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An *In silico* Study on Lipid Lowering Activity of Sophorin

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ABSTRACT: Hyperlipidemia is a well-known risk factor for cardiovascular disease. Some herbs, like sophorin, have been reported as having hypolipidemic properties, which means they could potentially lower cholesterol levels. Sophorin is also known as Rutin. It is difficult to test a plant compound directly for lipid disorder and this problem is overcome by the use of molecular docking study because it does not involve any ethical issue. While there is some evidence to support this claim, there is also conflicting data in the literature. Further research would be necessary to confirm these findings and fully understand their effects. To address this issue, scientists often use in silico studies, including computer simulations such as molecular docking, to investigate how different substances interact with proteins in the body. Molecular docking can aid in identifying potential compounds for lipid disorder treatment, providing valuable insights for drug discovery and development. The goal of study is to explore whether certain natural products may be effective in treating high cholesterol, or hyperlipidemia, using computational methods. Study began by selecting candidate compound based on existing scientific literature and then retrieved a digital model of the compound from the pubchem database. Next, accessed a crystallographic structure of the relevant protein (PDB ID: 1HW9) from the Protein Data Bank. After cleaning up the structure to remove any non-essential elements, we utilized special software called biovia discovery program to identify possible active binding sites where our chosen compound might fit perfectly into place. With all this preparation done, molecular docking simulation study has been conducted using pyrx tool. ADME study is also performed using pkCSM web tool. Analysis indicates that the selected natural product, namely saphorin, had higher affinity towards the protein compared to the commercial drug atorvastatin. As a conclusion, experiment demonstrates that saphorin has significant potential to serve as an alternative treatment option for patients suffering from hyperlipidemia.

Keywords: ADME, Cholesterol, Molecular Docking, Herb, HMG-CoA reductase**,** Antihyperlipidemic Agent, Lipid Disorder, Atorvastatin, quercetin-3-O-rutinoside.

INTRODUCTION

The advancement of computer-assisted drug design has taken on an important function in the search for medications to treat a variety of ailments. Finding substance from plants and animals is safer and more side-effect-free than using manufactured ones. Recent computational screening of herbal remedies has confirmed the plant's extract as a key source for drug design (Maryshyla and Nevaditha 2020). In accordance with the World Health Organization, 80% of the population globally relies on herbal therapy, and it is believed that around 25% of all current medications are derived either directly or indirectly from higher plants. However, when allopathic medicine fails to effectively cure an illness, the use of traditional medicines raises (Singh *et al.*, 2018). Dyslipidemia, high blood pressure, and diabetes mellitus are risk factors for cardiovascular illness mortality. Unhealthy eating habits and lifestyle changes may make heart-related illnesses worse. Yet, reducing triglycerides, low-density lipoprotein, and cholesterol might reduce the incidence of risk factors (Mohan *et al.*, 2022). Hyperlipidemia is a medical condition characterized by elevated levels of lipids, such as cholesterol and triglycerides, in the blood. It is a major risk factor for cardiovascular diseases, including atherosclerosis, coronary artery disease, and stroke (Grundy *et al*., 2018). One of the primary factors that increases the likelihood of cardiovascular disorders is hyperlipidemia. This is a medical disorder when the blood has unusually high quantities of plasma lipids such phospholipids, cholesterol esters, and triglycerides. The most critical health problem afflicting a disproportionately large number of the worldwide people is hyperlipidemia. It also poses a significant risk for heart disease. High plasma lipid levels are

commonly treated with anti-hyperlipidemic medications like statins and fibrates. However, adverse effects are a burden on such medications. The cell membrane depends on cholesterol to function. It regulates the homeostasis of the main ions, carbohydrates, and bones. Cholesterol is a vital biomolecule for the majority of biological processes because of these characteristics. Triglycerides play a crucial function in giving cells energy. These macromolecules have negative health effects in excess and cause hyperlipidemia. The body experiences several long-term negative effects as a result of hyperlipidemia. Plaques are more likely to develop as a result of hyperlipidemia, which raises the risk of heart attacks and stroke in those who have atherosclerosis and coronary heart disease (Dixit *et al*., 2022). Due to its low risk of side effects, the consumption of herbal medicines has increased significantly over the past several years in both advanced and developing countries. Many biologically active natural products are found in plant extracts, and these compounds are what give the plants their multiple medicinally beneficial applications. Plant-derived remedies are most frequently used to treat a variety of disorders due to the negative side effects of manufactured medications. Consequently, it is urgently needed at the moment to treat hyperlipidemia with plant-derived biomolecules that are available and require only moderately laborious medicinal synthesis. The therapy was effective with a variety of anatomical elements, including leaves, flowers, roots, barks, and the entire plant. These plants include a variety of bioactive substances that are what gives them their hypolipidemic properties. Over the last several decades, the worldwide health landscape has undergone a rapid transformation, and the number of hyperlipidemic cases is continuing to rise at an astonishing speed. Worldwide, heart disease continues to be the major cause of death. By the year 2030, it is anticipated that non-communicable illnesses would account for more than 75 percent of all deaths globally. More people will die from heart disease in low-income countries than from infectious diseases, maternal and perinatal illnesses, and dietary problems all together. Because of an increase in unhealthy lifestyles including alcohol and cigarette use, obesity, and a constant age-adjusted heart disease death rate, the incidence of heart disease has increased in India during the past several decades. The abundance of different plant products found in nature is a fantastic asset. In daily living, medications are of vital importance. Since ancient times, the environment has provided a source of therapeutic agents, and many new drugs have been separated from different natural sources. Since the beginning of human civilization, medicinal herbs and their byproducts have been utilized (Kalita and Hazarika 2021). Globally, cardiometabolic disorders are on the rise and are now the main cause of mortality in nations that are industrialized as well as developing. 1 Cardiometabolic illnesses are linked to hereditary variables as well as dyslipidemia, and other factors. One of the main risk factors for cardiovascular diseases (CVD) via the growth and development of atherosclerosis is dyslipidemia. The risk of problems from CVD is considerably increased by prolonged exposure to high glucose levels. Obesity, especially extreme obesity, has the potential to cause hemodynamic changes that affect heart shape and function and may hasten the onset of CVD. Cardiometabolic disorders sufferers are at an increased risk of stroke, myocardial infarction (MI), and heart failure (Chen *et al*., 2022). The significance of traditional medicines and their therapeutic benefits have been understood from the early stages of scientific inquiry. The old practical experiences taught the human race how to employ herbs as medicine. All conventional medical systems across the globe, which create systems that, rely on a holistic health approach, use plant species. Commercial drugs intended to treat cardiovascular disease and other issues are still produced on a wide scale using compounds that come from medicinal plants. Numerous ancient Indian texts, including the "Rig-Veda" and "Atharva- Veda," provide details about the origins of medicine and diseases in that country. Around a thousand years B.C., the use of traditional medicines and polyherbal preparations was illustrated in ancient texts like the "Charak Samhita" & "Susruta Samhita." Ayurveda System of medicine offers comprehensive details on 10,000 compositions and 1500 plants that are developed from many existing systems and folkloric traditions. India is renowned for having a wide variety of plants. In India, there are estimated to be 40,000 plant species that originate from different groupings. Most of them are used medically. For their medical requirements, about 70 percent of the total of the population relies on natural remedies or traditional systems of medicine. It is common knowledge that most emerging economies employ natural medicine and botanicals as medications for the preservation of better health. For their medical requirements, around 80 percent of the total of the world's population relies on conventional drugs and procedures. Diverse medicinal properties, including anti-oxidative are present in secondary metabolites derived from plants. Since synthetic drugs frequently have adverse health consequences for people, plant-based medications are often regarded as the least harmful options in the medical system. It is thought that lipid abnormalities linked to hyperlipidemia result in cardiovascular consequences. Lowering the risk of heart disease or the incidence of ischemia of the heart is the main goal of treating hyperlipidemia. Drugs made from medicinal plants are increasingly preferable to synthetic ones since they are more readily available locally and have higher patient acceptance. The path to a healthy life and good treatment with few

complications of these kinds of illnesses remains unfulfilled, despite the fact that numerous improvements in the treatment of illnesses have been undertaken (Kalita and Hazarika 2021). At present, lipid disorders, such as hyperlipidemia and dyslipidemia, continued to be a significant public health concern worldwide. These disorders are characterized by abnormal levels of lipids, including cholesterol and triglycerides, in the blood (Grundy *et al*., 2018). Lipid disorders are major risk factors for CVD, including atherosclerosis, coronary artery disease, and stroke, which are leading causes of morbidity and mortality globally (Virani *et al.,* 2021). Atherosclerosis, a leading cause of death worldwide, is mostly brought on by hyperlipidemia. It has been demonstrated that the phytochemical constituents of botanical extracts have a wide range of physiological effects. Particularly, in vitro and in vivo studies have demonstrated the anti-hyperlipidemia potential of polyphenolic phytoconstituents like flavonoids and flavones. Particularly mono-flavonoids have been demonstrated to block low-density lipoprotein (LDL) oxidation and lower triglyceride levels. In a mouse model of hyperlipidemia, the anti-atherogenic effects of mono-flavonoids including quercetin have demonstrated a decrease of atherosclerotic plaques. Bisflavanoids, on the other hand, are dimeric forms of flavonoids that are fairly common in several plant species. Even several herbal plants are rich in the dimeric flavonoids known as bisflavonoids, which have a variety of therapeutic actions. Bisflavonoids do have a little amount of anti-hyperlipidemic activity in vivo, though. For instance, amentoflavone, which is renowned for having a variety of pharmacological effects, is found in the genus Hypericum. The plant genus Araucaria, which is a member of the Araucariaceae family, is a significant source of previously identified and described bisflavanoids. Herbal extracts containing a variety of medicinal bioactive constituents have been proven to be effective in correcting hyperlipidemia-induced oxidative stress. Hyperlipidemia, is a prominent cause of atherosclerosis. The favorable impact of flavonoids on cholesterol transportation, and metabolism has recently been studied. It is well documented that plant-derived bioflavonoids, particularly mono-flavonoids and flavones, display hypolipidemic action in in vivo and in vitro model. Hesperetin and naringenin, two mono-flavones, have been demonstrated to influence cholesterol metabolism. Through the increased expression of the protein known as sterol regulated element binding protein, catechins have been demonstrated to expedite the LDL receptor binding activity in HepG2 cell lines. Mono-flavonoids from several therapeutic plants have been found to influence the activity of the lipoprotein lipase (LPL) in mouse muscle and adipose tissue, preventing the synthesis and accumulation of triglycerides in organs. Kolavarin A and B, two of the bisflavanoids found in Garcinia kola seed, demonstrated hypolipidemic activity in a rat model of experimental hyperlipidemia. It is widely understood that an elevated level of cholesterol and triglycerides might result in the formation of reactive oxygen species. Additionally, elevated LDL-C is linked to oxidative LDL modification, excessive lipid peroxidation, & oxidative stress. Furthermore, rats' atherogenic diet-induced hypercholesterolemia and hypertriglyceridemia were reversed by the bisflavonoids' fraction from A. bidwilli Hook. leaf extract. By reducing the accumulation of atherosclerotic lesions in the rat artery and increasing anti-oxidant levels in the blood, this impact was linked to the amelioration of oxidative stress and atherosclerosis. Bisflavanoids' potential function in the extrinsic transportation of dietary lipids, suppression of LDL oxidation, and anti-oxidant action in vivo may all contribute to their anti-hyperlipidemic effects. The fraction of bisflavonoids from A. bidwillii Hook. leaf extract that was given to high-fat-fed rats shown anti-hyperlipidemic efficacy by lowering blood cholesterol levels and shielding the heart cells from oxidative stress (Siddiqui *et al.,* 2020). The increasing prevalence of obesity, sedentary lifestyles, and unhealthy dietary habits has contributed to the growing burden of lipid disorders (Khera *et al.,* 2020). Given the substantial impact of lipid disorders on public health, there is a continuous need for the development of novel therapeutic agents to manage these conditions. One of the key enzymes involved in cholesterol biosynthesis is 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyzes the conversion of HMG-CoA to mevalonate, a precursor of cholesterol (Goldstein and Brown, 1990). HMG-CoA reductase is a key enzyme involved in cholesterol biosynthesis and has been identified as a target for managing lipid disorders. Recent studies have investigated therapeutic agents for managing hyperlipidemia by inhibiting the activity of HMG-CoA reductase. These compounds have been found to possess lipid-lowering properties and can potentially reduce the risk of cardiovascular diseases. The development of plant-based drugs targeting HMG-CoA reductase may provide new treatment options with fewer side effects and additional health benefits. Atorvastatin effectively lowers cholesterol levels in the blood. However, it has some drawbacks, including potential side effects such as muscle pain, liver damage, and an increased risk of developing type 2 diabetes (Zhang *et al.,* 2013). Statins constitute the most often used medications for normalizing elevated blood cholesterol, triglycerides, and LDL-C levels. HMG-CoA reductase activity is inhibited by statins. Statins work to lower total cholesterol synthesis and shift LDL cholesterol to High-Density Lipoprotein (HDL) cholesterol, which significantly lowers the incidence, morbidity, and mortality of cardiovascular disease. In spite of the substantial advantages of statins, many individuals,

especially those who have elevated blood pressure and/or blood sugar levels, frequently struggled to achieve their normal levels of Total Cholesterol (TC), Triglycerides (TG), LDL-C, as well as High-Density Lipoprotein Cholesterol (HDL-C) with statin monotherapy singly. Alternative methods are therefore necessary for the control of abnormal cholesterol levels. Citrus bergamia (Bergamot) drink as well as its flavonoids were found in latest researches to be capable of lowering blood levels of lipids and improve arterial thickening by altering enzyme reactions, anti-oxidation, & anti-inflammatory mechanisms. The flavonoid produced from bergamot juice has a distinct spectrum of bioflavonoids and glycosides, notably rutin, and comprises roughly 28–30% flavonoids. Investigations in both preclinical and clinical settings show that C. bergamia flavonoids have the ability to decrease cholesterol (Cai *et al.,* 2017). Statins, such as atorvastatin and simvastatin, are widely prescribed HMG-CoA reductase inhibitors; however, their use may be associated with side effects and intolerance in some patients. They may not respond well to statin therapy or may require alternative treatments due to contraindications or intolerance (Stroes *et al.,* 2015). Plant-derived compounds have been extensively studied for their potential as alternative or complementary treatments for hyperlipidemia. These compounds often exhibit fewer side effects and may provide additional health benefits (Kumar *et al.,* 2011). Given these limitations, there has been growing interest in exploring plant-derived compounds as alternative therapeutic agents for hyperlipidemia. Mother Nature endowed mankind with a variety of sources with beneficial therapeutic characteristics that are the basis for many of the current medications used in both allopathic and indigenous medical practices. The sources of pharmaceuticals in our environments include plants, animals, microorganisms, and minerals. The phytochemicals extracted from herbs are often secondary metabolites that have been found to have therapeutic impact on human beings. In the manufacturing of different synthetic medicinal compounds for the treatment of chronic illnesses, several of the bioactive molecules from herbs have been employed as lead molecules. Vegetables, grains, and fruits that are consumed by humans are discovered to have a variety of bioflavonoids, which are polyphenolic chemicals. There are several flavonoids subtypes recognized. There are over 3000 bioflavonoids whose beneficial qualities have been discovered. Research in the health benefits of polyphenolic compounds, particularly bioflavonoids, has increased recently. It is discovered that bioflavonoids have several, well-established medicinal benefits. It has been demonstrated that bioflavonoids have antioxidant, lipid peroxidation-hindering, and free radical scavenging properties to a greater level. The flavonoids are recognized to have numerous advantageous pharmacological effects within natural substances. Bioflavonoids' antioxidant ability supports a number of other medicinal processes. Rutin is a bioflavonoid that may be present in buckwheat bran, citrus fruits, black tea, clove, and rose. It has a number of medicinal qualities, such as antioxidant, cardioprotective, antiatherosclerotic, and antitumor effects. Although it has a variety of medicinal uses, its investigations in the field of medicine are greatly limited by its low solubility and bioavailability. This problem can be solved by altering the formulation and creating nanoformulations using different polymers that are a degradable type (Padmavathy and Kumar 2018). The biggest risk factor for heart attack or stroke is hyperlipidemia. A medication may have hypolipidemic effects to support the management of cardiovascular disorders. It is reported that individuals having hyperlipidemia may benefit from adjuvant therapy with cinnamonum zeylanicum. Further studies are required to elaborate the precise underlying mechanisms the hypolipidemic impact as well as its cellular mechanism of action (Abdelgadir *et al.,* 2020). Plant compounds, also known as phytochemicals, have been shown to possess various pharmacological properties, including antioxidant, anti-inflammatory, and lipid-lowering effects (Pandey and Rizvi 2009). One such compound is rutin, a flavonoid found in various plants, including buckwheat, apples, and tea and it has been shown to possess antioxidant, anti-inflammatory, and vasoprotective properties. Its mechanism of action is thought to involve the inhibition of HMG-CoA reductase, similar to statins, as well as the modulation of other lipid metabolism-related enzymes and pathways (Ganeshpurkar and Saluja 2017). Further research is needed to establish the efficacy and safety of rutin in human subjects and to determine its potential as a therapeutic agent for hyperlipidemia. Adipogenesis has been said to be suppressed by a number of natural compounds. The maturation and multiplication of adipocytes might be employed as a method for the prevention and management of obesity, in addition to the suppression of HMG-CoA reductase activity. There was a decrease in HMG-CoA activity & lipid droplet generation when bergamot extract was present, demonstrating that bergamot extract has the potential to operate like an anti-adipogenic substance to reduce cholesterol and body fat levels and avoid excess weight. Additionally, bergamot extracts contain significant amounts of flavonoid compounds. The DPPH free radical was significantly inhibited by bergamot extract, indicating a potent radical scavenging effect (Ballistreri *et al.,* 2021). Although hyperlipidemia plays a significant role in the development of heart disease, it can be controlled with dietary changes. In the past, a lot of effort has been put into raising public knowledge of the bioactive components of plants and their advantages

for health. Numerous substances known as nutraceuticals are included in the diet of humans from natural materials; although not considered to be nutrients, they play a crucial role in maintaining health. Numerous studies demonstrate the antiatherogenic effects of a diet high in polyphenols and antioxidants. Citrus sinensis and Citrus paradisi have been shown to have antioxidant, anti-inflammatory, and hypolipidemic properties, which are all well known for their health advantages. Hyperlipidemia is a broad category of disorders. The most common causes of sickness and mortality worldwide are heart disease. Moreover, the development of atherosclerosis and coronary heart diseases is brought on by elevated cholesterol levels, particularly total cholesterol and LDL. Cardiovascular diseases are the leading cause of mortality in western nations, and a 20 percentage reduction in cholesterol can reduce Coronary Heart Disease (CHD) incidence by 31 percent and death rates by 33%. The primary factor causing CVD is hypercholesterolemia, and controlling cellular cholesterol equilibrium is crucial to avoiding CVD. There are several approaches to lower plasma cholesterol levels, including reducing dietary lipid absorption, increasing fecal expulsion of cholesterol, reducing cholesterol production, and removing cholesterol from blood. Cholesterol acyl transferase antagonist and HMG-CoA reductase antagonists have been shown in several trials to have beneficial effects on hypercholesterolemia and atherosclerosis. Current lipid-lowering medications, unfortunately, have a number of side effects. Research interests in the positive effects of dietary phytochemicals, like the flavonoids found in citrus fruit, is growing. Citrus fruits naturally contain a bioflavonoid called naringin. The grapefruit was traditionally exclusively grown as an aesthetic plant, but it has recently gained notoriety for its therapeutic advantages. Members of the Rutaceae family, including grapefruit and sweet orange, have demonstrated hypolipidemic benefits in rat models of diet-induced hypercholesterolemia. The fact that oranges are a rich source of antioxidants has been linked to a variety of medical and dietary advantages. Oranges possess many flavonoids, and they have been said to possess potent anti-oxidant and anti-inflammatory properties. Flavonoid has been shown to decrease lipids (Mallick and Khan 2016). Plant-derived compounds offer promising alternatives to conventional statin therapy, and molecular docking is a valuable tool for identifying and optimizing these potential therapeutic agents. The use of plant compounds as drugs has gained significant attention in recent years due to their potential therapeutic benefits and fewer side effects compared to allopathic drugs. Recent studies have investigated the potential of various plant compounds as therapeutic agents for managing hyperlipidemia. These compounds have been found to possess lipid-lowering properties and can potentially reduce the risk of cardiovascular diseases. Traditional pharmacology has always benefited from the fresh insights provided by ethnopharmacological investigations. In hyperlipidemic rats, the watery basil extracts decreased blood cholesterol, TGs, and LDL cholesterol levels. Its antioxidant activity has been linked to its hypolipidemic effects. In rats, a decoction made from Olea europea leaves had a hypocholesterolemic impact as well as a reduction in oxidized LDL. In mice fed a high cholesterol diet, urtica dioica extract dramatically lowered the levels of total and LDL cholesterol. Studies on ethnobotany have also identified botanicals that can treat hyperlipidemia. To establish their effectiveness and safety, more human studies are necessary (Delfan *et al.,* 2016). CVD is becoming more common over time. Diabetes and CVD are comorbid conditions that increase the risk of early mortality. Citrus flavonoids have a variety of biological functions and are effective medicines for the management of CVD. Citrus flavonoids neutralize free radicals, enhance insulin sensitivity and glucose tolerance, regulate adipocyte differentiation and lipid metabolism, reduce swelling and apoptosis, and treat endothelial dysfunction. Consuming citrus flavonoids has been linked to better cardiovascular results. Citrus flavonoids have a variety of positive benefits, however their exact methods of action are yet unknown. Plant-based flavonoids are naturally occurring substances with a wide range of biological and medicinal uses. The fundamental structure of flavonoids consists of two phenolic rings with one or more hydroxyl groups and 15 carbon atoms (OH). Flavonoids can be categorized into six groups based on their structural differences. All dietary flavonoids, with the exception of flavanols, are present in glycosylated forms. While aglycones are more hydrophobic and harder to absorb, flavonoid glycosides are water-soluble. Citrus fruits are a significant source of nutritional flavonoids due to their notable flavonoid component richness. Numerous studies have documented the benefits of citrus flavonoids on wellness. Citrus flavonoids have biological functions that include scavenging free radicals, acting as antioxidants, and reducing inflammation. Citrus flavonoids are expected to offer safeguards against CVD, according to the information available. Citrus flavonoids may be effective in treating atherosclerosis and CVD because of their capacity to lower oxidative stress, hyperlipidemia, and inflammation while enhancing endothelial function, arterial blood pressure, and lipid metabolism. Citrus flavonoids appear to lower fatness and adipose tissue swelling enhances platelet function, and guard from ROS-induced cell damage, according to in vitro and in vivo studies. Citrus flavonoids alter a number of signaling pathways that regulate swelling and other actions including Nuclear Factor kappa B (NF-κB) (Mahmoud *et al.,* 2019). A popular dietary flavonoid called rutin has outstanding medicinal qualities like

anti-inflammatory and antioxidant effects (Ding *et al.,* 2022). Rutin is a natural antioxidant that is considerably less likely to have negative effects than synthetic medications. Due to their extensive variety of biological activity, cheap cost, and very good safety margins, bioflavonoids are currently gaining a role in the field of medical care. Rutin, also known as rutoside, and quercetin-3-rutinoside are polyphenolic bioflavonoids that are mostly derived from fruits and vegetables. Rutin, a crucial nutrient for plants, gets its given name from the Ruta graveolens plant that includes rutin. In terms of chemistry it is a glycoside made up of the disaccharide rutinose and the flavonol aglycone quercetin (Enogieru *et al*., 2018). Flavonoid-rich diets are frequently associated with favorable outcomes in the mainstay of avoiding cardiovascular events. When rats on a high-cholesterol diet are given rutin orally, it lowers levels of cholesterol except HDL, as well as an induction of a reduction in HMGCoA activity. Rutin may have positive benefits because of its antioxidant properties because oral treatment of rutin to healthy control does not change these variables (Zeka *et al.,* 2017). It has been determined how well the citrus genus controls dyslipidemia. Citrus items tend to regularly have strong effects on dyslipidemia, working to lower total cholesterol, LDL, & triglycerides while also raising HDL. Such outcomes are linked to the extracts' flavonoid content, which is extraordinarily high and works on pharmacological targets implicated in beta-oxidation and lipogenesis. The existence of active ingredients like flavonoids, which interact synergistically across a number of routes to decrease lipogenesis and activate β-oxidation, can be linked to these effects. To strengthen the clinical evidence of the impact of citrus fruit extracts on the management of dyslipidemia, more research is required because to the great variability of the existing findings (Carvalho *et al.,* 2022). A growing body of research has made formulations and substances based on plant extracts increasingly popular for the treatment of many cancers, heart disease, diabetes, and neurological illnesses. Rutoside, and sophorin are other names for rutin. Rutin has relatively few or no known negative effects, making it a safe medication. Rutin is a bioflavonoid that is present naturally and is widely known to be present in plants and herbs, fruits, foods. Rutin is a component that supports powerful biological activity in a number of natural goods. By modifying several days regulated signaling pathways associated with apoptosis, swelling, angiogenesis, and autophagy, rutin has been shown to employ a variety of mechanisms. Multitude intracellular signaling molecules are significantly hampered by this bioactive plant-derived substance (Pandey *et al.,* 2021). Numerous biological processes have been linked to rutin. Rutin's aglycone, quercetin, as well as sugar moiety, rutinose, make up its structural components. Like rutin, quercetin is extensively distributed in a variety of foods. Several research investigations have taken place using various models to examine the impact of rutin & quercetin on lipid metabolism. Regarding the capacity of rutin & quercetin to decrease cholesterol, these researches produced conflicting results (Liang *et al.,* 2021). Further research is needed to validate the efficacy and safety of these plant compounds as drugs for managing lipid disorders. Molecular docking has emerged as a valuable tool in drug discovery, enabling researchers to predict the binding affinity and orientation of small molecules, such as potential drug candidates, to target proteins, like HMG-CoA reductase (Kitchen *et al.,* 2004). Molecular docking plays a crucial role in the early stages of drug discovery by identifying lead compounds that can modulate the activity of target proteins (Morris and Lim-Wilby 2008). This computational technique helps researchers prioritize and optimize potential therapeutic agents, reducing the time and cost associated with experimental validation (Ferreira *et al.,* 2015). In the context of lipid disorders, molecular docking has been employed to investigate the binding of various compounds, including plant-derived phytochemicals such as polyphenols and terpenoids that may interact with HMG-CoA reductase and exhibit lipid-lowering effects (Kumar *et al.,* 2011). Molecular docking is a computational technique used to predict the binding affinity and orientation of small molecules, such as plant-derived compounds, to target proteins, like HMG-CoA reductase (Morris and Lim-Wilby, 2008). This approach helps researchers identify potential lead compounds that can modulate the activity of the target protein, providing valuable insights into the design and optimization of novel therapeutic agents (Kitchen *et al*., 2004). HMG-CoA reductase is a crucial enzyme in cholesterol biosynthesis, and its inhibition is an effective strategy for managing hyperlipidemia.

By identifying compounds that can effectively modulate these targets, molecular docking contributes to the development of novel lipid-lowering agents with improved efficacy and safety profiles (Kandhare *et al.,* 2016). Currently, lipid disorders remained a significant public health burden, necessitating the development of novel therapeutic strategies. Molecular docking has played a vital role in drug discovery, facilitating the identification and optimization of potential lipid-lowering agents that can help address the growing burden of lipid disorders and associated cardiovascular diseases.

MATERIAL AND METHODS

Ligand preparation. To obtain the structural information about the target compounds, the PubChem database was queried using a unique identifier known as Standard Molecular Identifier (SMILE). This allowed to retrieve the appropriate records and extract essential details related to 2D fingerprint representation

(canonical SMILE), as well as other descriptive features such as physiochemical properties. Next, the retrieved ligand data was further processed to generate accurate three dimensional representations using the Biovia software package designed specifically for this task.

Protein preparation. When seeking a suitable structure for use in computer simulations, none exist that could be classified as an 'Ideal structure', rather those that are available would be judged to fit the specific research needs through evaluation according to factors. These include bound ligand status, correlation of entry, mutational effect and original organism, and then selecting an appropriately matched item that fulfills these criteria, such as PDB Id 1HW9 as used here. After downloading in PDB format, preparatory work included removal of impurities, and conversion for use with Biovia software. Finally, the protein was transformed into pdbqt format ready for docking. To find the correct pose between protein HMGCoA reductase and the ligand of interest, various methods must be applied. The main challenge lies in finding energetically favorable orientations compatible with multiple flexible regions (including rotatable bonds) simultaneously when applying realistic physical force constants, so a large number of sampling techniques should be considered. PyRx uses several heuristics based on Monte Carlo simulation. This allows faster search speed than exhaustive enumeration but slower convergence. The structure chosen, PDB ID 1HW9, fulfils all necessary criteria, taking into consideration aspects such as species, resolution/R factor & protein/length data as well as being solved without any ligand occupation (native form). Ultimately, the aim was to achieve greater accuracy when utilizing this protein structure moving forward in the study.

Active binding site analysis. Biovia Discovery software was used to scan for active binding sites on the protein surface. This analysis identified regions of the protein that are involved in interactions with other molecules and provided insight into the restricted areas that cannot be accessed easily. To determine potential binding partners between target protein and small compound docking experiments was performed using a blind approach to avoid bias towards known ligands and instead explore novel associations.

Molecular docking analysis. In the field of virtual screening, numerous docking tools are available for use. In this study, PyRx software was utilized, which includes other applications such as AutoDock, AutoDock vina, and Open Babel. Protein-ligand interactions involve the binding of a ligand molecule to a specific site on a protein, resulting in a conformational change of the protein. These interactions are crucial in various biological processes, such as enzyme catalysis, signal transduction, and regulation of gene expression. Receptor-ligand interactions, in particular, play a pivotal role in cell signaling pathways, wherein a ligand binds to a specific receptor on the cell surface, causing a conformational change that triggers downstream signaling pathways. Nonspecific interactions such as hydrophobic interactions, van der Waals forces, and hydrogen bonding can also contribute to the binding affinity of a protein-ligand complex, in addition to specific interactions between a protein and its ligand. Targeting protein-ligand interactions is a primary focus of drug discovery research, as it can lead to the development of new therapeutic agents. Atorvastatin, a statin drug that lowers cholesterol levels in the body, works by inhibiting the enzyme HMG-CoA reductase, which is responsible for the synthesis of cholesterol. Atorvastatin binds to specific amino acid residues in the enzyme, including Val522, Cys527, Met534, Ile762, Gln814, and Cys817, through various interactions such as hydrophobic interactions and hydrogen bonding. Atorvastatin contains a large hydrophobic region that interacts with hydrophobic residues of the enzyme, such as valine and isoleucine, which helps stabilize the binding and prevent detachment. Atorvastatin also contains polar groups, such as amides and alcohols that can form hydrogen bonds with polar residues of the enzyme further increasing its affinity for the enzyme. Van der Waals forces also contribute to the overall stability of the atorvastatin-enzyme complex. The binding interactions between atorvastatin and specific amino acid residues in the enzyme are crucial to the effectiveness of atorvastatin as a cholesterol-lowering drug. Saphorin, a small molecule, binds to various amino acids in proteins and demonstrates versatility in its ability to bind to a variety of amino acids and regulate protein activity. The binding of saphorin to HMG-CoA reductase involves various interactions with specific amino acid residues in the enzyme, such as hydrogen bonding and van der Waals forces (Patel, 2023).

ADMET analysis – The ADMET properties were analyzed using pkCSM web tool.

RESULTS AND DISCUSSION

Lipid metabolism is critical to various physiological processes in the human body, which involves energy storage, hormone control, and nutrient distribution. When lipids become dysregulated, these mechanisms are interrupted, resulting in lipid diseases (Amadi *et al.,* 2022). Two of the most important and changeable cardiovascular disease risk variables are hypertension and dyslipidemia, both of which frequently exist together (Semianiv *et al.,* 2022). The top reasons for death worldwide are CVDs. The development and growth of CVD are significantly influenced by lipids along with lipoproteins (Bhargava *et al.,* 2022). Rutin was docked with HMG-CoA reductase. Compared to atorvastatin, rutin was found to have a stable ligand-receptor complex. The binding affinity of rutin with HMG-CoA reductase was found to be - 8.4 kcal/mol. The binding affinity of atorvastatin with HMG-CoA

reductase was determined to be - 7.8 kcal/mol Table 1. The ADMET properties were analyzed using pkCSM web tool. This involved predicting the pharmacokinetic properties of the ligands, including their solubility, permeability, and toxicity. A comparison of ADME analysis of Atorvastatin and Rutin was also performed Table 2. Atorvastatin and rutin are two compounds that have been studied for their potential to interact with HMG-CoA reductase, which is a key enzyme involved in cholesterol biosynthesis. Atorvastatin is a commonly prescribed allopathic drug that works by inhibiting the activity of HMG-CoA reductase, thereby reducing the production of cholesterol in the liver. Several studies have investigated the interaction of atorvastatin with HMG-CoA reductase using molecular docking. These studies have revealed that atorvastatin can bind to the active site of HMG-CoA reductase and form stable complexes with the enzyme. Moreover, the binding affinity of rutin for HMG-CoA reductase has been found to be comparable to that of atorvastatin. The interaction of atorvastatin and rutin with HMG-CoA reductase has important implications for the management of lipid disorders. The crystal structure of HMG-CoA reductase in complex with atorvastatin has been determined by X-ray crystallography (PDB ID: 1HW9) and provides insights into the mechanism of inhibition. The crystal structure shows that atorvastatin binds to the active site of the enzyme through hydrogen bonds and hydrophobic interactions with several key residues, including Val522, Cys527, Met534, Ile762, Gln814, and Cys817. The binding of atorvastatin induces conformational changes in the enzyme, which results in a decrease in the enzyme activity. The interaction of atorvastatin with HMG-CoA reductase has been extensively studied, and computational simulations have been used to understand the binding mechanism in detail. Molecular docking studies have identified key residues involved in the binding of atorvastatin to the enzyme and have provided insights into the binding affinity and specificity of the drug. The use of atorvastatin as an allopathic drug for managing hyperlipidemia is well-established, and the interaction of rutin with HMG-CoA reductase suggests that it may have potential as a natural alternative to atorvastatin. However, further research is needed to validate the lipid-lowering activity of rutin and its safety and efficacy for long-term use. Interaction of Rutin with receptor (PDB ID: 1hw9) involves amino acids Asn658, Asp767, Cys526, Gly656, Gly765, Gly806. In summary, the interaction of atorvastatin and rutin with HMG-CoA reductase has been studied using molecular docking and molecular dynamics simulations. This study has provided valuable insights into the potential of these compounds for managing lipid disorders and suggests that rutin may have potential as a natural alternative to atorvastatin. As an antioxidant, rutin has been shown to scavenge free radicals and reduce oxidative stress, thereby protecting cells from damage. Rutin's anti-inflammatory properties are attributed to its ability to inhibit the production of pro-inflammatory cytokines and modulate the activity of enzymes involved in the inflammatory response, such as cyclooxygenase-2 and inducible nitric oxide synthase. Rutin's vasoprotective effects are related to its capacity to enhance the production of nitric oxide, a potent vasodilator, and to inhibit platelet aggregation, which can help prevent thrombus formation and improve blood flow. Additionally, rutin has been reported to exert protective effects on the endothelium, the inner lining of blood vessels, by reducing oxidative stress and inflammation. Antioxidant and anti-inflammatory activities play an important role in the lipid-lowering potential of many natural compounds. Oxidative stress and inflammation are known to contribute to the development of hyperlipidemia and cardiovascular diseases. Antioxidants can scavenge free radicals and prevent oxidative damage to lipids, proteins, and Deoxyribonucleic Acid (DNA), which can lead to the development of hyperlipidemia. Anti-inflammatory compounds can reduce the production of pro-inflammatory cytokines and chemokines, which can contribute to the development of atherosclerosis and other cardiovascular diseases. Several natural compounds, such as polyphenols, flavonoids, and terpenoids, have been found to possess both antioxidant and anti-inflammatory activities, and have been studied for their potential to lower lipid levels. For example, resveratrol, a polyphenol found in grapes and red wine, has been found to possess both antioxidant and anti-inflammatory activities, and has been shown to reduce lipid levels in animal models and humans.

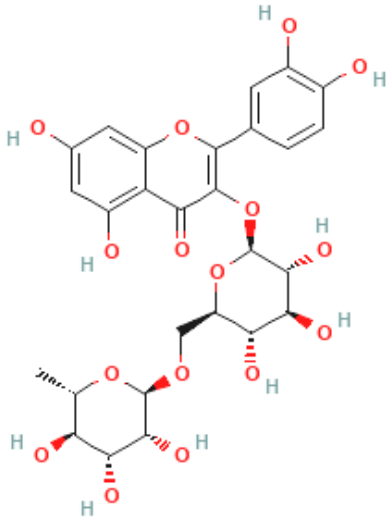

Fig. 1. 2D Chemical structure of Rutin.

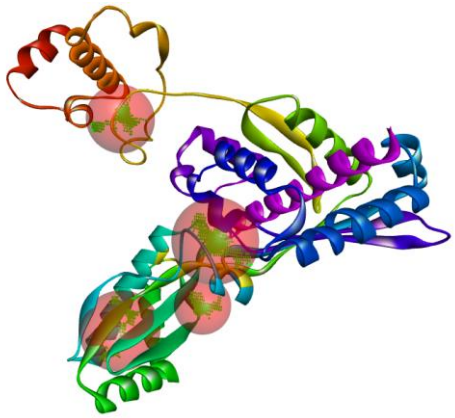

Fig. 2. Binding Sites in HMG-CoA reductase (Patel, 2023).

Similarly, curcumin, a polyphenol found in turmeric, has been found to possess both antioxidant and anti-inflammatory activities, and has been shown to reduce lipid levels in animal models and humans. The lipid-lowering potential of natural compounds with antioxidant and anti-inflammatory activities is likely due to their ability to reduce oxidative stress and inflammation, which can contribute to the development of hyperlipidemia and cardiovascular diseases. Moreover, these compounds have fewer side effects compared to allopathic drugs, making them a safer option for long-term use. In summary, the antioxidant and anti-inflammatory activities of natural compounds play an important role in their lipid-lowering potential. These compounds can reduce oxidative stress and inflammation, which can contribute to the development of hyperlipidemia and cardiovascular diseases. Further research is needed to validate the efficacy and safety of natural compounds with antioxidant and anti-inflammatory activities for managing lipid disorders. (Ganeshpurkar and Saluja 2017).

Table 1: Binding Affinity of Rutin and Atorvastatin.

PubChem ID	Ligand	Protein	Binding Affinity (kcal/mol)
5280805	Rutin	1HW9	-8.4
60823	Atorvastatin (+ve control)		-7.8

Table 2: ADME analysis of Atorvastatin and Rutin.

ADMET Properties	Model Name	Unit	Predicted Values	
			Atorvastatin	Rutin
Absorption	Water solubility	log mol/L	-4.531	-2.892
Absorption	Caco2 permeability	log Papp in 10^{-6} cm/s	0.23	-0.949
Absorption	Intestinal absorption (human)	% Absorbed	59.861	23.446
Absorption	Skin Permeability	log Kp	-2.735	-2.735
Absorption	P-glycoprotein substrate	Categorical	Yes	Yes
Absorption	P-glycoprotein I inhibitor	Categorical	No	No
Absorption	P-glycoprotein II inhibitor	Categorical	No	No
Distribution	VDss (human)	log L/kg	-1.918	1.663
Distribution	Fraction unbound (human)	Fu	0.089	0.187
Distribution	BBB permeability	log BB	-1.162	-1.899
Distribution	CNS permeability	log PS	-2.916	-5.178
Metabolism	CYP2D6 substrate	Categorical	No	No
Metabolism	CYP3A4 substrate	Categorical	Yes	No
Metabolism	CYP1A2 inhibitior	Categorical	No	No
Metabolism	CYP2C19 inhibitior	Categorical	No	No
Metabolism	CYP2C9 inhibitior	Categorical	Yes	No
Metabolism	CYP2D6 inhibitior	Categorical	No	No
Metabolism	CYP3A4 inhibitior	Categorical	No	No
Excretion	Total Clearance	log ml/min/kg	0.437	-0.369
Excretion	Renal OCT2 substrate	Categorical	No	No
Toxicity	AMES toxicity	Categorical	No	No
Toxicity	Max. tolerated dose (human)	log mg/kg/day	0.193	0.452
Toxicity	hERG I inhibitor	Categorical	No	No
Toxicity	hERG II inhibitor	Categorical	No	Yes
Toxicity	Oral Rat Acute Toxicity (LD50)	mol/kg	2.877	2.491
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	log mg/kg_bw/day	4.839	3.673
Toxicity	Hepatotoxicity	Categorical	Yes	No
Toxicity	Skin Sensitisation	Categorical	No	No
Toxicity	T.Pyriformis toxicity	log ug/L	0.285	0.285
Toxicity	Minnow toxicity	log mM	-0.63	7.677

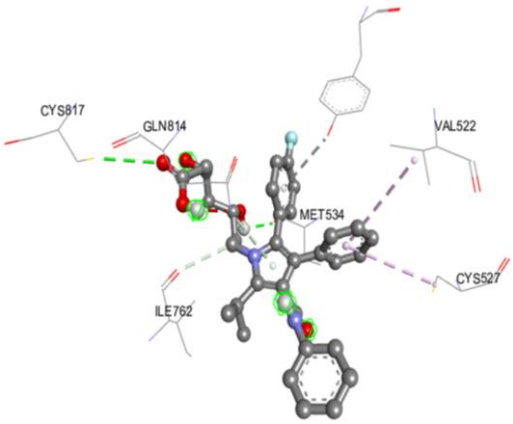

Fig. 3. 3D structure of Atorvastatin docked with HMG-CoA reductase ((Patel, 2023).

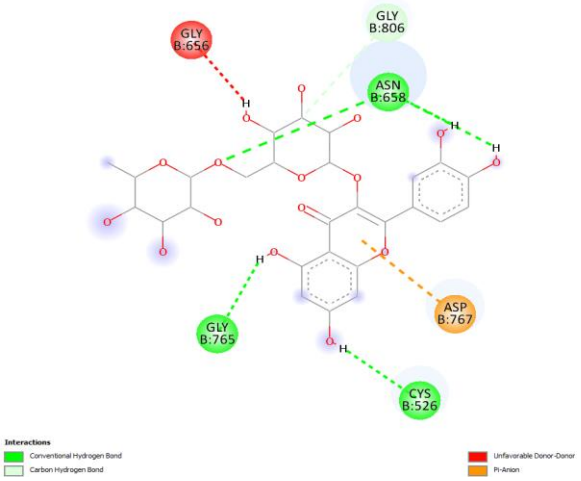

Fig. 4. Interaction of Rutin with receptor (PDB ID: 1hw9).

CONCLUSIONS

In conclusion, the use of plant compounds for managing lipid disorders has shown promising results as an alternative to allopathic drugs. Plant compounds such as flavonoids, polyphenols, and terpenoids have been found to possess lipid-lowering properties and can potentially reduce the risk of cardiovascular diseases. Moreover, plant compounds have fewer side effects compared to allopathic drugs, making them a safer option for long-term use. However, further research is needed to validate the efficacy and safety of plant compounds for managing lipid disorders. In the future, the use of plant compounds for managing lipid disorders may become more widespread, especially as more people seek natural and holistic approaches to healthcare. Additionally, the development of novel plant-based therapies and the identification of new plant compounds with lipid-lowering properties may lead to the discovery of new treatments for managing lipid disorders. The in silico study of rutin for lipid lowering activity against HMG-CoA reductase has provided valuable insights into the potential of rutin as a therapeutic agent for managing hyperlipidemia. The study utilized molecular docking and molecular dynamics simulations to investigate the binding interactions between rutin and HMG-CoA reductase, and the results suggest that rutin has a high binding affinity for the enzyme's active site. Additionally, the study revealed that rutin can potentially inhibit the activity of HMG-CoA reductase, which is a key enzyme involved in cholesterol biosynthesis. These findings provide a strong foundation for further studies to validate the lipid-lowering activity of rutin and its potential as a therapeutic agent for managing hyperlipidemia.

FUTURE SCOPE

The future scope of in silico studies of plant compounds for lipid-lowering activity is vast and promising. With the increasing demand for natural and holistic approaches to healthcare, the use of plant compounds for managing lipid disorders is likely to become more widespread. In silico studies can play a crucial role in identifying new plant compounds with lipid-lowering properties and in understanding the molecular mechanisms underlying their activity. Moreover, in silico studies can help in optimizing the structure of plant compounds to enhance their efficacy and specificity towards lipid-lowering targets. In the future, in silico studies can be combined with in vitro and in vivo studies to validate the efficacy and safety of plant compounds for managing lipid disorders. Additionally, the development of novel computational tools and techniques can further enhance the accuracy and efficiency of in silico studies of plant compounds for lipid-lowering activity. Overall, the future scope of in silico study of rutin for lipid-lowering activity is promising and can lead to the discovery of new and effective treatments for managing lipid disorders.

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Conflict of Interest. None.

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