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# A Molecular Docking Study of Solasodine against HMG-CoA Reductase

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**ABSTRACT: In silico methods are becoming an essential component of the drug discovery process. This is mostly because they have the ability to have an impact on the entire drug development path, finding and discovering new prospective medications at a markedly reduced cost and time. Hyperlipidemia is a recognized risk factor for cardiovascular disease. It is common to treat hyperlipidemia with herbs. Yet, it presents ethical questions to test the effectiveness of herbal remedies for hyperlipidemia on humans and animals directly. Consequently, before conducting animal research and human clinical trials, in silico studies are required to assess the safety and efficacy of phytoconstituents. The atomic-level interaction between a ligand and a protein can be mimicked via molecular docking. The purpose of the study is to use molecular docking to assess the effectiveness of natural compounds against hyperlipidemia. One of the major challenges in molecular docking studies of solasodine is the accurate prediction of the binding affinity. After reading several literary sources, natural products were chosen. A molecular structure file for each substance was downloaded from the Pub Chem database. The Protein Data Bank provided the protein's crystal structure (PDB ID: 1HW9). The solvent molecules, cofactors, and ligands were released from the protein molecule. The Biovia Discovery software was used to find active binding sites. Docking tests for natural products against the 1HW9 protein were carried out using PyRx. Pyrx generates multiple conformations of ligand which improves the accuracy of the docking. According to the molecular docking research, solasodine binds to the HMG-CoA receptor more robustly and has a lower binding energy value than atorvastatin. It was discovered that atorvastatin was not as stable toward HMG-CoA as solasodine. Solasodine has the ability to act as a hypolipidemic agent.**

**Keywords:** Molecular Docking, Natural Compounds, Lipid Disorder, Insilico Study.

## INTRODUCTION

Hyperlipidemia is a common condition and a prominent component of the metabolic syndrome, caused by a variety of circumstances. When paired with other prevalent conditions such as diabetes, hypertension, and cardiovascular disease, this disease increases morbidity and mortality. A higher-than-normal concentration of one or more lipids in plasma is referred to as hyperlipidemia, which is clinically categorized as high-density lipoproteinemia, mixed hyperlipidemia, hypercholesterolemia, and hypertriglyceridemia. Elevated levels of cholesterol, triglycerides, or low-density lipoprotein cholesterol are the main causes of atherosclerotic cardiovascular disease, according to epidemiological research and clinical trials (Li *et al.,* 2022). With rising incidence and prevalence all over the world, hyperlipidemia is a significant public health issue (Makowski, 2015). Triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol are the current clinical biomarkers; however, they lack the essential specificity and sensitivity and only dramatically rise after severe dyslipidemia (Chen *et al.,* 2014). Numerous randomised clinical trials have demonstrated the high effectiveness and safety of statins, which made them the unstoppable first line of treatment for atherogenic dyslipidemia. However, 60% to 80% of recurrent cardiovascular risk persists even with appropriate statin therapy. A mainstay of the management of dyslipidemia is statin medication. It has been demonstrated to be both safe and effective for avoiding future cardiovascular events in multiple randomised clinical trials. Even with appropriate statin medication, a sizable portion of patients are intolerant or unresponsive to statin therapy, and a significant level of residual atherosclerotic cardiovascular disease risk still exists. In the fight against atherogenic dyslipidemia, there are numerous researchers and pharmaceutical firms engaged, and there have been many encouraging developments that are now being applied in actual clinical settings. The development of new medication classes outside of statins may help anti-atherosclerosis treatment advance. To determine the best and most effective treatment option for patients with dyslipidemia, clinicians should keep a close eye on the outcomes of upcoming trials using new classes of medications (Ahn and Choi 2015). The adverse effects of today's lipid-lowering medications have strengthened the trend toward conventional and alternative remedies.

Epidemiology findings show that alternative therapies, medicinal plant use, food, and fruit consumption have had positive impacts on the consequences of hyperlipidemia in many countries. It should be emphasized that in the majority of nations, including affluent ones, the use of lipid-lowering medicinal herbs has grown significantly (Bahmani *et al.,* 2015). In the treatment of hyperlipidemia, statins are the drugs of choice (Fischer *et al.,* 2015). Statins, which are HMG-CoA reductase inhibitors, lower high LDL cholesterol (Liao, 2005). Despite the fact that these medicines have been used for over four decades, several side effects such as diabetes, statin-induced myalgia, and possible hepatotoxicity, nephrotoxicity, and neurotoxicity of statins should not be overlooked (Sirtori, 2014). Rashes, diarrhea, bloating, stomach discomfort, nausea, vomiting, myalgia, skin flushing, sleeplessness, and headaches are some of the side effects of statins (Thompson *et al.,* 2016). In statin-treated individuals, immune-mediated necrotizing myopathy has been documented (Meyer *et al.,* 2020). Cerivastatin was taken off the market by its maker in 2001 due to an increased risk of rhabdomyolysis (Tobert, 2003).

Nature provides a vast range of plants for healing many human illnesses. Because of their low toxicity and cost-effectiveness, medicinal plants have been used to treat a variety of diseases by many countries since time immemorial. As a result, medicinal plants have attracted a lot of attention in the creation of herbal medications and are credited with phytoconstituents. According to World Health Organization statistics, approximately 80% of the world's population relies mostly on medicinal plants for basic health care (Dey *et al.,* 2021). The products of plants have an important role in the treatment of hyperlipidemia. Plant compounds might be a viable therapy option for hyperlipidemia. Herbs offer a benefit over statin medication in terms of safety and avoiding unwanted effects. Even when administered at large doses and over long periods of time, human testing revealed no or moderate negative effects of the herbs (Domenech *et al.,* 2019). Herbs that lower cholesterol may reduce hyperlipemia, preventing atherosclerosis and vascular endothelial damage (Cragg and Newman 2013). Garlic, turmeric, artichoke, green tea, grape, mastiha, red yeast rice, and olive leaf have all shown promise in randomized controlled clinical trials and meta-analyses (Đuric *et al.,* 2021). In vivo investigations indicate that daily treatment of diabetic rats with Castanea sativa spiny-budded ethanolic extract for 4 weeks alleviated hyperlipidemia (Jovanovic *et al.,* 2017). *Trichosanthes dioica* methanolic extract included a variety of bioactive phytochemicals, including phenols and flavonoids. Thus, the existence of phenolic and flavonoid concentrations suggests the antioxidant qualities of medicinal plants. *Trichosanthes dioica* has high levels of phenolic and flavonoid content. According to the findings, *Trichosanthes dioica* possesses high antioxidant activity and scavenges free radicals. In this study, the methanolic extract of *Trichosanthes dioica* demonstrated a hyperlipidemic effect, with a drop in total cholesterol and triglyceride levels and an increase in high-density lipoprotein levels in Wistar rats with high-fat diet-induced hyperlipidemia (Shrivastava *et al.,* 2021). A methanolic extract of *Piper sarmentosum* administered to fructose-induced obese mice significantly reduced obesity and hyperlipidemia by decreasing adipocytes and inhibiting HMG-CoA reductase. Piper sarmentosum may be used as an alternate or supplemental treatment for hyperlipidemia (Kumar *et al.,* 2021). Curcumin, puerarin, leoligin, and geraniol are examples of bioactive chemicals that decrease cholesterol production by inhibiting the expression of HMG-CoA reductase (Ji *et al*., 2019).

Molecular docking is a technique for fitting a small ligand's computer-generated 3D structure onto a receptor structure in a range of orientations, conformations, and locations. This approach is important in drug development and medicinal chemistry since it provides information on molecular recognition. Docking is now an essential component of computer-aided drug design and discovery. Docking is increasingly being used to screen vast chemical libraries for new medicines (Jakhar *et al.,* 2020). Molecular docking is an appealing framework for understanding drug biomolecular interactions for rational drug design and discovery, as well as mechanistic investigation, by predominantly placing a ligand into the preferred binding site of the target-specific region of the receptor in a non-covalent manner. The outcome of a protein-ligand or protein-protein interaction in terms of a stable protein-ligand complex is predicted by molecular docking. Protein-ligand complexes have been found to aid in a wide range of biological processes. The ligands can bind to proteins by hydrogen bonds and Vander Waals forces (Maryshyla and Nevaditha 2020). The information gathered from the docking technique may be used to propose the binding energy, free energy, and stability of complexes. Obtaining a ligand-receptor complex with an optimal shape and the idea of having less binding free energy is the main goal of molecular docking. The entire internal energy as well as the energy of the unbound system as well as the hydrogen bond, electrostatics, torsional free energy, dispersion and repulsion, desolvation, and other factors are used to show the net anticipated binding free energy (Dar and Mir 2017).

## MATERIAL AND METHODS

**Ligand Preparation.** Using the PubChem database, all of the chosen chemicals (Ligand) were downloaded in the SDF (Standard Data Format). These were examined using Marvin View, a sophisticated chemical viewer for 2D or 3D chemical structures and related data. All of the selected ligands' canonical SMILES IDs were recorded, and the PubChem database was used to estimate the physico-chemical characteristics of these ligands. The chosen ligands were then made into 3D structures using Biovia Discovery software for later usage (Kavitapu and Sharma 2021).

**Protein preparation**. PDB ID 1HW9 was chosen based on criteria such as species, resolution and R factor,

protein, length of structure solved, and whether the structure is native or ligand-bound. The protein was obtained in PDB format from the Protein Data Bank (PDB ID: 1HW9) and then refined and purified using Biovia Discovery Studio. The protein had all co-crystals, heteroatoms, and water molecules taken out of it.

**Active Binding Site Analysis.** The molecular docking procedure normally begins with determining the active binding site of the selected proteins, which identifies the specific protein-restricted area. The prediction of ligand binding sites on the surface of proteins using a fast, accurate, and automated technique is a key difficulty in virtual screening. The Biovia discovery tool was used to identify active binding sites. A blind docking approach was used in this investigation between the target protein and ligand.

**Molecular Docking Analysis.** Estimating and locating the proper target for effective docking is a key stage in molecular docking. Using the known three-dimensional structure of target proteins, a suitable docking program may be used to search for the optimal binding site of ligand and target protein (Dallakyan and Olson 2015). For docking-based virtual screening, several docking solutions are available. PyRx (https://pyrx.sourceforge.io/), an open-source program, was used. PyRx provides additional applications such as Open Babel, AutoDock, and AutoDock Vina. Once the docking has been finished, the ranking is done using the dock score function (Trott and Olson 2010). As illustrated in Fig. 5, solasodine binds to numerous amino acids in proteins. Solasodine binds to HMG-CoA reductase via a number of interactions with particular amino acid residues in the enzyme, including hydrogen bonding and van der Waals forces. The total binding interactions reveal solasodine's versatility in binding to a wide range of amino acids and regulating protein function.

## RESULTS AND DISCUSSION

The selected compounds were docked with HMG-CoA reductase, and the top three compounds have more negative energy than the positive control drug, atorvastatin. The more stable ligand-receptor complexes were found with solasodine. Solasodine appears as an aglycone section of glycoalkloids in most solanaceous plants, such as solasonine and solamargine. In the steroid drug industry, solasodine is used as a hormone precursor in the production of corticosteroids, anabolic steroids, antifertility medications, etc. (Kumar *et al*., 2019). This study explains that plant-derived products may be useful for hyperlipidemia. For the management of lipid disorders, plant-derived drugs are highly necessary at this stage. The molecular docking study shows that solasodine has a stronger negative binding affinity than atorvastatin and may be useful for the treatment of hyperlipidemia; further study is required to evaluate anti-hyperlipidemic activity in different models. Solasodine forms chemical bonds with a number of amino acids, including CYS527, VAL530, MET530, VAL538; PRO813; and CYS817. According to Table 1, solasodine has a higher negative value in molecular docking, resulting in a more stable ligand-receptor complex. HMG-CoA reductase was docked with solasodine and atorvastatin. Solasodine was discovered to have a stable ligand-receptor complex compared to atorvastatin. Solasodine and atorvastatin were shown to have binding affinities for protein 1HW9 of 8.9 kcal/mol and 7.8 kcal/mol, respectively (Table 1). Table 2 compares additional atorvastatin and solasodine characteristics.

The rate-limiting step in the production of cholesterol is the conversion of HMG-CoA to mevalonate, which is catalyzed by the enzyme HMG-CoA reductase. Anti-hypercholesterolemic medications (statins) aim to reduce blood cholesterol levels by inhibiting the process mediated by HMG-CoA reductase. The endoplasmic reticulum is where the enzyme is attached. Cellular cholesterol homeostasis critically depends on HMG-CoA reductase (Friesen and Rodwell 2004). The rate-limiting enzyme in the cholesterol biosynthesis pathway, HMG-CoA reductase, was an appealing target in the hunt for medicines to lower plasma cholesterol levels (Tobert, 2003). Inhibitors of HMG-CoA reductase, such as statins, are the main treatments for hypercholesterolemia. A statin medicine called atorvastatin is used to reduce the body's cholesterol levels. It functions by preventing the production of cholesterol by blocking the HMG-CoA reductase enzyme. Several interactions with certain amino acid residues in HMG-CoA reductase enable atorvastatin to bind to the enzyme.

It was discovered that atorvastatin binds to the HMG-CoA reductase enzyme residues Val522, Cys527, Met534, Ile762, Gln814, and Cys817. It is through hydrophobic interactions that atorvastatin binds to the 1HW9 amino acids. Atorvastatin has a sizable hydrophobic area that can interact with the enzyme's hydrophobic residues, such as valine and isoleucine. These interactions support atorvastatin's binding to the enzyme and keep it from easily detaching. Hydrogen bonds play a role in yet another binding interaction between atorvastatin and the 1HW9 amino acids. A number of polar groups in atorvastatin, including amides and alcohols, can establish hydrogen bonds with the polar residues of the enzyme. These hydrogen bonds aid in further stabilizing and boosting the affinity of atorvastatin for the enzyme. Van der Waals forces are another mechanism via which atorvastatin interacts with 1HW9 amino acids, besides hydrophobic and hydrogen bonding interactions. The atorvastatin-enzyme complex is often stable because of these forces, despite their lower strength compared to the other binding interactions. The binding of atorvastatin to HMG-CoA reductase involves a variety of interactions with certain amino acid residues in the enzyme, including hydrophobic forces, hydrogen bonds, and van der Waals forces. These interactions aid in complex stabilization and raise atorvastatin's affinity for the enzyme, enabling it to successfully reduce the body's production of cholesterol. The efficiency of atorvastatin as a medication for decreasing cholesterol depends on these binding interactions.

Solasodine is one of the possible glycoalkaloids found in *Solanum khasianum. Solanum khasianum*, an essential medicinal plant, is a member of the Solanaceae family. Solanaceae is a family of ninety genera with 3000 species and a global distribution. Solanum is the biggest genus, with over 2,000 species, and is well known for its vast variety of medicinal applications. The plant was discovered to include phenols, flavonoids, alkaloids, and a variety of other phytoconstituents that help to reduce inflammation, oxidative stress, and blood glucose levels. Solasodine from Solanum plants has antioxidant, antibacterial, antinociceptive, antiandrogenic, cytotoxic, anti-inflammatory, hepatoprotective, and antiobesity effects. The biological actions of steroidal glycoalkaloids are mostly attributed to functional groups such as hydroxyl, acetyl, and sugar moieties (Kumar *et al.,* 2019). In a rat model of bronchial asthma, solasodine inhibits the excessive Th2-immune response caused by ovalbumin (Arora *et al*., 2022). A steroid glycoalkaloid called solasodine may be discovered in the Solanum genus (family Solanaceae). The plant Solanum is frequently used as a traditional medicine. The findings showed that solasodine extracts had an active anti-proliferative effect on colon and bone cancer cell lines, pointing to the potential use of these extracts as innovative targeted therapies for colon and bone malignancies (Deshmukh *et al.,* 2022). Solasodine and its glycosylated derivatives can be utilized to create potential medications to treat a variety of human ailments (Chidambaram *et al.,* 2022). Animals exposed to solasodin showed signs of liver healing (Malik *et al.,* 2018).

Solasodine is a naturally occurring compound found in eggplant, potatoes, tomatoes, bell peppers, and several species of nightshade plants. The most significant glycoalkloids in solanaceous plants are solasonine and solamargine, whose main aglycone is solasodine (Smith *et al.,* 2008). Solasodine, a spiroketal alkaloid sapogenin, has a C27 cholestane skeleton that is attached at the 3-OH region of the aglycone by 1–5 carbohydrate side chains (Jayakumar and Murugan 2015). Many solanum plants of the Solanaceae family contain the active ingredient solasodine (Hussain *et al*., 2012; Patel *et al.,* 2013). In a carrageenan-induced rat paw oedema model, solasodine has shown anti-inflammatory activity (Pandurangan *et al.,* 2011; Emmanuel *et al.*, 2006). In lipopolysaccharide-induced inflammation, the anti-inflammatory effects of solasodine were found (Chiu and Lin 2008). Solasodine is an anticonvulsant, CNS depressant, antioxidant, anti-nociceptive, anti-inflammatory, cytotoxic, hepatoprotective, anti-atherosclerotic, anti-fungal, and anti-obesity agent. It may also have other biological effects. Hence, solasodine and its derivatives appear to be potential medicines for the treatment of a variety of ailments as well as for various industrial applications (Kumar *et al.,* 2019).

It has been used for centuries as an herbal remedy to treat a variety of ailments, including skin conditions, digestive issues, and even cancer. In recent years, solasodine has gained attention from the scientific community due to its potential therapeutic applications. Solasodine is being studied for its anti-inflammatory properties. The adjuvant-induced oedema in rat paws was dramatically reduced after solasodine administration. These findings imply that solasodine has anti-inflammatory properties (Pandurangan *et al.,* 2011). By acting as an antioxidant, solasodine shields the rat brain from ischemia and reperfusion damage (Sharma *et al.,* 2014). Additionally, it may have benefits as an antioxidant that can help protect cells from oxidative damage caused by free radicals or environmental toxins like air pollution or cigarette smoke exposure. This may contribute to its potential anti-hyperlipidemic effect. Phytochemicals with anti-inflammatory and antioxidant activities have the capacity to alter lipid metabolism (Pereira *et al.,* 2021). The primary active ingredient in solasodine is the glycoalkaloid solasonin, which acts as an anti-inflammatory agent by inhibiting the production of inflammatory mediators such as prostaglandins and leukotrienes. Antioxidants are essential in reducing oxidative stress because they maintain a balance between free radical generation and oxidative stress. Because synthetic antioxidants offer a significant health risk, they are often supplemented with natural food antioxidants. Natural compounds having antioxidant activity have the potential to be used in the treatment of hyperlipidemia. The assessment of natural items having such properties is critical for the creation of novel medications in pharmacology and medicine (Kumar *et al.,* 2019). By reducing oxidative stress and inflammation in the body, solasodine may help reduce levels of lipids in the blood and improve cardiovascular health. Overall, there are many potential benefits associated with using solasodine therapeutically; however, more research needs to be done before any definitive conclusions can be drawn regarding safety and efficacy profiles when administered systemically over long periods of time.

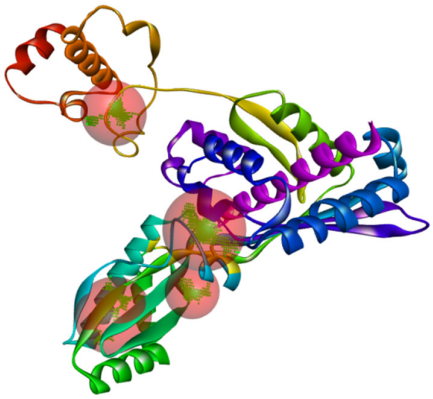


**Fig. 1.** 3D Structure of HMG-CoA reductase.

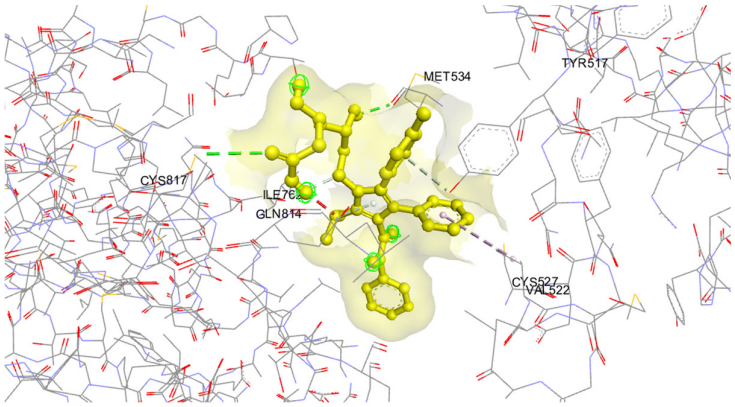
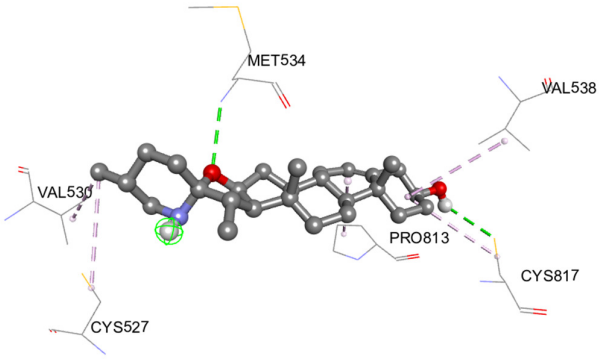
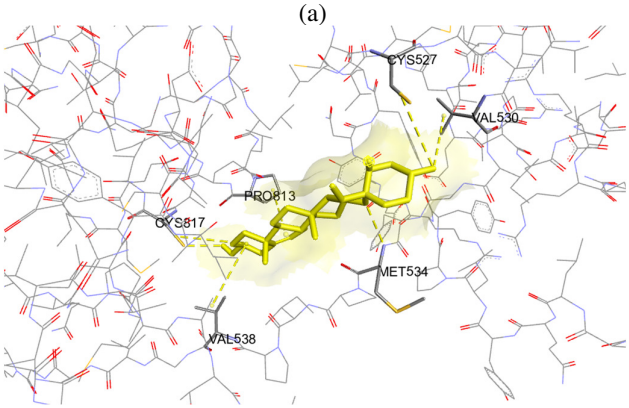



**Fig. 2.** 3D structure of Atorvastatin (+ve control) docked compound with 1HW9 including amino acids (CYS817, GLN814, ILE762, MET534, CYS527 and VAL522)




(a)




(b)

**Fig. 3:** (a) & (b) 3D structure of Solasodine docked compound with 1HW9.

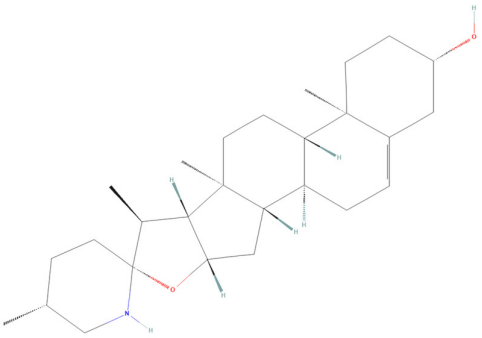


**Fig. 4.** 2D structure of Solasodine.

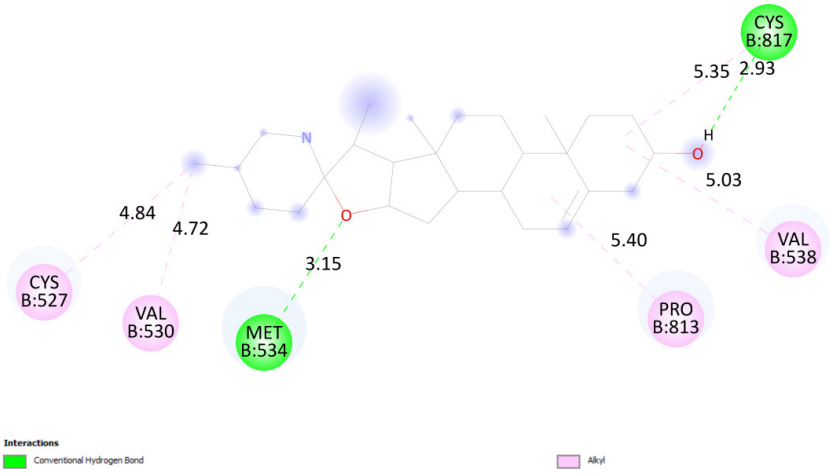



**Fig. 5.** 2D image of docked pose of Solasodine.

**Table 1: Binding Affinity of Solasodine and Atorvastatin.**

| PubChem ID | Ligand | Protein | Binding Affinity (kcal/mol) |
|---|---|---|---|
| 442985 | Solasodine | 1HW9 | -8.9 |
| 60823 | Atorvastatin (+ve control) | | -7.8 |

**Table 2: Comparison of various parameters of Solasodine and Atorvastatin.**

| Parameters | Solasodine | Atorvastatin |
|---|---|---|
| Formula | $C_{27}H_{43}NO_2$ | $C_{33}H_{35}FN_2O_5$ |
| Molecular weight | 413.64 g/mol | 558.64 g/mol |
| Number of heavy atoms | 30 | 41 |
| Number of aromatic heavy atoms | 0 | 23 |
| Number of rotatable bonds | 0 | 13 |
| Number of H-bond acceptors | 3 | 6 |
| Number of H-bond donors | 2 | 4 |
| Molar Refractivity | 127.23 | 158.26 |
| Topological Polar Surface Area (TPSA) | 41.49 Å² | 111.79 Å² |
| Lipophilicity (Log $P_{o/w}$) | 4.94 | 3.48 |
| Solubility | Moderately soluble | Moderately soluble |
| Gastrointestinal Tract Absorption | High | Low |
| Druglikeness | Yes; 1 violation: MLOGP>4.15 | Yes; 1 violation of Lipinski rule: MW>500 |
| Leadlikeness | No; 2 violations: MW>350, XLOGP3>3.5 | No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 |

## CONCLUSIONS

Hyperlipidemia is currently a big issue. Traditional therapies can have negative consequences. This has sparked interest in alternative treatments, particularly in developed countries. There are several therapeutic plants and herbs in nature. Around 200 herbs have historically been used to prevent and cure hyperlipidemia. The link between reduced LDL cholesterol levels and lower cardiovascular disease mortality is widely established. The lipid-lowering benefits of medicinal plants are now being researched as part of phytomedicine research for various disorders all over the world. There are, however,

a few plants that can benefit people suffering from the aforementioned illnesses. Plants' antihyperlipidemic qualities are critical for lowering atherosclerosis. As a result, natural lipid-lowering medicines are gaining popularity. It is more helpful to use traditional medicinal herbs when creating novel medications to treat lipid diseases. Herbal compounds offer a potentially safer and more health-beneficial alternative to statins. Positive primary findings on the usage of herbal remedies point to potential uses for these medications in a range of patient groups. The bioactive components of herbal medications are also often safe and well-tolerated. This study has explained that plant-derived products may be useful for hyperlipidemia. For the management of lipid disorders, plant-derived drugs are highly necessary at this stage.

The molecular docking study shows that solasodine has a stronger negative binding affinity than atorvastatin and may be useful in treating hyperlipidemia. But, additional investigation is required to discover the processes behind these compounds' lipid-lowering actions, to understand anti-hyperlipidemic activity in different animal models, and to determine the best way to employ them in human beings.

## FUTURE SCOPE

The future scope of molecular docking studies of solasodine against HMG-CoA reductase could include optimization of solasodine derivatives, screening of other protein targets, in vitro and in vivo validation, and combination therapy.

The results can be used for the optimization of the chemical structure of solasodine for improved activity and to screen solasodine against other protein targets involved in cholesterol metabolism or other disease pathways, potentially leading to the discovery of new therapeutic applications. The results of the molecular docking study can provide a starting point for in vitro and in vivo validation of the activity of solasodine against HMG-CoA reductase and for further development of solasodine-based drugs. The results can be used to investigate the potential synergistic effects of solasodine with other drugs used in the treatment of hypercholesterolemia, such as statins. Overall, the future scope of this study of solasodine against HMG-CoA reductase is promising and could lead to the development of new therapies to treat hypercholesterolemia and other related diseases.

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**Conflict of Interest.** None.

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