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Inhibition of HMG-CoA Reductase Activity from Date Palm (Phoenix dactylifera L.) Fruit's Polyphenols: In-Silico Study

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ABSTRACT

Background: *Hyperlipidemia is a group of conditions, both inherited and acquired, where there is too much fat in the body. While the condition itself often doesn't cause noticeable symptoms, it can lead to serious diseases that may be dangerous. HMG-CoA Reductase (HMGCR) is the enzyme that antihyperlipidemic medicines target. Recent studies suggest that eating diets based on date fruits may provide several health benefits, mainly because they are rich in plant-based polyphenols.*
Objective: *This study looked at how polyphenols from date palms might stop HMG-CoA reductase from working. The polyphenols tested came from Phoenix dactylifera L. fruit and included gallic acid, catechin, rutin, quercetin, isoquercetin, kaempferol, ferulic acid, caffeic acid, cinnamic acid, syringic acid, and vanillic acid.*
Methods: *The study used a computer-based method called molecular docking to predict how well these compounds could block the enzyme. Binding affinity scores were used to measure how strongly they could stop the enzyme. The process included preparing the chemicals and protein, running the docking simulation, and checking if the compounds were likely to be used as drugs.*
Results: *The study found that date palm polyphenols could be useful in lowering lipids, with catechin showing the strongest effect, having a binding score of −8.5.*
Conclusion: *Polyphenols in dates can act as natural agents to lower lipids by stopping the HMG-CoA reductase enzyme, making them a possible addition to treatments for high lipid levels.*

Keywords: *Date palm; polypheno; HMG-CoA reductase; antilipidemic; molecular docking*

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INTRODUCTION

In humans, cholesterol is made inside the body through a process called the mevalonate pathway. In this process, an enzyme named 3-hydroxy-3-methylglutaryl-coenzyme A reductase, or HMG-CoA reductase, plays a key role. This enzyme helps turn HMG-CoA into mevalonate and is important for making cholesterol and other substances called isoprenoids. Because of its role, this enzyme is a main target for a group of drugs called statins, which are used to lower cholesterol level. The human version of HMG-CoA reductase has 888 building blocks called amino acids. The first part, from amino acid 1 to 339, forms a part of the enzyme that connects to the inside of a cell structure called the endoplasmic reticulum. Then there's a connecting section from amino acid 340 to 449.

The last part, from 450 to 888, is the part of the enzyme that works inside the cell and is responsible for the actual chemical reaction. This part of the enzyme comes together as a group of four proteins, each with an active site where the reaction happens. One important part of the active site is called the cis-loop, which helps in the process of breaking down HMG-CoA. Some plant compounds called polyphenols, like the catechins found in tea, especially those with a gallate ester group, have been shown to help lower cholesterol in both lab tests and in living creatures. These compounds also act as antioxidants. Scientists think that polyphenols affect how the body handles fats in several ways, such as by helping the body make more receptors that take in bad cholesterol, reducing how much cholesterol the intestines absorb, and affecting both the making and breaking down of cholesterol. Because the activity of HMG-CoA reductase is controlled by many factors and the enzyme doesn't last very long in the body, it is difficult to clearly see and understand the direct effects these compounds have on it. [1,2]

Phoenix dactylifera, which is part of the A reaccede family, has many health benefits found in different parts of the plant, like the leaves, bark, seeds, fruits, and pollen. It has been reported to have several useful effects on the body, such as helping to fight free radicals, reducing cancer risk, protecting the liver, supporting brain health, protecting the stomach, controlling blood sugar, lowering bad fats, fighting bacteria, and improving sexual health. These many health benefits come from the plant's high levels of active substances like phenolic compounds, flavonoids, carotenoids, vitamins, minerals, amino acids, fatty acids, and various organic acids. [3,4] Plant-based polyphenols have been studied a lot and are still getting more attention from scientists and doctors because they have many good health effects. These effects include helping to fight free radicals, lowering bad fats in the blood, and offering other health benefits like reducing the chances of getting cancer, diabetes, and heart problems.[5]

The date palm, Phoenix dactylifera, has a high amount of total phenolic compounds, which range from 10.47 to 22.11 mg per 100 grams of fresh weight. The Ajwa Al Madinah type had the highest level at 22.11 mg per 100 grams of dry weight, followed by Nabt Saif at 22 mg per 100 grams of dry weight. Khla Al Qassim had the lowest amount at 10.47 mg per 100 grams of dry weight. Among the different types of phenolics, derivatives of gallic acid, p-coumaric acid, and ferulic acid were the most common. Also, several types of flavonoids were found in these date varieties, including quercetin, luteolin, apigenin, isoquercitrin, and rutin. [4,6]

Table 1. Phenolic classes of and identified compounds in date fruits[7]

Class	Identified compound
Benzoic acids and derivatives	Syringic acid , protocatechuic acid, p- hydroxybenzoic acid, vanillic acid, sinapic acid, and gallic acid
Cinnamic acid and derivative	dicaffeoylsinapoyl hexosid , hydrocaffeic acid, ferulic acid, p-coumaric acid, dactyliferic acid, 2 caffeoylshikimic acidhexosides, 3-caffeoylshikimic acid, Caffeic acid, 4-caffeoylshikimic acid,5-caffeoylshikimic acid, and caffeoylsinapoyl hexoside.
Flavonoid glycosides and esters	Isorhamnetin hexoside , Luteolin, chrysoeriol rhamnosyl-hexoside, quercetin , apigenin, quercetin rhamnosyl-hexoside sulfate, quercetin 3-O- rutinoside (rutin), ,quercetinacetyl-hexoside, isorhamnetin-3-O rutinoside, , isorhamnetin acetyl-hexoside, quercetin hexoside sulfate , quercetin 3- O-glucoside (isoquercitrin), chrysoeriol hexoside sulfate, andchrysoeriol hexosid
Flavan-3-ols	(+)-Catechin, and (−)-epicatechin

Catechins and their gallate derivatives are a big group of polyphenolic compounds that scientists are really interested in because they have many health benefits. These compounds work in different ways by affecting various signals in the body that are involved in both normal and disease processes. While they are best known for their strong ability to fight harmful free radicals, they can also act as pro-oxidants under certain conditions depending on their concentration. Many studies show that catechins can stop important steps in cancer growth, like cell division, survival, spread, and the formation of new blood vessels. They also help control how the body handles fats and sugar, making them useful for preventing and managing issues like obesity and type 2 diabetes, and lowering the risk of heart problems.[8]

Kaempferol is a naturally occurring flavonoid found in many fruits, vegetables, and plants. It has several health benefits, including acting as an antioxidant, reducing inflammation, preventing cancer, and helping with weight management. One important effect of kaempferol is that it can stop fat cells from forming by reducing the buildup of fat in these cells.[9]

Quercetin is one of the most common flavonoids in plants and has been shown to help lower high levels of fats in the blood and prevent the development of plaques in arteries. One of the ways it does this is by improving reverse cholesterol transport, which helps remove cholesterol from tissues around the body, thus preventing and treating atherosclerosis. Both quercetin and its sugar-bound form, rutin, have been found to protect the liver from damage and reduce inflammation caused by a diet high in cholesterol. [10,11] Chlorogenic acid (CGA) is one of the most common polyphenols found in the diet. It has been suggested as a promising compound for preventing atherosclerosis because it can lower lipids, reduce inflammation, and act as an antioxidant. Its effects in the body are believed to be partly due to its main breakdown products, such as caffeic acid, ferulic acid, and gallic acid. [12]

A study on Paspalum scrobiculatum L. (kodo millet) found that it contains several phenolic compounds, including quercetin, ferulic acid, vanillic acid, and syringic acid (SA). Syringic acid is a naturally occurring phenolic substance that has been studied for its ability to help with various health issues like diabetes, heart diseases, cancer, stroke, and problems in the brain and liver. It has several health benefits, such as fighting free radicals, killing harmful bacteria, reducing inflammation, and protecting against endotoxins. In experiments, syringic acid was found to be very effective in protecting the liver and reducing high levels of lipids, even better than silymarin, which is a standard medicine used for liver protection. (5,10,11) Even though polyphenols are known to improve how the body handles fats, there is not enough proof that they directly block the enzyme HMG-CoA reductase (HMGR), which is the main enzyme involved in making cholesterol. [5,10,11]

Because the date fruit, Phoenix dactylifera, has a wide variety of bioactive compounds, this study used a computer-based molecular docking method to look at how well these polyphenols bind to HMGR. This helps in understanding if they could be used as alternative treatments for managing high lipid levels.

MATERIAL AND METHOD

Ligand Preparation

The chemical structures of phytochemical compounds found in Phoenix dactylifera fruit were collected from scientific studies. The 3D structures, SMILES codes, and compound IDs were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) as shown in Table 1. All ligand structures were then refined using Avogadro software and saved in PDB format.

Table 2. ID Number and Canonical Smiles of Phoenyx Dactylifera fruit compound[13]

Compound	ID Number	Canonical SMILES
Gallic Acid	370	C1=C(C=C(C(=C1O)O)O)C(=O)O
Vanillic Acid	8468	COC1=C(C=CC(=C1)C(=O)O)O
Syringic Acid	10742	COC1=CC(=CC(=C1O)OC)C(=O)O
Caffeic Acid	689043	C1=CC(=C(C=C1/C=C/C(=O)O)O)O
Cinnamic Acid	444539	C1=CC=C(C=C1)C=CC(=O)O
Ferulic Acid	445858	COC1=C(C=CC(=C1)/C=C/C(=O)O)O
Cathechin	9064	C1[C=H]([C=H](OC2=CC(=CC(=C21)O)O)C 3=CC(=C(C=C3)O)O)O
Quercetin	5280343	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3 O2)O) O)O)O)O
Kaempferol	5280863	C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O 2)O) O)O)O
isoquercetin	5280804	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3 O2)O)O)O[C=H]4[C=H]([C=H]([C-H]([C=H](O4)CO)O)O)O)O)O
Rutin	5280805	CC1C(C(C(C(O1)OCC2C(C(C(C(O2)OC3=C(OC 4=CC (=CC(=C4C3=O)O)O)C5=CC(=C(C=C5)O)O)O) O)O)O)O)O

Target Selection

Prediction of protein targets was done using PharmMapper (http://lilab.ecust.edu.cn), SuperPred (http://prediction.charite.de), and Swiss Target Prediction (https://www.swisstargetprediction.ch). The predicted targets were checked with UniProt (https://www.uniprot.org). The 3D structure of the chosen protein, HMG-CoA reductase, was obtained from the Protein Data Bank (https://www.rcsb.org/) with PDB ID: 5HF5. The protein structure was processed with PyMOL v1.7.4.5 to remove any non-protein parts before running the molecular dockin.

Molecular Docking

Molecular docking was carried out using AutoDock Vina in PyRx 0.8. The selected ligands were gallic acid, catechin, rutin, quercetin, isoquercetin, kaempferol, ferulic acid, caffeic acid, cinnamic acid, syringic acid, and vanillic acid. HMG-CoA reductase was the target protein, and atorvastatin was used as the reference. The interaction between ligands and proteins was visualized and analyzed using PyMOL v1.7.4.5 to examine how they bind and interact

Drug-Likeness Test

To check if the ligands are suitable as drugs, their physical and chemical properties were tested using Lipinski's Rule of Five. This includes molecular weight, hydrogen bond donors, hydrogen bond acceptors, and lipophilicity (LogP). The compounds that met these criteria were believed to have good chances of being taken orally.

RESULT AND DISUCUSSION

Ligand Preparation

The ligands used in this study were active compounds found in Phoenix dactylifera fruit. Based on scientific research, eleven phytochemicals were picked, including gallic acid, catechin, rutin, quercetin, isoquercetin, kaempferol, ferulic acid, caffeic acid, cinnamic acid, syringic acid, and vanillic acid. Atorvastatin was used as the standard reference (positive control). All the ligand structures were downloaded from the PubChem database in SDF format and then converted into PDB format to make them compatible with the docking process. The 2D structures of all the ligands used are shown in Figure 1.

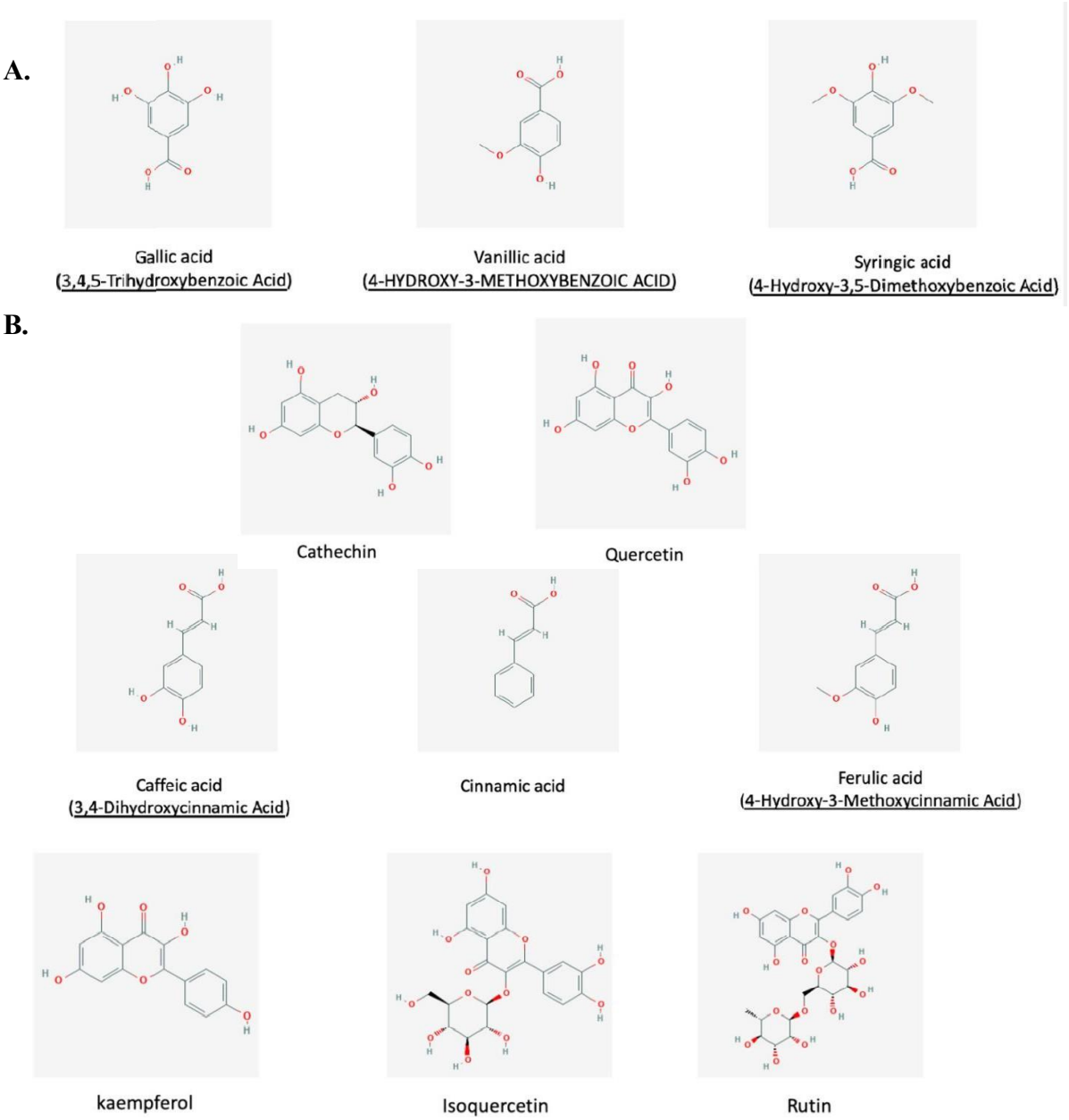

Figure 1. Chemical structures of the polyphenols used in this study. (A) Benzoic acid and cinnamic acid derivatives. (B) Flavonoids. Images retrieved from PubChem (www.pubchem.ncbi.nlm.nih.gov [16]

Target Selection

The main target in this study was the HMG-CoA reductase enzyme, which was obtained from the Protein Data Bank. Blocking this enzyme is a common way to treat certain conditions, because it stops the conversion of HMG-CoA into mevalonate in liver cells. This step is the first and slowest part of the process that makes cholesterol in the body. Once we got the structure of the protein, we used PyMOL v1.7.4.5 to remove unnecessary parts like water molecules and extra residues.[15]

Molecular Docking and Discussion

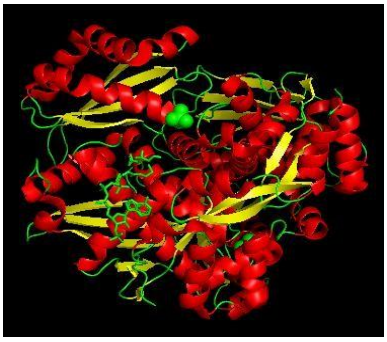

Figure 2. HMG-CoA Reductase

In silico approaches utilize computational tools and biological databases to support drug discovery and research. A widely used in silico method is molecular docking, which predicts how chemical compounds may bind to specific target proteins and the potential biological outcomes of these interactions before performing laboratory experiments. This approach is advantageous because it allows early identification of promising bioactive compounds, reducing the likelihood of failure in subsequent animal or clinical studies.

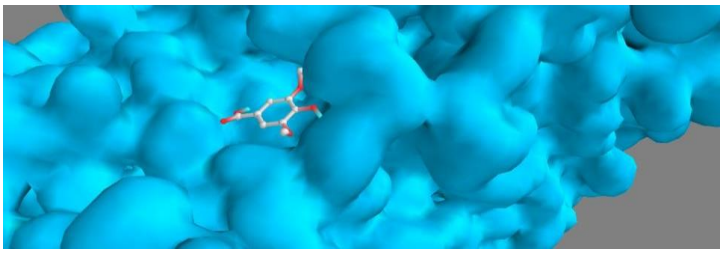

Figure 3 .The Binding site of HMG co-A reductase (Blue) and Cathechin (grey) with PyMol v1.7.4.5

Table 3 presents the results of molecular docking simulations for compounds identified in *Phoenix dactylifera* fruit. Binding affinity reflects the strength of interaction between a molecule and its target protein, where lower (more negative) values indicate stronger binding. In this study, catechin demonstrated the strongest binding among all tested compounds (Figure 3), with a value closest to that of atorvastatin, which served as the reference drug. These findings indicate that catechin from *Phoenix dactylifera* may have the highest potential for managing dyslipidemia.

Table 3. Binding affinity of P.Dactylifera fruit polyphenols compound

Compound	Binding Affinity
Atorvastatin (control)	-8.2
Cathechin	-8.5
Kaempeferol	-8.0
Quercetin	-7.7
Rutin	-7.6
Isoquercetin	-7.6
Caffeic Acid	-6.9
Gallic Acid	-6.1
Ferulic Acid	-5.7
Cinnamic Acid	-5.6
Syringic Acid	-5.6
Vanillic Acid	-5.2
Ferulic Acid	-5.7

After completing the docking process, a drug-likeness evaluation was performed to determine whether the compounds possess suitable physicochemical characteristics to function effectively inside the body. Drug-likeness refers to how well the structural features of a molecule support its potential as a therapeutic drug. This assessment was carried out using Lipinski's Rule of Five, a guideline that predicts the likelihood of a compound being orally active. The criteria include molecular weight not exceeding 500 Da, lipophilicity (LogP) of 5 or less, a maximum of 5 hydrogen bond donors, and no more than 10 hydrogen bond acceptors. Compounds meeting these requirements are generally capable of permeating cell membranes efficiently through passive diffusion.

Lipophilicity (LogP) indicates the balance between a molecule's ability to dissolve in fats and in water. The ideal LogP range is −0.4 to 5. If a compound is too lipophilic, it may accumulate in tissues and potentially lead to toxicity, whereas a very low (negative) LogP can limit its permeability through cell membranes. In addition, molecules with a molecular weight greater than 500 Da may have difficulty crossing biological membranes. The number of hydrogen bond donors and acceptors also influences absorption efficiency—an excessive amount requires more energy for the molecule to pass through membranes, which can reduce its oral bioavailability. The results from the drug-likeness test are in Table 4.

Table 4. Drug-likeness result of P.Dactylifera fruit polyphenols compound

Compound	Molecular weight	Hydrogen bond donor	Hydrogen bond receptor	(LogP)
Atorvastatin	558.6398032	4	7	6.38
Gallic Acid	170.12 g/mol	4	5	0.16
Vanillic Acid	168.15 g/ml	2	4	0.74
Syringic Acid	198.17 g/mol	2	5	0.77
Caffeic Acid	180.16 g/mol	3	4	0.75
Cinnamic Acid	148.16 g/mol	1	2	1.90
Ferulic Acid	194.18 g/mol	2	4	1.26
Cathechin	290.27 g/mol	5	6	0.98
Quercetin	302.24 g/mol	5	7	-0.56
Kaempferol	286.24 g/mol	4	6	0.03
isoquercetin	464.38 g/mol	8	12	-0.59
Rutin	610.52 g/mol	10	16	-3.89

All examined substances, with the exception of rutin, conformed to Lipinski's rule for oral medication candidates. This suggests rutin might not easily pass through cell membranes by simple diffusion. However, it may still be absorbed in the body through other ways. Statins function by inhibiting the body's natural cholesterol synthesis and facilitating the liver's removal of excess cholesterol from the blood. A key enzyme named HMG-CoA reductase is responsible for cholesterol formation, and it changes HMG-CoA into mevalonate. Statins inhibit the enzyme by mimicking mevalonate, preventing the syntesis of cholesterol. As a result, the liver increases the number of LDL receptors, enhancing the uptake of LDL cholesterol from the bloodstream and reducing its overall levels. In this study, molecular docking showed that most of the compounds from Phoenix dactylifera fruit, except rutin, strongly bind to HMG-CoA reductase. .[14,15] This suggests that these compounds might be good candidates for new treatments for high cholesterol. In order to further evaluate the stability of ligand–protein interactions, future research is advised to validate the current docking results using improved computational techniques including molecular dynamics simulations and MM-PBSA/MM-GBSA binding free energy studies. The results would be more reliable if the screening library was expanded, docking techniques were optimized across various software and scoring functions, and more

thorough ADME-toxicity assessments were included. The possible multi-target effects of Phoenix dactylifera polyphenols on other dyslipidemia-related proteins as PCSK9, CETP, or PPAR-α should also be investigated by researchers. To validate the anticipated biological activity, in vitro and in vivo experiments are still necessary. To further improve the translational relevance of these findings, future research may employ structure–activity relationship (SAR) analysis, explore potential synergistic effects among the identified compounds, employ updated protein structures, and conduct comparative studies with a wider range of clinically used statins.

CONCLUSION

In conclusion, atechin from Phoenix dactylifera was the best at binding to HMG-CoA reductase, showing it could be a strong candidate for treating high cholesterol. All the tested compounds followed Lipinski's rules for being a good drug, except rutin. Rutin may not pass through the body's cell membranes easily, but it might still be absorbed through other ways in the body.

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