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An Insilico Study of Stigmasterol Glucoside for Hypolipidemic Activity

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ABSTRACT: Hyperlipidemia is a well-known indicator of cardiovascular disease risk. Herbal treatment for hyperlipidemia is widely used. Direct trials in animals and people to check the effectiveness of herbal therapies for dyslipidemia, on the other hand, involve ethical difficulties. Insilico research is used to overcome this challenge. One of the key advantages of in silico studies is that they can be used to predict the effects of different drugs and interventions on lipid metabolism, without the need for costly and time-consuming experiments. For example, in silico studies can be used to predict the binding affinity of different drugs to specific lipid targets, as well as their potential side effects and toxicity. In silico studies can be used to identify new drug targets and develop novel therapies for lipid disorders. By analyzing the structure and function of lipid-related proteins and enzymes, researchers can identify potential drug targets and design new drugs that specifically target these molecules. In silico studies have become an essential tool in the field of lipid disorders, providing valuable insights into the molecular mechanisms underlying these disorders and helping to develop new and more effective treatments for these conditions. The purpose of this research is to use molecular docking to assess the efficacy of Stigmasterol glucoside towards dyslipidemia. After examining several scholarly articles, stigmasterol glucoside was chosen as the ligand. The PubChem database was used to acquire a molecular structure file. The Protein Data Bank was used to get the target's crystal structure. All linked components as well as solvent molecules were removed from the protein molecule. The Biovia Discovery software was used to identify active binding sites. The PyRx program was used to conduct a molecular docking study with Stigmasterol glucoside against HMG-CoA reductase. According to a molecular docking research, stigmasterol glucoside binds to the HMG-CoA reductase receptor with a stronger affinity than atorvastatin. It is possible to infer that Stigmasterol glucoside seems to have the ability to function like a hypolipidemic agent.

Keywords: Stigmasteryl 3-beta-D-glucoside, Molecular Docking, Plant Compound, HMG-CoA Reductase, Hypolipidemic Agent, Lipid, Heart Disease.

INTRODUCTION

Hyperlipidemia is a medical condition characterized by elevated levels of lipids, such as cholesterol and triglycerides, in the bloodstream (Grundy *et al.,* 2018). It is a major risk factor for the development of cardiovascular diseases, including atherosclerosis, coronary artery disease, and stroke (Ference *et al.,* 2022). The prevalence of hyperlipidemia has been increasing worldwide, partly due to unhealthy lifestyle choices, such as poor diet, physical inactivity, and tobacco use (Goff *et al.,* 2014). There are several types of hyperlipidemia, classified based on the specific lipid abnormalities present in the blood. These include elevated levels of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) (Nordestgaard *et al.,* 2016). Genetic factors, such as familial hypercholesterolemia, can also contribute to the development of hyperlipidemia (Safarova *et al.,* 2016). The management of hyperlipidemia involves a combination of lifestyle modifications and pharmacological interventions. Lifestyle changes, such as adopting a healthy diet, engaging in regular physical activity, and maintaining a healthy body weight, are the first-line approach to managing hyperlipidemia (Grundy *et al.*, 2018). Pharmacological interventions for hyperlipidemia primarily target the reduction of LDL-C levels, as this has been shown to significantly decrease the risk of cardiovascular events (Ference *et al.*, 2022). In conclusion, hyperlipidemia is a significant risk factor for cardiovascular diseases, and its management requires a combination of lifestyle modifications and pharmacological interventions. Ongoing research into the underlying mechanisms of lipid metabolism and the development of novel therapeutic agents promises to further improve the prevention and treatment of hyperlipidemia and its associated complications.

Statins are a class of lipid-lowering medications that are widely prescribed for the prevention and treatment of

cardiovascular diseases, particularly in individuals with hyperlipidemia (Grundy *et al.,* 2018). They work by inhibiting the enzyme HMG-CoA reductase, which plays a crucial role in cholesterol synthesis in the liver (Istvan and Deisenhofer 2001). Despite their proven efficacy, statins are associated with several side effects, which can range from mild to severe. The most common side effects include muscle-related symptoms, such as myalgia (muscle pain), weakness, and cramps (Stroes *et al.,* 2015). In rare cases, statins can cause a severe muscle condition called rhabdomyolysis, which can lead to kidney failure and even death (Vinci *et al*., 2021). The risk of muscle-related side effects is higher in patients taking higher doses of statins or in combination with other medications that can increase statin levels in the blood (Mancini *et al.,* 2018). Another potential side effect of statins is an increased risk of developing type 2 diabetes mellitus (T2DM). Several studies have reported a modest increase in the incidence of T2DM among statin users, particularly in those with pre-existing risk factors for the disease (Sattar *et al.,* 2010; Preiss *et al*., 2011). The exact mechanism underlying this association remains unclear, but it has been suggested that statins may impair insulin secretion and sensitivity (Cederberg *et al.,* 2015). Statins have also been associated with mild to moderate elevations in liver enzymes, which can be a sign of liver injury (Bays *et al*., 2004). However, serious liver injury due to statins is extremely rare, and the risk of liver-related side effects is generally outweighed by the cardiovascular benefits of statin therapy (Björnsson *et al.,* 2012). In conclusion, while statins are effective in reducing the risk of cardiovascular events, they are associated with several side effects, including muscle-related symptoms, an increased risk of T2DM, and potential liver and cognitive effects. Clinicians should carefully consider the potential risks and benefits of statin therapy for each individual patient, taking into account their specific risk factors and medical history.

Plants have been used for centuries as a source of medicine, and many of their constituents have been found to have therapeutic effects on lipid disorders. Some of the most commonly studied plant constituents for the treatment of lipid disorders include flavonoids, terpenoids, and phenolic acids. Flavonoids are a group of polyphenolic compounds found in many plants, and they have been shown to have a variety of health benefits, including the ability to lower cholesterol levels. One study found that the flavonoid quercetin, found in onions and apples, was able to reduce total cholesterol levels in rats fed a high-fat diet (Egert *et al.,* 2009). Another study found that the flavonoid hesperidin, found in citrus fruits, was able to reduce LDL cholesterol levels in humans (Morand *et al*., 2011). Terpenoids are a diverse group of compounds found in many plants, and they have been found to have a variety of health benefits, including the ability to lower cholesterol levels. One study found that the terpenoid limonene, found in citrus fruits, was able to reduce total cholesterol levels in rats fed a high-fat diet (Kim *et al.,* 2014). Another study found that the terpenoid guggulsterone, found in the resin of the guggul tree, was able to reduce LDL cholesterol levels in humans (Szapary *et al.,* 2003). Phenolic acids are a group of compounds found in many plants, and they have been found to have a variety of health benefits, including the ability to lower cholesterol levels. One study found that the phenolic acid chlorogenic acid, found in coffee, was able to reduce total cholesterol levels in rats fed a high-fat diet (Shimoda *et al.,* 2006). Another study found that the phenolic acid ellagic acid, found in berries, was able to reduce LDL cholesterol levels in humans (Basu and Lyons 2012). In conclusion, plant constituents have been found to have therapeutic effects on lipid disorders. These compounds can be found in a variety of plant-based foods and supplements, and may be a useful addition to a healthy diet and lifestyle for those looking to manage their cholesterol levels.

Molecular docking is a computational technique used to predict the binding affinity and orientation of a ligand within the active site of a target protein, such as an enzyme or receptor (Morris *et al.,* 2009). In the case of stigmasterol glucoside, a molecular docking study can be performed to investigate its potential inhibitory effect on HMG-CoA reductase, the rate-limiting enzyme in the cholesterol biosynthesis pathway (Istvan and Deisenhofer 2001). HMG-CoA reductase has been a primary target for cholesterol-lowering drugs, such as statins, which competitively inhibit the enzyme by binding to its active site (Endo, 2010). Given the known cholesterol-lowering effects of stigmasterol (Bouic, 2001), it is plausible that stigmasterol glucoside may also interact with HMG-CoA reductase and inhibit its activity.

MATERIAL AND METHODS

A. Ligand preparation

Stigmasterol glucoside molecule was obtained in standard data format from the PubChem database. For inspection, the Marvin View program was deployed. Stigmasterol glucoside's canonical SMILES ID was recorded, and the physical parameters of Stigmasterol glucoside were determined utilizing PubChem database. Biovia Discovery tool was then used to construct 3D structures of the Stigmasterol glucoside.

B. Protein preparation

Protein Data Bank (PDB) ID 1HW9 was chosen based on criteria such as organisms, accuracy and R factor, protein, extent of structure solved, as well as if the architecture is native or ligand-bound. The enzyme was obtained in PDB format and then processed and prepared using Biovia Discovery Studio. The protein was stripped of all co-crystals, heteroatoms, and molecules of water.

C. Active binding site analysis

Active binding sites were identified using Biovia Discovery tool. The active protein binding locations chosen disclose details about each protein's confined area. The target molecule and compound were docked then use a blind procedure in this investigation.

D. Molecular docking analysis

There are several docking tools available to use. PyRx, an accessible and user-friendly program, is employed in this investigation. The docked proteins were examined when docking was accomplished. The findings were then stored, and the docking score was used to rank all compounds. Protein-ligand interactions occur when a ligand molecule binds to a given region on a protein, causing the protein's shape to change. These interactions are crucial in many biological processes. Nonspecific interactions and specific interactions among a protein and its ligand, can all influence to the binding affinity of a protein-ligand complex (Patel, 2023b).

RESULTS AND DISCUSSION

A highly prevalent changeable factor contributing to atherosclerotic heart disease is hyperlipidemia Ezeh and Ezeudemba (2021). Dyslipidemias, or abnormalities of lipid metabolism, are a heterogeneous collection of illnesses that can strike at any age and either be temporary or persist over life. Lipid metabolism is influenced by a wide range of variables, involving genetic make-up, environmental conditions, as well as a combination of these (Wójcik, 2022). Cardiovascular disease (CVD) is a leading cause of death and morbidity, with plasma lipid abnormalities being common CVD risk factors (Lee *et al.,* 2021). Better understanding and awareness of these illnesses might save the lives of many people Farzam (2022). HMG-CoA reductase is an enzyme that plays a crucial role in the biosynthesis of cholesterol in the liver. According to Brown and Goldstein (1980), HMG-CoA reductase is the rate-limiting enzyme in the mevalonate pathway, which is responsible for the production of cholesterol and other isoprenoids. The activity of HMG-CoA reductase is tightly regulated by a variety of mechanisms, including feedback inhibition by cholesterol and other sterols. Inhibition of HMG-CoA reductase by statins, a class of drugs commonly used to lower cholesterol levels has been shown to be an effective strategy for reducing the risk of cardiovascular disease (Endo, 2004). Overall, HMG-CoA reductase is a key target for the development of drugs aimed at reducing cholesterol levels and preventing cardiovascular disease.

Stigmasterol glucoside 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 binding interactions reveal Stigmasterol glucoside's flexibility in binding to a range of amino acids and regulating protein function. Stigmasterol Glucoside most likely interacts with the enzyme via hydrogen bonding along with hydrophobic interactions. It has been proposed that the Stigmasterol Glucoside's hydroxyl group may engage with amino acid residues in the enzyme's active site, while the hydrophobic side chains may interact with neighboring hydrophobic residues. Stigmasterol Glucoside interacts enzyme via amino acid residue Asn771, Ala768, Ala556, Gly765, Ile536, Ile762, Thr758, Tyr761.

Atorvastatin is a statin medication that is used to reduce the amount of cholesterol in the human body. It acts by blocking the enzyme HMG-CoA reductase, which is in charge of lipid production. Atorvastatin binds to HMG-CoA reductase via various interactions using distinct amino acid residues in the enzyme. Atorvastatin was discovered to interact to the HMG-CoA reductase enzyme residues Val522, Cys527, Met534, Ile762, Gln814, and Cys817. Hydrophobic interactions between atorvastatin and amino acids occur. Atorvastatin has a large hydrophobic area that can interact with the enzyme's hydrophobic residues, such as valine and isoleucine. These interactions serve to solidify atorvastatin's binding to the enzyme and prevent it from being easily removed. Another way that atorvastatin interacts with amino acids is through hydrogen bonding. Atorvastatin has various polar groups that can create hydrogen bonds with the enzyme's polar residues. These hydrogen bonds serve to maintain atorvastatin's binding to the enzyme and boost its affinity for the enzyme. Atorvastatin can also interact via van der Waals forces. These interactions were weaker compared to other ones, but they do play a role in the overall stability of the atorvastatin-enzyme complex. Many interactions with particular amino acid residues in the enzyme are involved in the binding of atorvastatin to HMG-CoA reductase. These interactions aid in the stabilization of the complex and boost atorvastatin's affinity for the enzyme, enabling this to significantly suppress cholesterol production in the body. Such binding interactions are crucial to atorvastatin's efficacy as a cholesterol-lowering medication (Patel, 2023b).

Lipid disorders, such as dyslipidemia and atherosclerosis, are complex conditions that involve multiple factors, including oxidative stress and inflammation. Oxidative stress is a state of imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms, leading to cellular damage and dysfunction. Inflammation, on the other hand, is a complex biological response to harmful stimuli, such as infections, injuries, and chronic diseases, characterized by the activation of immune cells and the release of pro-inflammatory cytokines. Several studies have shown that oxidative stress and inflammation play a crucial role in the development and progression of lipid disorders. For example, in a study published in the Journal of Lipid Research, researchers found that oxidative stress-induced lipid peroxidation can lead to the formation of oxidized low-density lipoprotein (oxLDL), which is a key factor in the development of atherosclerosis (Steinberg, 1989). Similarly, in a review article published in the Journal of Clinical Lipidology, the authors highlighted the role of inflammation in the pathogenesis of dyslipidemia, particularly in the context of obesity and metabolic syndrome (Kaur and Asea 2016). Moreover, recent studies have shown that oxidative stress and inflammation are closely interrelated, with each factor influencing the other. For instance, in a study published in the Journal of Clinical

Endocrinology and Metabolism, the authors found that oxidative stress can activate pro-inflammatory pathways, leading to the release of cytokines and chemokines that promote inflammation (Furukawa *et al.,* 2004). Similarly, in a review article published in the Journal of Lipid Research, the authors highlighted the role of inflammation in promoting oxidative stress by activating NADPH oxidase, a key enzyme involved in ROS production (Griendling and FitzGerald 2003). In conclusion, oxidative stress and inflammation are important factors in the pathogenesis of lipid disorders, and their interplay is complex and multifaceted. Further research is needed to fully understand the mechanisms underlying their interactions and to develop effective therapeutic strategies targeting these pathways. HMG-CoA reductase and stigmasterol glucoside were docked. Stigmasterol glucoside was discovered to have a robust ligand-receptor interaction in comparison to atorvastatin. Stigmasterol glucoside was discovered to bind to HMG-CoA reductase enzyme (1HW9) with an affinity of -8.5 kcal/mol. It was discovered that atorvastatin's binding affinity for protein 1HW9 was -7.8 kcal/mol (Table 1). The various parameters of Stigmasterol glucoside and Atorvastatin ware also compared (Table 2).

Phytosterols are steroids that come from plants. Each plant species includes a distinctive phytosterol composition. Stigmasterol glucoside is a natural compound that belongs to the class of plant sterols. Numerous studies have documented the amazing pharmacological benefits of phytosterols, including their ability to serve as antidiabetic, antioxidant, anti-inflammatory agent, and anti-atherosclerotic drug, as well as anticancer drug. According to different studies, taking phytosterols reduced TC and LDL-C levels by inhibiting dietary cholesterol absorption and influencing its metabolism (Salehi *et al.,* 2021). It is a glycoside of stigmasterol, which is a common plant sterol found in many plant species. The chemical structure of stigmasterol glucoside consists of a stigmasterol molecule attached to a glucose molecule through a β-glycosidic bond. The chemical formula of stigmasterol glucoside is $C_{35}H_{60}O_6$, and its molecular weight is 574.83 g/mol. Stigmasterol glucoside is a naturally occurring compound that belongs to the class of phytosterols, specifically a steryl glucoside (SG) (Valitova *et al.,* 2016). It is derived from stigmasterol, a plant sterol commonly found in various plant species, including soybean, rapeseed, and sunflower (Piironen *et al*., 2000). Stigmasterol glucoside is formed by the attachment of a glucose molecule to the stigmasterol molecule, resulting in a glycosylated compound (Valitova *et al.*, 2016). Stigmasterol glucoside has been reported to exhibit various biological activities, such as antioxidant, anti-inflammatory, and immunomodulatory properties (Valitova *et al.,* 2016). These activities are attributed to the presence of the stigmasterol moiety, which is known to possess a wide range of health benefits, including cholesterol-lowering effects and potential anticancer properties (Bouic, 2001; Alamu *et al.,* 2000). In addition to its biological activities, stigmasterol glucoside has been found to play a role in plant growth and development. It has been suggested that stigmasterol glucoside may function as a signaling molecule, regulating various cellular processes such as cell division, differentiation, and gene expression (Valitova *et al.,* 2016). Moreover, stigmasterol glucoside has been implicated in plant defense mechanisms against pathogens, as it has been shown to accumulate in response to pathogen infection (Borner *et al.*, 2005). A study investigated the anti-inflammatory activity of stigmasterol glucoside in vitro and in vivo. The study found that stigmasterol glucoside inhibited the production of pro-inflammatory cytokines and reduced inflammation in a mouse model of acute lung injury.

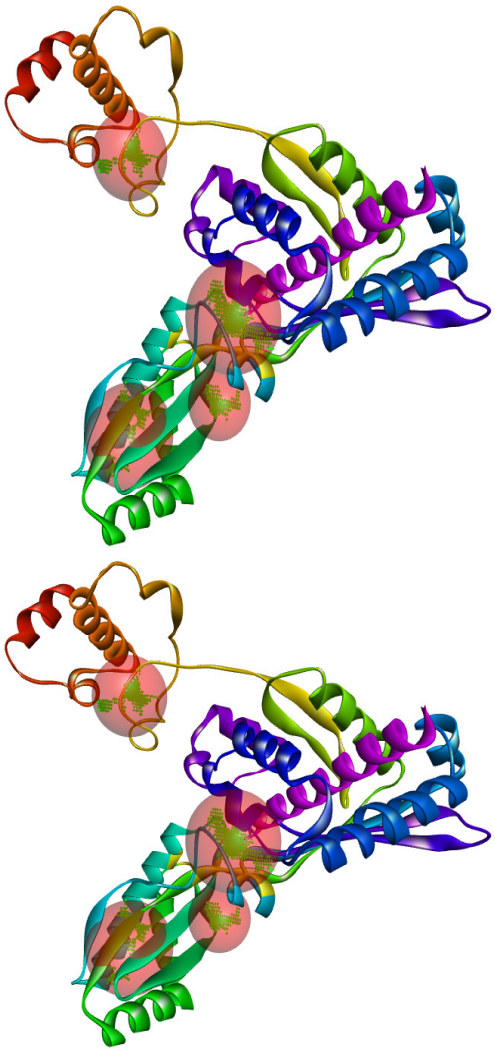


Fig. 1. 3D structure of HMG-CoA reductase (Patel, 2023).

The authors suggested that stigmasterol glucoside may have potential as an anti-inflammatory agent (Morgan *et al.,* 2021). A study found that stigmasterol glucoside had strong antioxidant activity, which was attributed to its ability to scavenge free radicals and inhibit lipid peroxidation.

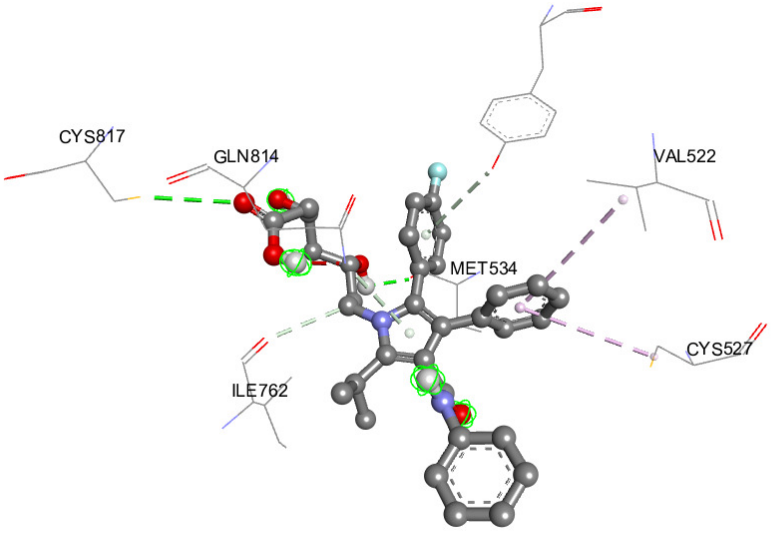
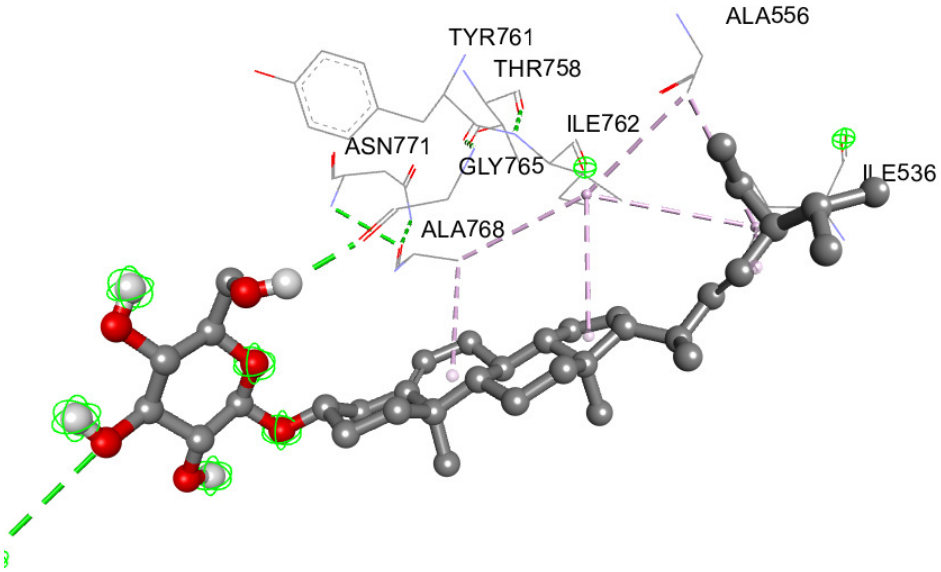
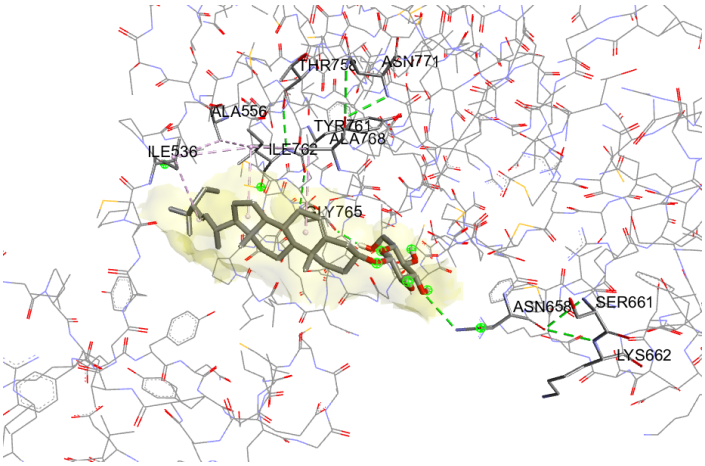


Fig. 2. 3D structure of Atorvastatin docked with HMG-CoA reductase ((Patel, 2023).



(a)



(b)

Fig. 3. (a) & (b) 3D structure of Stigmasterol glucoside docked with 1HW9.

The authors suggested that stigmasterol glucoside may have potential as a natural antioxidant (Bakrim *et al.*, 2022). Another study investigated the anti-cancer activity of stigmasterol glucoside. Stigmasterol reduced tumor volume, packed cell volume, and viable cell count while improving mean survival time and extending the lives of Ehrlich Ascites Carcinoma tumor-bearing mice. As indicated by structurally identical phytosterol, the anticancer effect of stigmasterol may be achieved via ceramide stimulation of protein phosphatase 2A, resulting in apoptosis. (Ghosh *et al.,* 2011). Examining the molecular processes by which stigmasterol exerts its neuroprotective benefits in human brain cells, stigmasterol exhibits protective properties against hydrogen peroxide-induced damage. Oxidative stress may result from an imbalance between the synthesis of reactive oxygen species and antioxidants (Pratiwi *et al.*, 2021).

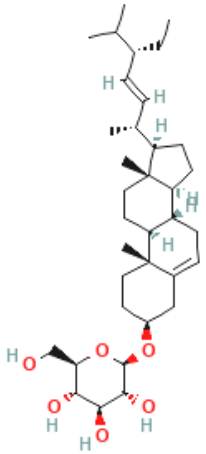


Fig. 4. 2D structure of Stigmasterol glucoside.

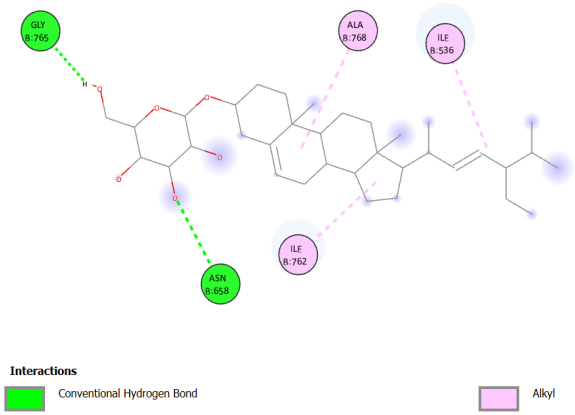


Fig. 5. 2D image of docked pose of Stigmasterol glucoside.

Table 1: Binding Affinity of Stigmasterol glucoside and Atorvastatin.

PubChem ID	Ligand	Protein	Binding Affinity (kcal/mol)
6602508	Stigmasterol glucoside	1HW9	-8.5
60823	Atorvastatin (+ve control)		-7.8

Table 2: Comparison of various parameters of Stigmasterol glucoside and Atorvastatin.

Parameters	Stigmasterol glucoside	Atorvastatin
Formula	C35H58O6	C33H35FN2O5
Molecular weight	574.83 g/mol	558.64 g/mol
Number of heavy atoms	41	41
Number of aromatic heavy atoms	0	23
Number of rotatable bonds	8	13
Number of H-bond acceptors	6	6
Number of H-bond donors	4	4
Molar Refractivity	165.14	158.26
Topological Polar Surface Area (TPSA)	99.38 Å²	111.79 Å²
Lipophilicity (Log $P_{o/w}$)	5.63	3.48
Solubility	Poorly soluble	Moderately soluble
Gastrointestinal Tract Absorption	High	Low
Druglikeness	Yes; 1 violation of Lipinski rule: MW>500	Yes; 1 violation of Lipinski rule: MW>500
Leadlikeness	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5

CONCLUSIONS

Hyperlipidemia is a serious issue right now. Traditional therapies may have negative side effects. It is generally established that reducing low-density lipoproteins is associated with a decreased death rate from cardiovascular disease. Nonetheless, certain herbs can be beneficial for those who have the aforementioned illnesses. The ability of plants to lower hyperlipidemia is essential for lowering atherosclerosis. As a result, demand for natural lipid-lowering treatments is rising. Herbal medicines' bioactive ingredients could be able to regulate the complex interventions in lipid metabolism. The key conclusions point to good uses for these medications in a range of patient populations. The bioactive components in herbal medications are also often harmless and well-tolerated. Overall, the use of herbal molecules to treat hyperlipidemia offers a

potential alternative to statins that may be safer and provide additional health benefits. However, further research is needed to fully understand the mechanisms behind the lipid-lowering effects of these molecules and to determine their optimal use in clinical practice.

FUTURE SCOPE

This research shows the probable efficacy of stigmasterol glucoside as a natural remedy for hyperlipidemia. The use of molecular docking has assisted in the identification of probable binding sites for Stigmasterol glucoside on target proteins, leading to a deeper insight of its mode of action. This research gives a good beginning point for the development of novel treatments for hyperlipidemia, but further research is required to discover the ideal dose and delivery of stigmasterol glucoside. Overall, these molecular docking studies provide valuable insights into the potential of plant compounds for the treatment of lipid disorders. Further research is needed to confirm the therapeutic potential of plant compound and its mechanisms of action. Stigmasterol glucoside is a biologically active compound with potential health benefits and roles in plant growth and development. Research is needed to fully understand its mechanisms of action and explore its potential applications in medicine.

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Conflict of Interest. None

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