaluate the antihypercholesterolemic effect of chemical constituents of W. coagulans by determining inhibitory effect of the compounds against HMG-CoA reductase, using in-silico methods.*
***Method:*** *Docking simulations of twenty-one chemical constituents, found in the fruits of W. coagulans were performed against HMGCR(PDB ID: 2Q1L) using Molegro Virtual Docker software. The best docked poses were then selected, based on the docking score and amino acids involved in the interaction within the ligand and active site of protein.*
***Results:*** *Five compounds viz. Coagulin D (comp no. 11), Ergosta-5,25-diene-3β,24ε-diol (comp no. 13), Withacoagulin (comp no. 15), and Withaferin (comp no. 16), showed the highest MolDock scores. These compounds with highest docking score, also formed hydrogen bond interactions with His (752), Lys (692, 735), Asp (690), Glu (559) within the binding site of HMG-CoA reductase, thus, halting enzyme activity. Whereas, Withanolide D (comp no. 17) with high MolDock score did not show hydrogen bonding interactions.*
***Conclusion:*** *The high MolDock score and maximum binding with catalytic region of the enzyme indicate that compounds selected from the fruits of W. coagulans are potential blockers of HMG-CoA reductase. Thus, the compounds may be useful for the management of hypercholesterolemia, which untreated, often leads to coronary artery disease.*

***Keywords:*** *Withania coagulans, Coronary artery disease, HMG-CoA reductase, Molegro virtual docker, Hypercholesterolemia, In silico studies*



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## INTRODUCTION

High blood cholesterol level is one of the key factor for progression of Coronary artery disease (CAD) one of the key factors [1]. Many nonclinical and human trials have proved that the risk of coronary complications could be minimized by halting the function of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), a major cholesterol biosynthesis enzyme [2]. Hypercholesterolemia can be treated with statins and other known drugs (niacins, fibrates etc) by inhibiting HMGCR activity [3]. However, these commercially available drugs have many adverse signs like hyperuricemia, nausea, diarrhea, gastric irritation, myositis, and abnormal liver function [4].

In the recent era, researchers have diverted their attention towards medicinal plants to explore the phytochemicals with HMGCR inhibiting activities that could be used to design a new hypolipidemic drug with minimum or no side effects. With the advancement in technology, computational methods have been widely used in evaluating the therapeutic potential of medicinal plants, by determining their activity against the target protein along with their possible mechanism of action.

Molecular docking methods predict interactions of protein and ligand with their binding affinities and the binding orientation of protein-ligand complexes [5,6]. The binding ability of a ligand with a specific protein is associated with its molecular structure, orientation and conformation. There are two steps in docking methods: energy-based scoring and geometric sampling to determine ligand/protein binding affinity [7]. Based on scoring function of docking procedures, the best complementary protein-ligand binding arrangement is found depends on their predicted binding affinities [8]. There is a direct relation between high energy scores and protein-ligand binding affinity [9,10].

During this study, *in silico* methods were used in order to identify the compounds, found in *Withania coagulans* fruits as effective inhibitors of HMGCR by using Molegro Virtual Docker (MVD) software.

*Withania coagulans* Dunal (family: *Solanaceae*) commonly found in Central and South Asia, with many well-reported pharmacological properties of its fruits, like anticancer, antidiabetic, hepatoprotective [11,12]. Reported *in vivo* study showed that methanolic fruit extract of this plant was found effective in reducing the coronary risk index by bringing the lipid profile within its normal level in high fat-induced hyperlipidemic rabbits [13]. Therefore, the present *in silico* study is designed to validate previous finding by investigating the inhibitory effect of isolated compounds [14,15] of fruits of *W. coagulans* on HMGCR.

## METHODS

### Ligand selection

Twenty-one compounds (Table 1), isolated from fruits of *W. coagulans,* were selected for docking studies against HMGCR. Chemsketch (version 12.01) was used to draw the structures of these selected compounds, and shown in Figure 1 (A and B).

### Structural features of enzyme

The crystal structure of HMG-CoA reductase with protein data bank ID 2Q1L was selected based on resolution. The non-mutated *Homo sapiens enzyme was*, downloaded from the protein Databank (PDB) (URL: (http://www.rcsb.org/pdb)) [16] to the MVD workspace. It is a tetramer protein with resolution 2.05 Å (Figure 2). The binding site of tetrameric HMGCR is symmetrical and made up of its chains C and D together, whereas, chains A and B were removed while preparing the molecule for the docking studies. It was revealed through structural analysis of HMGCR that it has single polypeptide chain with membrane-anchor, linker and catalytic domains [17].

HMGCR converts HMG-CoA into mevalonate, producing mevaldyl-CoA and mevaldehyde as intermediates, utilizing two NADPH + $2H^+$ molecules and releasing $NADP^+$ and CoA-SH upon reduction [17]. The enzyme has active site at interface of its dimer, one monomer linked with nicotinamide dinucleotide, and the other with HMG-CoA. During catalysis, a flap domain present at extreme carboxy terminus of each enzyme closes over the active site. It also contains a binding site with 3-dimensional fold structurally containing a nucleotide-binding motif which is used for NADPH catalysis [18]. The four key catalytic residues, preserved in all HMGCR classes are histidine, lysine, aspartate and glutamate [19,20].

The protonation of departing CoA thioanion is carried out by histidine (His-866). CoA elimination is crucial as it might strike mevaldehyde and block the completion of this complete process, if retained [17]. Lysine (Lys-735, and Lys-691), are involved in building the H-bonds with carbonyl group of HMG-CoA and also participates in stabilizing the mevaldyl-CoA intermediate [21]. Aspartate (Asp-690, Asp-767), is also found within the active site of this protein, contributing in two reductive stages of reaction, hydrogen bonding and play part in proton shuttle [22]. Whereas, in the second reductive stage mainly glutamate (Glu-559) contributes [23]. Few other amino acids, such as, asparagine (Asn-755), tyrosine (Tyr-479) and serine (ser-864), also contributes in the catalytic activity [22]. These amino acids connect carboxylate group of HMG-CoA by forming hydrogen bonds, make hydrophobic pocket over HMG-CoA and down regulate HMGCR catalytic activity [24].

### Docking procedure

At first, all the 21 compounds (ligands) and

protein structures were downloaded to the MVD work space in 'sdf' and 'pdb' format, followed by preparing each molecule via putting on charges, explicit hydrogen and pliable torsions at the lacking regions and bond orders. Valences and hydrogen atoms were examined properly in all the ligand molecules. In the next step, cavities were detected within the protein molecule by using the cavity detection algorithm of the software, to which ligand binding could effectively take place. Ten docking runs were then performed, where, each ligand was docked within the active site of the protein, it results in ten docking poses for each compound. After docking, the ten poses of ligand-protein interaction, have been organized according to MolDock and re-rank scores, with pose with highest moldock score at the top. These highest MolDock score poses were recognized as effective HMGCR inhibitors. The amino acids interaction with ligands was individually examined.

## RESULTS

The docking results indicated that compounds *viz*. compounds 13 (ergosta-5,25-diene-3β,24ε-diol), 15 (withacoagulin), 17 (withanolide D), 11 (coagulin D) and 16 (withaferin), out of 21 docked compounds gave highest MolDock score and maximum hydrogen bonding (Table 2 A). However, withanolide (compound 17) did not show any hydrogen bond interaction with active amino acids of HMGCR as it was unable to fit accurately in binding area (Figure 3). In contrast, the other 4 compounds interacted with the active site and showed hydrogen bond formation with key amino acids of HMGCR (Figure 4).

With the greatest score of -85.2867 kcal/mol, 2 H-bonds were formed with Asp-690 (oxygen) and nitrogen of Arg-568 by compound 13. Maximum 7 hydrogen bonds were formed by compound 15 (-79.101 kcal/mol) with Ser-852, Ser-565, Glu-559, His-752, Ala-751, Lys-692 and Lys-735. The docking of compound 11 (-71.4056 kcal/mol) revealed 3 H-bonds with Ser-565 and Cys-561. Six hydrogen bonds were formed with Lys-692, Asp-690, Asn-755, Ser-565 and His-752 by compound 16 (-68.943 kcal/mol). In addition, all selected compounds formed few hydrogen bonds with Arg-568, Ser-852, His-752, Ala-751, Cys-561, Asn-658, Ser-661, Gly-560, Glu-550 and Met-657 which may or may not be involved in catalysis (Table 2 B).

**Table 1:** Chemical constituents of *W. coagulans* fruit

| Structure no. | Compound | Plant part |
|---|---|---|
| 1 | 17β-hydroxywithanolide K | |
| 2 | 20β, hydroxy-1-oxo-(22R)-witha-2, 5, 24-trienolide | |
| 3 | 3β hydroxyl-2,3-dihydrowithanolide H | |
| 4 | 3β hydroxyl-2,3-dihydrowithanolide F | |
| 5 | 5α, 17α-dihydroxy-1-oxo-6α, 7α-epoxy-22 R-witha-2, 24-dienolide | Fruits |
| 6 | 5α, 20α (R) dihydroxy-6α, 7α-epoxy-1-oxowitha-2, 24-dienolide | |
| 7 | 5α, 27-dihydroxy-6α, 7α-epoxy-1-oxowitha-2, 24-dienolide | |
| 8 | Ajugin E | Aerial part (fruit) |
| 9 | Coagulanolide | Fruits |
| 10 | Coagulin C | |
| 11 | Coagulin D | Aerial part (fruit) |
| 12 | Coagulin L | |
| 13 | Ergosta-5, 25-diene-3β, 24ε-diol | |
| 14 | B-sitosterol glycoside | |
| 15 | Withacoagulin | Fruits |
| 16 | Withaferin | |
| 17 | Withanolide D | |
| 18 | Withanolide F | |
| 19 | Withanolide H | |
| 20 | Withanolide L | Aerial part (fruit) |
| 21 | (22R)-14α, 15α, 17β, 20β-tetrahydroxy-1-oxowitha-2, 5, 24-trien-26, 22-olide | Aerial part (fruit) |

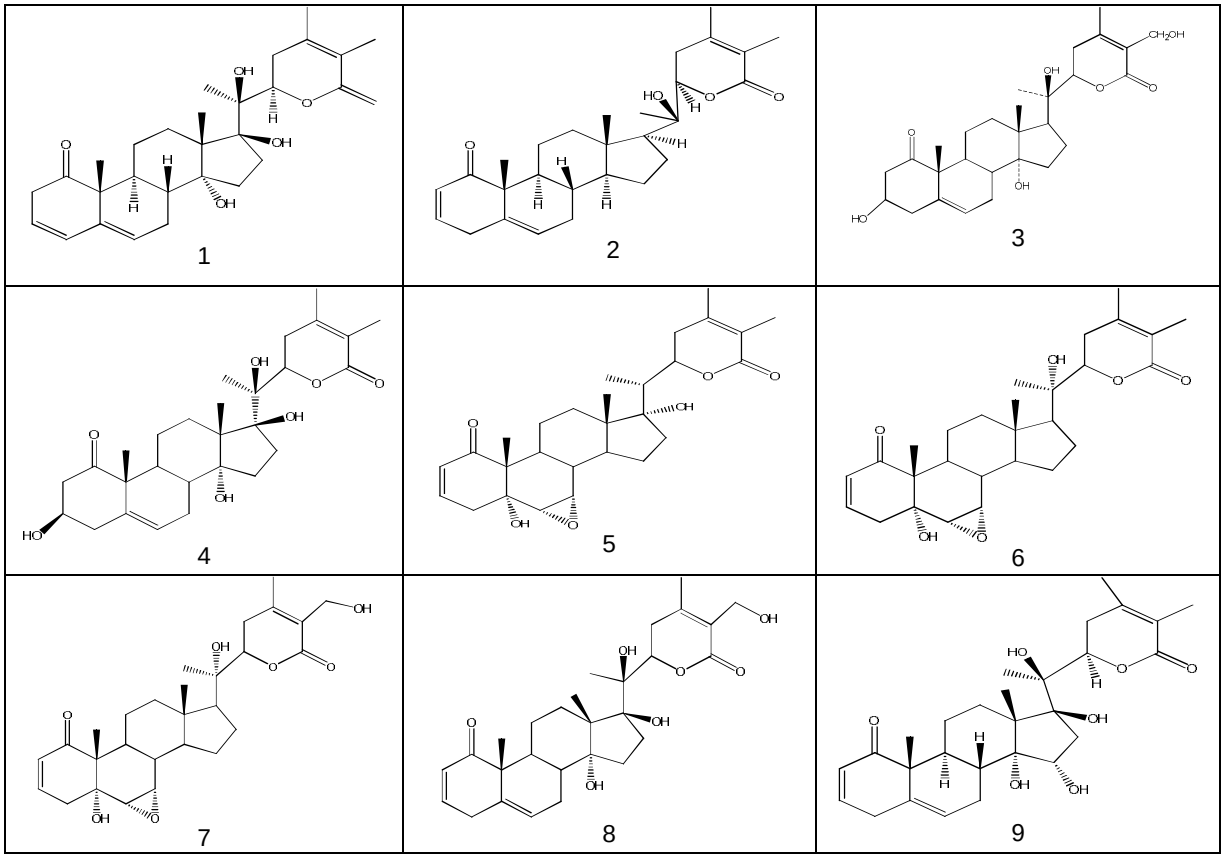



**Figure 1:** Structures of compounds 1-19 found in fruits of *W. coagulans* drawn by using Chemsketch software

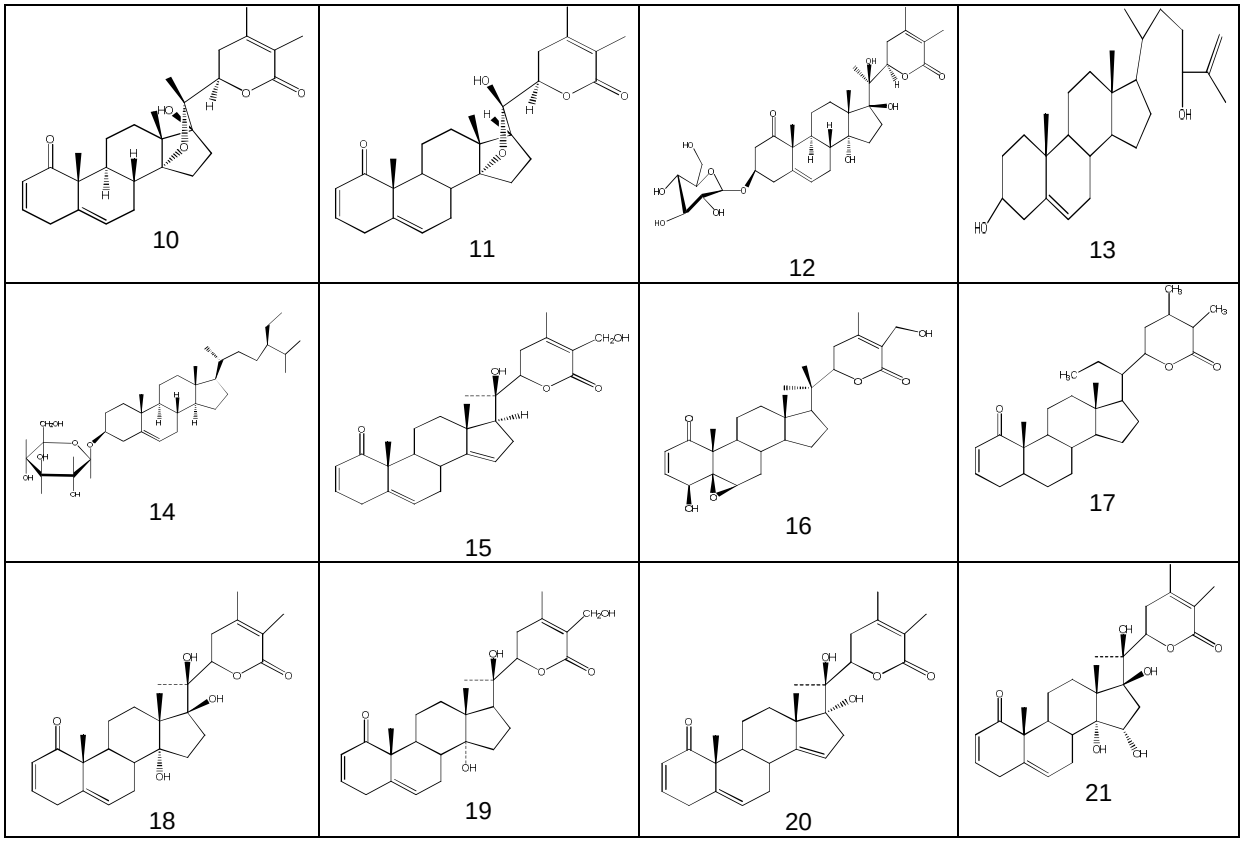



**Figure 2:** Structures of compounds 10-21 found in *W. coagulans* fruits drawn by using Chemsketch software

**Table 2:** Docked compounds of *W. coagulans* with HMGCR having high MolDock and Re-rank scores

| Compound | MolDock score (kcal/mol) | Re-rank score (kcal/mol) | H bond interaction energy (kcal/mol) | Amino acids participate in H-bond interaction* | No. of H bonds |
|---|---|---|---|---|---|
| Compound 13 | -85.2867 | -47.042 | -1.14885 | **Asp690**, Arg568 | 2 |
| Compound 15 | -79.101 | 46.9845 | -3.9575 | **Ser852**, **Ser565**, **Glu559**, **His752**, **Ala751**, **Lys692**, **Lys735** | 7 |
| Compound 17 | -76.284 | -42.8076 | 0 | - | 0 |
| Compound 11 | -71.4056 | -48.3911 | -4.61084 | **Ser565** (2 H bonds), **Cys561** | 3 |
| Compound 16 | -68.943 | 31.143 | -4.63614 | **Lys692**, **Asp690**, **Asn755** (2 H bonds), **Ser565**, **His752** | 6 |

*Common interacting amino acids are showed in specific colors

**Table 3:** Docking scores of compounds of *W. coagulans* with HMGCR

| Compound | MolDock score (kcal/mol) | Re-rank score (kcal/mol) | H bond interaction energy (kcal/mol) | Amino acids involved in H bond interaction* | No. of H bonds |
|---|---|---|---|---|---|
| Compound 14 | -62.7411 | -34.0732 | -2.5 | Ala859, Ala856 | 2 |
| Compound 5 | -60.602 | -35.9428 | -3.9936 | **Asn-755** (2 H bonds), **Glu559**, **His752**, **Ser565**(2 H bonds), **Ser852** | 7 |
| Compound 7 | -59.8841 | -25.7322 | -6.96578 | **Lys691**, **Asn755**, **Glu559** (2 H bonds), **Arg590**, Asn658 | 6 |
| Compound 20 | -57.819 | 4.51588 | -9.44222 | **Arg590** (2 H bonds), **Lys691**, **Glu559** (2 H bonds) | 5 |
| Compound 6 | -57.6141 | 23.2209 | -8.6313 | **Arg590** (2 H bonds), **Ser684**,**Ser661** (2 H bonds) | 5 |
| Compound 19 | -56.639 | 44.3148 | -10.5715 | **Cys561**, **Ser565**, **Glu559**, **Lys691**, **Asn755**, **Lys735**, **Ala751** | 7 |
| Compound 10 | -56.0248 | 1.51919 | -6.35735 | **Cys561**, **Gly560**, **Asn755**, **Lys691** | 4 |
| Compound 8 | -53.3322 | -14.2715 | -11.2089 | **Arg590**, **Ser684** (2 H bonds), **Lys735**, **Lys692** (2 H bonds), **Asp690**, **Ala751** | 8 |
| Compound 2 | -50.8894 | -24.2584 | -2.40062 | **Arg590** | 1 |
| Compound 9 | -45.1089 | 9.55983 | -10.5578 | **Lys735**, **Arg590** (4 H bonds), **Asp690**, Glu550, **Asn755**, **His752** | 9 |
| Compound 21 | -44.0928 | -24.4729 | -7.34256 | **Ser661** (2 H bonds), **Arg590** (3 H bonds) | 5 |
| Compound 3 | -41.1982 | 46.2271 | -10.9583 | **Ser684**, **Arg590** (2 H bonds), **His752**, **Glu559**, **Asn755**, **Gly560**, Met657, **Ser661** | 9 |
| Compound 12 | -40.1114 | 28.7312 | -18.712 | Arg568, **Ser565**, **Ser852** (2 H bonds), **Glu559** (2 H bonds), **Asn755**, **Arg590** (2 H bonds), **Asp690**, **Lys691**, **Asn755** | 13 |
| Compound 1 | -38.8102 | 27.8834 | -4.61066 | **Gly560** (2H bonds), **Glu559** (2 H bonds), **Asn755**, **His752** | 6 |
| Compound 18 | -34.993 | 2.31703 | -8.21098 | **Glu559**, **Asp690**, **Arg590** (3 H bonds) | 5 |
| Compound 4 | -30.8657 | 30.8832 | -8.03073 | **Gly560**, **Glu559** (2 H bonds), **Arg590**, **Ser684**, **His752**, **Asn755** | 7 |

*Common interacting amino acids are showed in specific colors

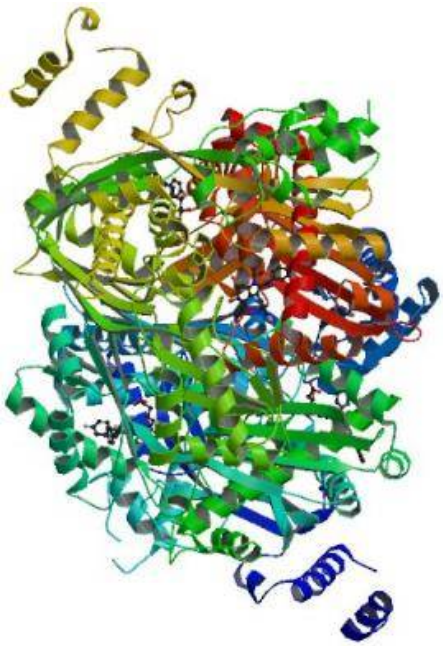


**Figure 3:** Structure of HMG-CoA reductase protein (PDB ID: 2Q1L)

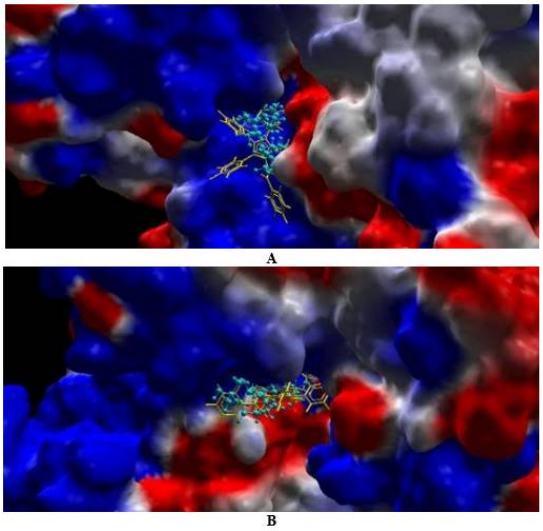
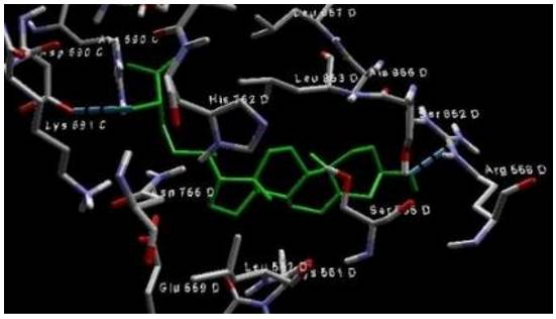
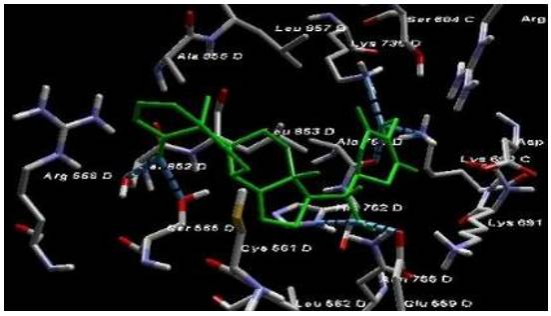


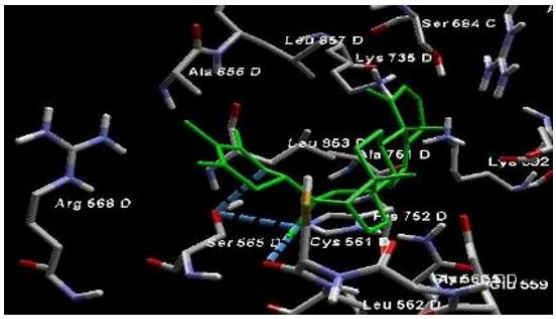
**Figure 3:** Representing binding mode of (A) compound 17 and (B) compound 13 within the catalytic region of enzyme. The electrostatic potential of the protein surface with negative and positive charge is represented in red and blue colors, respectively



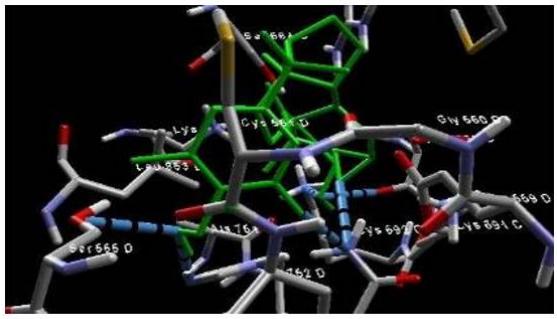
**A. Compound 13**



**B. Compound 15**



**C. Compound 11**



**D. Compound 16**

**Figure 4 (A – D):** Interactions of HMGCR with high MolDock score compounds (A: comp 13, B: Comp 15, C: Comp 11, D: Comp 16), (Ligand molecule= green solid line, Hydrogen bonding = blue dotted line)

## DISCUSSION

The technique of molecular docking is a significant tool used in computer-aided drug design and structural biology in determining and describing the well-suited interaction of specific target protein and ligands [25]. HMG-CoA reductase is target protein, catalysing the reductive transformation of HMG-CoA into mevalonate, rate-regulatory step in controlling endogenous cholesterol biosynthesis [26]. Over activity of this enzyme is observed in hypercholesterolemic condition which promotes cardiovascular disease [3]. Hypocholesterolemic drugs (statins) are structural analogues of HMG-CoA but inhibitors of HMGCR. It was confirmed by docking studies that statins form complex with HMGCR by interacting with the residues Arg-

590, Asn-755, Glu-559, Lys-735, Lys-691, Lys-692 and Ser-684 found in the catalytic site of the same enzyme which are important for catalysis, thereby inhibiting the activity of enzyme [19,20,23,27,28].

Therefore, twenty-one reported compounds, from the *W. coagulans* (fruits), were selected from literature [13,14]. Each of thecompound was docked within the active site of HMGCR. Based on high MolDock score, the best pose was chosen.

Docking results presented that five compounds viz. 13, 15, 17, 11 and 16 showed high MolDock score and maximum hydrogen bonding, out of twenty-one compounds. These compounds interacted with the catalytic site of HMGCR as statins usually bind to inhibit the activity of enzyme [17,19,27,28].

Study showed that another blocker of this enzyme: (3R, 5R)-7-[5-(anilinocarbonyl)-3,4-Bis(4-fluorophenyl)-1-Isopropyl-1H-pyrrol-2-YL]-3,5-dihydroxyheptanoic acid (882) interacts by forming hydrogen bonds with the key amino acids including Arg-590, Asp-690, Asn-755, Lys-735, Ser-684, Lys-691, Glu-559 and Ser-565 of same protein (PDB ID: 2Q1L). These amino acids are involved in catalytic function and inhibit the activity of same enzyme. It has been reported that this inhibitor (882) binds to HMGCR in the same mode as statins, indicating inhibition of enzyme activity [16,28]. Interestingly, the top scored compounds efficiently interacting with Ala-571, Lys-692, Lys-735, Asp-690, Arg-568, Ser-852, Glu-559, His-752, Ser-565, Cys-561, and Asn-755, that are crucial for catalytic activity of this enzyme [19,20,23,27,28] thereby, predicted to be inhibitors of HMGCR.

Therefore, the compounds: coagulin D (comp no. 11) , ergosta-5,25-diene-3β,24ε-diol (comp no. 13), withacoagulin (comp no. 15), withanolide D (comp no. 17) , and withaferin (comp no. 16) are predicted as effective interceptors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase based on their high MolDock scores and best fit within the main catalytic region of same enzyme. In future, further *in-vivo* studies will be performed and these compounds could be used as possible drugs for the treatment of hypercholesterolemia [13].

## CONCLUSION

The results confirm that some of the compounds found in *W. coagulans* fruits fit well in the catalytic region of HMG-CoA reductase by interacting with key residues of active site. However, four compounds, *viz,* coagulin D, ergosta-5,25-diene-3β,24ε-diol, withacoagulin, withanolide D, and withaferin are projected as powerful inhibitors of HMGCR.

## DECLARATIONS

### *Conflict of interest*

No conflict of interest is associated with this work.

### *Contribution of authors*

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. This project was under the supervision of Dr. Shamim A. Qureshi, whereas the lab facility with guidance for molecular docking was were provided by Dr. Sadaf Naeem. Dr Tooba Lateef (PhD student) had done practical work and manuscript writing.

### *Open Access*



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