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Original Article

# *In silico* Analysis of the Polyphenolic Metabolites of *Zea mays* L. "Purple Corn" on HMG-CoA Reductase

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## ABSTRACT

This research aims to identify the polyphenolic metabolites, reported in ears and grains of *Zea mays* L. "purple corn" according to the current literature, with more significant interaction on HMG-CoA reductase, through *in silico* assays. Using the keyword combination "*Zea mays* L" AND "polyphenols", a search was made in Google Scholar, PubMed, ScienceDirect and Scopus databases, identifying 22 polyphenolic compounds. Polyphenolic ligands and control molecules were prepared with the OpenBabel program and parameterized with AutoDock Tools. In addition, the crystallized structure of HMG-CoA reductase (1DQA) was downloaded from the Protein Data Bank database, then prepared in PyMOL and parameterized with AutoDock Tools. Molecular docking was performed in AutoDock Vina with a 100-time repetition for each ligand-target interaction. The results show that the hydrogen bonds with amino acids of importance in HMG-CoA reductase are ASN 658, ARG 590, and GLU 559. Protocatechuic acid, caffeic acid, vanillic acid, ferulic acid, p-coumaric acid, and 4-hydroxybenzoic acid presented lower affinity energy (ΔG°). The physicochemical and pharmacokinetic properties of the molecules with the best pharmacodynamic interaction were analyzed with the SwissADME and pkCSM servers, showing that protocatechuic, caffeic, vanillic, ferulic, p-coumaric and 4-hydroxybenzoic acids have the best physicochemical and pharmacokinetic profile. Therefore, this study gives us a clearer idea of the action of polyphenols on HMG-CoA reductase, which will allow obtaining new drug candidates for the treatment of hypercholesterolemia.

**Key words:** Polyphenols, Flavonoids, *Zea mays* L., *In silico*, HMG-CoA reductase.

## INTRODUCTION

Cardiovascular diseases (CVD) are one of the main causes of mortality worldwide.[1] According to the World Health Organization (WHO), in 2016 there were around 17.9 million deaths from CVD.[2] There are different risk factors for CVD, however, the most important are hypertension and hypercholesterolemia.[2,3]

Hypercholesterolemia is strongly associated with the risk of atherosclerosis, subsequent heart attack, and stroke.[4] In fact, evidence has shown that high cholesterol levels are linked to the risk of atherosclerotic cardiovascular events, due to the accumulation of cholesterol in atherosclerotic plaques.[5,6] Cholesterol, a key molecule in this entire process, plays a significant role in a variety of homeostatic systems.[7] Most mammalian cells can acquire cholesterol from two independent sources. The first is *de novo* biosynthesis, a pathway catalyzed by multiple enzymes, and the second is through the uptake of exogenously derived cholesterol associated with plasmatic lipoproteins.[8] In *de novo* biosynthesis, the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) catalyzes the reductive cleavage of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, the precursor of cholesterol and other isoprenoids, using two NADPH molecules and proceeding through two successive hydride transfers.[9,10] The crystallographic structure of human HMG-CoA reductase is described as a single polypeptide chain of 888 amino acids, divided into three domains: membrane-anchoring, linker and catalytic. The binding pocket for HMG-CoA is characterized by a "*cis*-loop," amino acid residues 682 to 694. Its catalytic portions form a protein tetramer containing four active sites, located at the interface of two monomers.[11]

HMG-CoA reductase is a therapeutic target for statins, a hypocholesterolemic drug group.[8] Statins reduce cholesterol synthesis by competitively inhibiting the enzyme HMG-CoA reductase.[12] The HMG-like portion of statins occupies the HMG part of the HMG-CoA binding pocket, and the nonpolar region partially occupies a portion of the coenzyme-A binding site.[13] These not only compete with the normal substrate for the active site but also alter the conformation of the enzyme, preventing it from attaining a functional structure.[14] Statins are the most prescribed drugs to reduce cholesterol and the risk of cardiovascular diseases.[15] However, the main reason for stopping treatment with statins is the appearance of myopathies[16] and other adverse effects such as type 2 diabetes mellitus, increased liver transaminases, headache, peripheral neuropathy, sensory disturbances due to prolonged use.[11,17]

Currently, alternative therapies are emerging to reduce cholesterol levels.[18] Special attention has been paid to polyphenols, the most numerous and widely distributed bioactive compounds of secondary metabolites in plants, fruits, and vegetables; commonly classified as flavonoids and non-flavonoids.[19,20] Research results indicate that polyphenols are related to health benefits, including cardiovascular diseases, type II diabetes, cancer, and neurodegenerative diseases such as Alzheimer's

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and Parkinson's. The probable mechanisms include effects on blood pressure, endothelial function, glucose metabolism, inflammation, biomarkers of oxidative stress, platelet function and cholesterol.[21,22] Referring to elevated cholesterol levels, *in vitro* and *in vivo* studies support that the activity of polyphenols, especially compounds such as anthocyanins, catechins and chlorogenic acid, effectively lowered and suppressed cholesterol levels.[23-25] One of the vegetable sources recognized for containing polyphenols is purple corn,[26,27] pigmented variety of *Zea mays* L. that has been cultivated for centuries in the Andean Region of South America,[28] in Peru from about 900 BC.[29] Polyphenols present in purple corn can help reduce inflammation caused by diabetes,[30] increase levels of endogenous antioxidant enzymes[31] and decrease elevated cholesterol levels.[32]

On the other hand, the current development of programs based on Bioinformatics and Cheminformatic algorithms, allow the *in silico* study of molecules with therapeutic potential; the programs and software involved make it possible to work with several molecules, reducing time, the number of tests on animals and the cost of research. In addition, they can be a complement to experimental studies such as *in vitro*, *ex vivo* and *in vivo*.[33,34] These computational methods have been widely used to help understand molecular mechanisms, as well as for the discovery and development of new active ingredients or drugs, and thus propose new treatment options for various diseases.[33,35] Molecular docking is a bioinformatic method that facilitates predicting the binding of drug-like molecules (ligands) to an active site of target proteins (target); the more stable, specific and favorable the ligand-target binding, the greater biological activity.[35,36] In Cheminformatics, there are a variety of *in silico* methods that predict the pharmacokinetic and physicochemical properties of molecules based on the chemical structure.[37,38]

Therefore, the *in silico* analysis of the polyphenols of *Zea mays* L. "purple corn", on the HMG-CoA reductase enzyme, will allow knowing the molecules with the best interaction prognosis, better pharmacokinetic and physicochemical properties, proposing new structures as potential alternatives for the treatment of hypercholesterolemia.

# METHOD

## Information search

A search was made for studies identifying polyphenolic metabolites of *Zea mays* L. "purple corn" in the Google Scholar, PubMed, ScienceDirect and Scopus databases, from September 30 to October 3, 2021, the year range of publication considered was from 2006 to the date indicated.

The following combination of terms and Boolean operators was used: "*Zea mays* L." AND "Polyphenols".

## Preparation of ligands

The ligands were the polyphenolic compounds that have been identified in *Zea mays* L. "purple corn". The 2D structures of the compounds were downloaded as SDF files from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The resulting compounds were entered into the Open Babel program.[39] With Open Babel, the 3D structures of the ligands were made, polar hydrogens and charges at physiological pH 7.4 were added; then the energy was minimized and optimized using a force field MMFF94.

Ligand structures were parameterized using the AutoDock Tools program[40] to add Gasteiger loads, identify rotary links, and save the resulting structure in the required format, pdbqt, for use with AutoDock Vina.[41]

As positive controls, known chemical structures with activity on HMG-CoA reductase were prepared, these were: Simvastatin and Atorvastatin. Both Simvastatin and Atorvastatin were worked in the same way as described for the ligands.

## Preparation of target

The crystal structure of HMG-CoA reductase was obtained from the Protein Data Bank (PDB) database with the entry code 1DQA;[42] bound ligands, ions, and water molecules were manually removed using the PyMOL Molecular Graphics System 2.4 program.[43]

For molecular docking, the structure of the selected protein was parameterized using the AutoDock Tools program,[40] polar hydrogens were added, nonpolar hydrogens were removed, and Kollman charges were added.

## Molecular docking "ligand-target interaction" and visualization

The docking protocol was performed using AutoDock Vina[41] based on the Lamarckian genetic algorithm and the default procedures for directed and rigid docking.

The amino acid residues Arginine 590, Lysine 691 and Aspartic Acid 690, were defined as constituents of the potential binding site;[44] proceeding to create a grid box in the identified catalytic site, whose coordinates were: Center_x = 129.809, Center_y = 125.784, Center_z = 186.557, Size_x = 18.0, Size_y = 17.2 and Size_z = 14.4; Each of the polyphenolic compounds identified in *Zea mays* L. variety "purple" were coupled to this site of the enzyme, determining the most probable and energetically favorable union conformations. The exhaustivity was 100 times for each ligand-protein. The resulting structures and binding docking poses were graphically inspected for interactions using the PyMOL Molecular Graphics System 2.4 programs and BIOVIA Discovery Studio.[43,45]

## Selection of the most active conformation

The conformations that presented the lowest affinity energy were selected, a more negative value means a greater affinity; the greater number of hydrogen bond type interactions, and total interactions.

## Physicochemical and pharmacokinetic analysis

The physicochemical analysis was performed using the SwissADME server[37] and the kinetic analysis of the polyphenolic compounds under study was performed on the pkCSM server,[38] for which the SMILES formats of each of the polyphenolic compounds were required, these were obtained from the PubChem database.

## Pharmacodynamic data analysis

**Gibbs free energy (ΔG°):** to specify whether a reaction is energetically favorable or not. If ΔG° < 0, all chemical reactions proceed spontaneously in the energetically favorable direction.[46] This value was obtained using Vina.

**Inhibition constant (Ki):** Necessary concentration of the substrate, metabolite, in the active site of the receptor, enzyme; to exert an inactivation or inhibition.[47]

$\Delta G° = -2.303RT(\log Ki)$

Where:

R = Gas constant expressed in terms of energy

T = Temperature in degrees Kelvin

Ki = Inhibition constant

**Ligand Efficiency (LE):** Provides an idea of the amount of binding energy per non-hydrogen atom[41].

$LE = \Delta G°/n$

Where:

n = number of non-hydrogen atoms.

**Number of interactions:** Number of attracting or repelling forces between molecules and atoms.[48]

## Physicochemical and pharmacokinetic data analysis

**Lipinski rule:** Associated with solubility and permeability, it establishes that if a compound violates two or more of the postulates, it will have poor absorption or permeation. The postulates are the following:[49]

There are more than 5 H-bond donors (expressed as the sum of OH and NH);

The molecular weight exceeds 500 g/mol;

Log P is greater than 5 (or MLog P is greater than 4.15);

There are more than 10 H-bond acceptors (expressed as the sum of Ns and Os).

**Log P:** Partition coefficient, represents the lipophilicity.[37]

**Log S:** Represents aqueous solubility.[37]

**Veber's Rule:** It suggests that compounds meeting only the following two criteria will have a high probability of good oral bioavailability. The two criteria are:[50]

10 or fewer rotatable bonds.

Polar surface area (PSA) ≤ 140 Å.$^2$

Both Lipinski's rule and Veber's rule predict that drug-like compounds would be orally bioavailable.

**ADME Parameters and Toxicity:** The pharmacokinetic profile of a chemical structure defines its absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties, stages that a drug goes through in the body to reach the target site in concentrations sufficient to produce the physiological effect.[38] Toxicity results from the combination of a direct toxic mechanism of the drug or its metabolite and an inflammatory or immunological mechanism.[51]

# RESULTS

An information search was carried out in the Google Scholar, PubMed, ScienceDirect and Scopus databases to recognize studies where polyphenolic compounds have been identified in ears and grains of purple corn. In total, 14 studies were recognized (Figure 1), with 22 polyphenolic compounds reported in the different studies, including Anthocyanins: cyanidin 3-O-glucoside, pelargonidin 3-O-glucoside, peonidin 3-O-glucoside, cyanidin 3-( 6"-malonylglucoside), pelargonidin 3-(6"-malonylglucoside), peonidin 3-(6"-malonylglucoside), cyanidin-3-rutinoside, cyanidin-3-sambubioside; Flavonols: quercetin 3-O-rutinoside, quercetin 3-O-glucoside, quercetin, kaempferol, and morin; Flavanone: naringenin; Phenolic acids: protocatechuic acid, vanillic acid, p-coumaric acid, caffeic acid, ferulic acid, 4-hydroxybenzoic acid, syringic acid and chlorogenic acid.[31,52–58]

# DISCUSSION

Two known molecules, Atorvastatin and Simvastatin, were chosen as controls against HMG-CoA reductase, to verify if the molecular

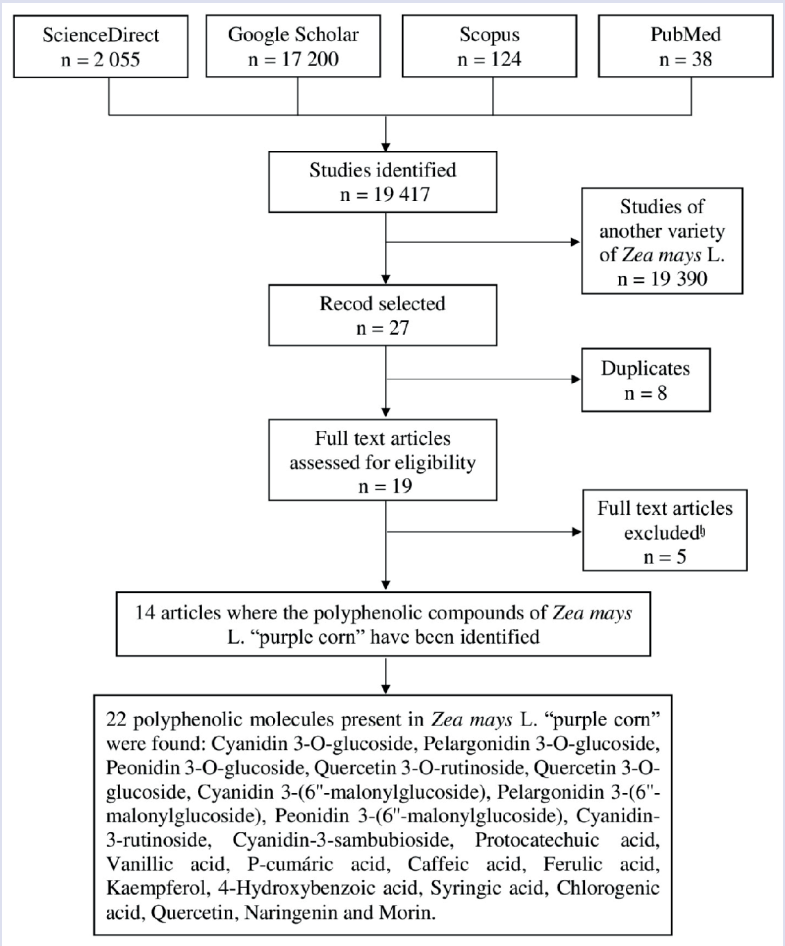


**Figure 1:** Search for information on the polyphenolic metabolites of *Zea mays* L. "purple corn", reported in databases. ♭ = *Zea mays* L. "purple corn" from Latin America, polyphenolic metabolites identified in ears and/or grains.

docking parameters were correct. The assay was made in the AutoDock Vina program. The result, Table 1, shows that these molecules do indeed interact with important amino acid residues found in the "*cis*-loop" of the protein, forming hydrogen bonds. Both molecules interact with LYS 692 but only Atorvastatin interacts with SER 684 and ASP 690. These data are corroborated by the study by Istvan, *et al* (2001), which indicates that several polar interactions are formed between the HMG rest of statins and residues SER 684, ASP 690, LYS 692. At the same time, both interact through hydrogen bonds with ARG 590 and LYS 735, finally, only Atorvastatin interacts with SER 565. Istvan, *et al* (2001) also mentions that the fluorophenyl group of statins like Atorvastatin has polar interactions with ARG 590 atoms, the terminal carboxylate residue like HMG forms polar interaction with LYS 735, and only in Atorvastatin and Rosuvastatin there are hydrogen bonds between SER 565 and a carbonyl oxygen atom (Atorvastatin). Many hydrogen bonds and ion pairs result in charge and shape complementarity between the protein and the rest similar to HMG of statins. Observing identical binding interactions between protein and natural substrate HMG.[59] The coupling scores presented, in this study, by Atorvastatin and Simvastatin were good with -9.4 kcal/mol and -7.9 kcal/mol, respectively.

The molecular docking of the twenty-two polyphenolic molecules reported in ears and grains of *Zea mays* L. "purple corn", the polyphenols type Anthocyanins cyanidin 3-O-glucoside, pelargonidin 3-O-glucoside, peonidin 3-O-glucoside, cyanidin 3 -(6''-malonylglucoside), Pelargonidin 3-(6''-malonylglucoside), Peonidin 3-(6''-malonylglucoside), Cyanidin-3-rutinoside, Cyanidin-3-sambubioside and two flavonols Quercetin 3-O-rutinoside and quercetin 3-O-glucoside, presented positive affinity energy so they were discarded from the study. These ligands do not interact with HMG-CoA reductase or that additional energy would be needed for the interaction to be favorable.[46] However, these molecules could interact with another class of target proteins involved in other diseases, for example, Type II Diabetes Mellitus, as reported by Damián-Medina K, *et al* (2020), who point out that anthocyanidins such as delphinidin 3- glucoside, cyanidin 3-glucoside, and petunidin 3-glucoside and a Flavonol as the catechin that exhibited the best affinity energy and formed polar interactions with important amino acids of 11 β-hydroxysteroid dehydrogenase 1, Glutamine fructose-6-phosphate aminotransferase, Protein tyrosine phosphatases, Peroxisome proliferator-activated gamma receptor, can refer compounds with novel antidiabetic molecular pathways.[60]

Flavonols quercetin, kaempferol, morin; Flavanone naringenin, and the phenolic acids protocatechuic acid, vanillic acid, p-coumaric acid, caffeic acid, ferulic acid, 4-hydroxybenzoic acid, syringic acid and chlorogenic acid, presented lower affinity energy varying between -6.8 kcal/mol and -3.4 kcal/mol, Table 02. Mainly the highest affinity for HMG-CoA reductase belongs to protocatechuic acid (-6.8 kcal/mol), caffeic acid (-6.7 kcal/mol), vanillic acid (-6.4 kcal/mol), ferulic acid (-6.2 kcal/mol), p-coumaric acid (-6.0 kcal/mol) and 4-hydroxybenzoic acid (-6.0 kcal/mol). The interactions through hydrogen bonds of these six molecules (Figure 02) show how polyphenols could act on HMG-CoA reductase. Caffeic, ferulic and p-coumaric acids form hydrogen bonds with ASN 658 and protocatechuic, vanillic, and 4-hydroxybenzoic acids with ARG 590 and GLU 559. ASN 658, ARG 590, and GLU 559 are amino acids of HMG-CoA reductase where the Nicotinamide portion of $NADP^+$ binds,[42] therefore, they can affect $NADP^+$ binding. Islam B, *et al* (2015), found something similar, the twelve polyphenols he tested could bind to the same region as the Adenine ring of $NADP^+$, with this he concluded that they could act as inhibitors of $NADP^+$ binding.[44] In addition, the binding of NADP(H) causes a conformational change that results in the order of the C-terminal residues, closing the active site and orienting HIS 866 within the H bond distance of the CoA thiol.[10] On the other hand, the polar union of protocatechuic, vanillic, and 4-hydroxybenzoic acids to GLU 559 could prevent it from donating protons to mevaldehyde by preventing catalysis.[10] In general, the twelve polyphenols interact via hydrogen bonds with important amino acids, LYS 691 and LYS 692, of HMG-CoA reductase, as described above (Figure 2).

Molecular Docking considers two additional important aspects, the inhibition constant (Ki) and the ligand efficiency (LE). In Table 2, it is shown that the Ki for the six molecules with the lowest affinity energy is small, this is important because it not only indicates that these molecules can bind HMG-CoA reductase at low concentrations but also indicates that the potency of the inhibitors is favorable. On the other hand, LE is the ability of the ligand to produce a biological response when bound to the target receptor, and the quantitative magnitude of this response; for the six molecules the values are between -0.44 and -0.62 kcal/mol/non-hydrogen atoms. Good to excellent LE is less than 0.4, and changes as the drug discovery process progresses, being -0.41 for Hits, -0.39 for leading compounds, and -0.42 kcal for Phase II compounds/mol/non-hydrogen atoms.[41] Therefore, the values reported in the present study are values that are within the acceptable range to consider these compounds as molecules with potential pharmacological properties.

Although ΔG, Ki and LE data are essential to initiate a study on certain molecules, other properties such as physicochemical and pharmacokinetic properties are important in the selection of the best drug candidates.[41,61] Table 3 reveals that the structures of protocatechuic acid, vanillic acid, p-coumaric acid, caffeic acid, ferulic acid, kaempferol, 4-hydroxybenzoic acid, syringic acid, quercetin, naringenin and morin do not violate any of the Lipinski rules. The Log P presented by these eleven structures is within the optimal range of lipophilicity to achieve good bioavailability, Log P between 0 and 3. Log P is important because it contributes to the solubility and permeability across membranes of drug candidates.[62] Chlorogenic acid violates a Lipinski rule as this molecule has six H-bond donors, a greater number of hydrogen donors would lead to lower permeability,[52] this is also reflected in the fact that it presents a Log P -0.38. Regarding the Veber criteria, the eleven structures mentioned above meet them, unlike chlorogenic acid, which does not meet one of them, its polar surface area is 164.75 $Å^2$ or the sum of donors and acceptors of hydrogen bonds is 15 (higher than the stipulated which is 12 or less); would again have a low permeability.[50] Here it should be noted that when the polar surface area is < 70 $Å^2$ there is probably activity at the level of the central nervous system (CNS) by the molecules,[63] in this case, vanillic, p-coumaric, ferulic and 4-hydroxybenzoic acids have a polar surface area < 70 $Å^2$. About the solubility, Log S, the twelve molecules presented good and intermediate solubility (naringenin Log S -3.49). Solubility is a fundamental property for absorption, likewise, having a soluble molecule greatly facilitates many drug development activities, mainly manipulation and formulation.[61,63] However, it should be noted that work could be done on formulations to improve lipophilicity and hydrophilicity to have potential drug candidates with good bioavailability.[64]

As the solubility property of the twelve polyphenolic molecules, gastrointestinal absorption was predicted (Table 4), evidenced as favorable since it exceeds 30%. This value could be affected if they were substrates of P-gp, an efflux transporter that affects absorption and distribution, in this case, kaempferol, syringic acid, chlorogenic acid, quercetin, naringenin and morin are, something favorable is that none is an inhibitor of the transport of P-gp I and P-gp II, which would avoid interactions with the substances that are administered concomitantly and that are substrates.[38,63] In addition, protocatechuic acid, vanillic acid, p-coumaric acid, caffeic acid, ferulic acid and 4-hydroxybenzoic acid have an unfavorable volume of distribution (< -0.15), however, the fact that they are not substrates of P-gp counteracts it, the one which has greater distribution problems is syringic acid not only because it is a substrate of P-gp but also because it has a distribution volume of -1.443.[38]

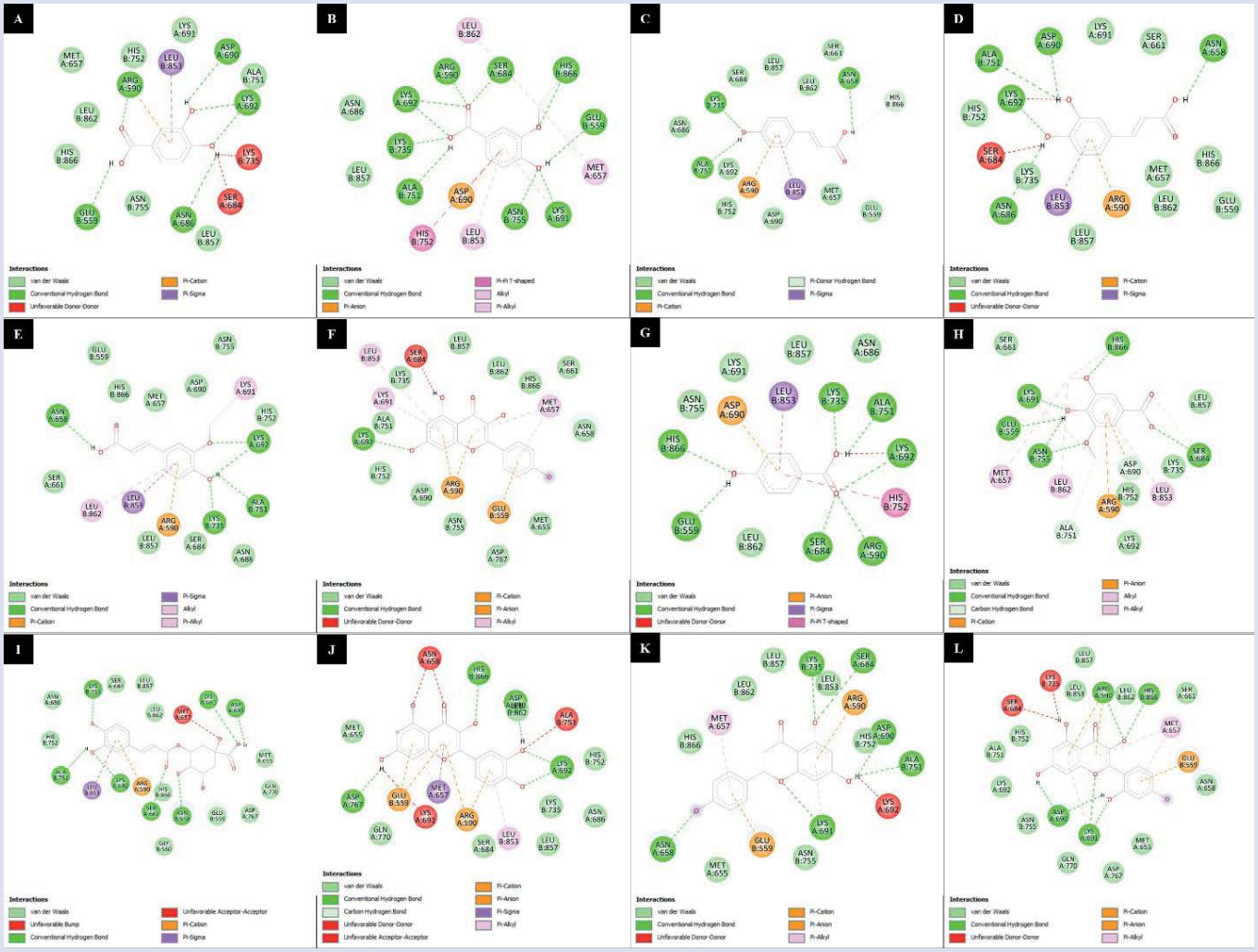

**Figure 2:** Interaction of polyphenolic compounds from *Zea mays* L. "purple corn" against HMG-CoA reductase in 2D format. A. Protocatechuic acid; B. vanillic acid; C. p-coumaric acid; D. caffeic acid; E. ferulic acid; F. kaempferol; G. 4-hydroxybenzoic acid; H. Syringic acid; I. Chlorogenic acid; J. Quercetin; K. Naringenin and L. Morin.

**Table 1: Affinity Energy and the number of interactions of known inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase). Data was obtained through the PubChem database and the BIOVIA Discovery Studio program. ΔG°= Gibbs free energy; Ki= Inhibition Constant; LE= Ligand Efficiency.**

| Molecule | Formula | Affinity Energy (ΔG°) kcal/mol | Ki (M) | LE kcal/mol/non-hydrogen atoms | Number of Total Interactions | Total Binding Amino Acids | Number of Hydrogen Bonds | Linking Amino Acids with Hydrogen Bonds |
|---|---|---|---|---|---|---|---|---|
| Atorvastatin | $C_{33}H_{35}FN_2O_5$ | -9.4 | $1.27x10^{-7}$ | -0.23 | 16 | SER 565, ALA 564, CYS 561, ALA 856, VAL 683, ARG 590 (2), LYS 735, SER 684, LYS 692, ASP 690, ASN 755, GLU 559, LEU 853 (3) | 7 | ARG 590 (2), LYS 692, LYS 735, SER 565, SER 684, ASP 690 |
| Simvastatin | $C_{25}H_{38}O_5$ | -7.9 | $1.60x10^{-6}$ | -0.26 | 13 | LEU 853, LEU 562, HIS 752, ASP 690, LYS 692 (2), LYS 735, ALA 751, VAL 683, LEU 857, ARG 590 (2), LYS 691 | 6 | ARG 590 (2), LYS 692 (2), LYS 735, ALA 751 |

**Table 2: Affinity Energy and the number of interactions of the polyphenolic compounds of *Zea mays* L. "purple corn", by the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase). Data was obtained through the PubChem database and the BIOVIA Discovery Studio program. ΔG°= Gibbs free energy; Ki= Inhibition Constant; LE= Ligand Efficiency.**

| Molecule | Formula | Affinity Energy (ΔG°) kcal/mol | Ki (M) | LE kcal/mol/ non-hydrogen atoms | Number of Total Interactions | Total Binding Amino Acids | Number of Hydrogen Bonds | Linking Amino Acids with Hydrogen Bonds |
|---|---|---|---|---|---|---|---|---|
| Protocatechuic acid | $C_7H_6O_4$ | -6.8 | $1.03x10^{-5}$ | -0.62 | 10 | LEU 853, ARG 590 (2), GLU 559, ASN 686, SER 684, LYS 735, LYS 692 (2), ASP 690 | 6 | ARG 590, GLU 559, ASN 686, LYS 692 (2), ASP 690 |
| Vanillic acid | $C_8H_8O_4$ | -6.4 | $2.02x10^{-5}$ | -0.53 | 17 | LEU 862, SER 684, ARG 590, LYS 692 (2), LYS 735, ALA 751, ASP 690, HIS 752, LEU 853, ASN 755, LYS 691 (2), MET 657, GLU 559, HIS 866 (2) | 10 | SER 684, ARG 590, LYS 692 (2), LYS 735, ALA 751, ASN 755, LYS 691, GLU 559, HIS 866 |
| p-coumaric acid | $C_9H_8O_3$ | -6.0 | $3.97x10^{-5}$ | -0.50 | 6 | ASN 658, LYS 735, ALA 751, ARG 690, LEU 853, HIS 866 | 3 | ASN 658, LYS 735, ALA 751 |
| Caffeic acid | $C_9H_8O_4$ | -6.7 | $1.22x10^{-5}$ | -0.52 | 9 | ASP 690, ALA 751, LYS 692 (2), SER 684, ASN 686, LEU 853, ARG 590, ASN 658 | 5 | ASP 690, ALA 751, LYS 692, ASN 686, ASN 658 |
| Ferulic acid | $C_{10}H_{10}O_4$ | -6.2 | $2.83x10^{-5}$ | -0.44 | 9 | ASN 658, LYS 691, LYS 692 (2), ALA 751, LYS 735, LEU 853, ARG 590, LEU 862 | 5 | ASN 658, LYS 692 (2), ALA 751, LYS 735 |
| Kaempferol | $C_{15}H_{10}O_6$ | -4.8 | $3.01x10^{-4}$ | -0.23 | 9 | SER 684, LEU 853, LYS 691, LYS 692, ARG 590 (2), GLU 559, MET 657 (2) | 1 | LYS 692 |
| 4-hydroxybenzoic acid | $C_7H_6O_3$ | -6.0 | $3.97x10^{-5}$ | -0.6 | 11 | ASP 690, HIS 866, GLU 559, SER 684, ARG 590, HIS 752, LYS 692 (2), ALA 751, LYS 735, LEU 853 | 7 | LYS 735, HIS 866, GLU 559, SER 684, ARG 590, LYS 692, ALA 751 |
| Syringic acid | $C_9H_{10}O_5$ | -5.8 | $5.56x10^{-5}$ | -0.41 | 16 | HIS 866 (2), LYS 691 (2), GLU 559, MET 657, ASN 755 (2), LEU 862, ALA 751, ARG 590, ASP 690 (2), LEU 853, SER 684 (2) | 6 | HIS 866, LYS 691, GLU 559, ASN 755 (2), SER 684 |
| Chlorogenic acid | $C_{16}H_{18}O_9$ | -3.4 | $3.21x10^{-3}$ | -0.14 | 10 | LYS 735, ALA 751, LEU 853, LYS 692, ARG 590, SER 661, ASN 658, ASP 690, LYS 691, MET 657 | 7 | LYS 735, ALA 751, LYS 692, SER 661, ASN 658, ASP 690, LYS 691 |
| Quercetin | $C_{15}H_{10}O_7$ | -4.7 | $3.57x10^{-4}$ | -0.21 | 18 | ASN 658 (2), HIS 866 (2), ASP 690, ALA 751, LYS 692 (2), LEU 853, ARG 590 (2), MET 657 (2), LYS 691, GLU 559 (2), ASP 767, MET 655 | 5 | HIS 866, ASP 690, LYS 692 (2), ASP 767 |
| Naringenin | $C_{15}H_{12}O_5$ | -4.9 | $2.54x10^{-4}$ | -0.25 | 11 | LYS 735, SER 684, ARG 590, ASP 690, ALA 751, LYS 692, LYS 691 (2), GLU 559, ASN, 658, MET 657 | 6 | LYS 735, SER 684, ASP 690, ALA 751, LYS 691, ASN 658 |
| Morin | $C_{15}H_{10}O_7$ | -5.2 | $1.53x10^{-4}$ | -0.24 | 14 | LYS 735, SER 684, ASP 690 (2), LYS 691 (3), GLU 559, MET 657 (2), HIS 866, ARG 590 (3) | 6 | ARG 590, HIS 866, LYS 691 (2), ASP 690 (2) |

**Table 3: Physicochemical characteristics of the polyphenolic compounds of interest from *Zea mays* L. "purple corn", which have an affinity for the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase). Data was obtained through the SwissADME server. TPSA=Topological Polar Surface Area; *= Data obtained through the ESOL algorithm.**

| Molecule | Molecular weight (g/mol) | Rotatable bonds | Hydrogen Bond Acceptors | Hydrogen Bond Donors | TPSA (Å²) | Log P (Lipophilicity) | Log S* (aqueous solubility) | Log S* (Interpretation) | "Compliance with the rules, violations" | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Lipinski | Veber |
| Protocatechuic acid | 154.12 | 1 | 4 | 3 | 77.76 | 0.65 | -1.86 | Very soluble | Yes, 0 | Yes |
| Vanillic acid | 168.15 | 2 | 4 | 2 | 66.76 | 1.08 | -2.02 | Soluble | Yes, 0 | Yes |
| p-coumaric acid | 164.16 | 2 | 3 | 2 | 57.53 | 1.26 | -2.02 | Soluble | Yes, 0 | Yes |
| Caffeic acid | 180.16 | 2 | 4 | 3 | 77.76 | 0.93 | -1.89 | Very soluble | Yes, 0 | Yes |
| Ferulic acid | 194.18 | 3 | 4 | 2 | 66.76 | 1.36 | -2.11 | Soluble | Yes, 0 | Yes |
| Kaempferol | 286.24 | 1 | 6 | 4 | 111.13 | 1.58 | -3.31 | Soluble | Yes, 0 | Yes |
| 4-hydroxybenzoic acid | 138.12 | 1 | 3 | 2 | 57.53 | 1.05 | -2.07 | Soluble | Yes, 0 | Yes |
| Syringic acid | 198.17 | 3 | 5 | 2 | 75.99 | 0.99 | -1.84 | Very soluble | Yes, 0 | Yes |
| Chlorogenic acid | 354.31 | 5 | 9 | 6 | 164.75 | -0.38 | -1.62 | Very soluble | Yes, 1 | No, 1 |
| Quercetin | 302.24 | 1 | 7 | 5 | 131.36 | 1.23 | -3.16 | Soluble | Yes, 0 | Yes |
| Naringenin | 272.25 | 1 | 5 | 3 | 86.99 | 1.84 | -3.49 | Soluble | Yes, 0 | Yes |
| Morin | 302.24 | 1 | 7 | 5 | 131.36 | 1.2 | -3.16 | Soluble | Yes, 0 | Yes |

**Table 4: Pharmacokinetic properties of the polyphenolic compounds of interest from *Zea mays* L. "purple corn", which have an affinity for the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase). Data was obtained through the pkCSM server. S = Substrate; Inh. = Inhibitor; OCT2 = Organic Cation Transporter 2.**

| Molecule | Absorption (%) | P-gp (Yes/No) | | | VDss (LogL/kg) | BBB (Log BB) | CYP (Yes/No) | | | | | | | Total Clearance (Log ml/min/kg) | S OCT2 renal (Yes/No) | AMES test (Yes/No) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | S P-gp | Inh. P-gp I | Inh. P-gp II | | | S CYP 2D6 | S CYP 3A4 | Inh. CYP 1A2 | Inh. CYP 2C19 | Inh. CYP 2C9 | Inh. CYP 2D6 | Inh. CYP 3A4 | | | |
| Protocatechuic acid | 71.174 | No | No | No | -1.298 | -0.683 | No | No | No | No | No | No | No | 0.551 | No | No |
| Vanillic acid | 78.152 | No | No | No | -1.739 | -0.38 | No | No | No | No | No | No | No | 0.628 | No | No |
| p-coumaric acid | 93.494 | No | No | No | -1.151 | -0.225 | No | No | No | No | No | No | No | 0.662 | No | No |
| Caffeic acid | 69.407 | No | No | No | -1.098 | -0.647 | No | No | No | No | No | No | No | 0.508 | No | No |
| Ferulic acid | 93.685 | No | No | No | -1.367 | -0.239 | No | No | No | No | No | No | No | 0.623 | No | No |
| Kaempferol | 74.29 | Yes | No | No | 1.274 | -0.939 | No | No | Yes | No | No | No | No | 0.477 | No | No |
| 4-hydroxybenzoic acid | 83.961 | No | No | No | -1.557 | -0.334 | No | No | No | No | No | No | No | 0.593 | No | No |
| Syringic acid | 73.076 | Yes | No | No | -1.443 | -0.191 | No | No | No | No | No | No | No | 0.646 | No | No |
| Chlorogenic acid | 36.377 | Yes | No | No | 0.581 | -1.407 | No | No | No | No | No | No | No | 0.307 | No | No |
| Quercetin | 77.207 | Yes | No | No | 1.559 | -1.098 | No | No | Yes | No | No | No | No | 0.407 | No | No |
| Naringenin | 91.31 | Yes | No | No | -0.015 | -0.578 | No | No | Yes | No | No | No | No | 0.06 | No | No |
| Morin | 75.408 | Yes | No | No | 1.229 | -1.18 | No | No | Yes | No | No | No | No | 0.486 | No | No |
| Atorvastatin | 59.861 | Yes | No | No | -1.918 | -1.162 | No | Yes | No | No | Yes | No | No | 0.437 | No | No |
| Simvastatin | 94.339 | Yes | Yes | Yes | 0.2 | -0.26 | No | Yes | No | No | No | No | Yes | 0.827 | Yes | No |

The CNS is protected by the blood-brain barrier (BBB), the ability of a drug to cross the BBB is an important parameter to consider. The polyphenols presented (Table 4) do not easily cross the blood-brain barrier because they have a logBB <0.3, or they distribute poorly chlorogenic acid logBB -1.407, quercetin logBB -1.098 and morin logBB -1.180, clearly, they would have lesser effects secondary. Additionally, none is a substrate and inhibitor of cytochrome P450 (CYP450) enzymes, specifically CYP2D6 and CYP3A4, the two main isoforms responsible for drug metabolism.[61] The results were found to correlate with the study by Lin, *et al* (2015), where it was found that five of the ten structures analyzed *in silico* with DS 3.5 ADMET Descriptor have polyphenolic residues and which did not show CYP2D6 inhibition.[65] This analysis is important because the interactions between drugs-drugs, drugs-other substances, and the presence of adverse effects occur when one is a substrate or inhibitor of the same CYP isoforms.[66]

Excretion is another important parameter, the total clearance of polyphenols is low (Table 4) but when compared to controls, the values are close, with the exception of naringenin, which has the lowest value of 0.06 log ml/min/kg, the fact that they have a low clearance does not mean that there will be a greater permanence of the drug in the body, remember that these values may vary in the different stages of drug discovery and the route of administration.[67] The renal organic cation transporter 2 (OCT2) plays an essential role in the renal clearance of drugs and endogenous compounds. Polyphenols are not OCT2 substrates, OCT2 substrates have the potential for adverse interactions with co-administered OCT2 inhibitors.

No molecule reports mutagenicity with the algorithm of the AMES test. The AMES test is a widely used method to assess the mutagenic potential of compounds or substances using bacteria. A positive test indicates that the compound is mutagenic and therefore may be a potential carcinogen[38].

Based on the results of this study, knowing the prediction of molecular docking, the physicochemical properties, and the pharmacokinetic properties of natural molecules by *Zea mays* L. can help in the process of optimization and selection of new drug candidates.

## CONCLUSIONS

The *in silico* analysis shows that polyphenols of the flavonol, flavanone, and phenolic acid types present a greater interaction with HMG-CoA reductase. Protocatechuic acid, vanillic acid, p-coumaric acid, caffeic acid, ferulic acid and 4-hydroxybenzoic acid presented lower energy, better physicochemical and pharmacokinetic profiles, so these compounds can serve as the basis for the creation of new molecules for the treatment of hypercholesterolemia.

## CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

## CONTRIBUTIONS OF AUTHORS

AMHR and JALG prepared the first draft. CRSC and WASG collected information about the plant and target. CDGS and VEVLT did parameters for docking. AMHR and JALG did pharmacokinetics parameters.

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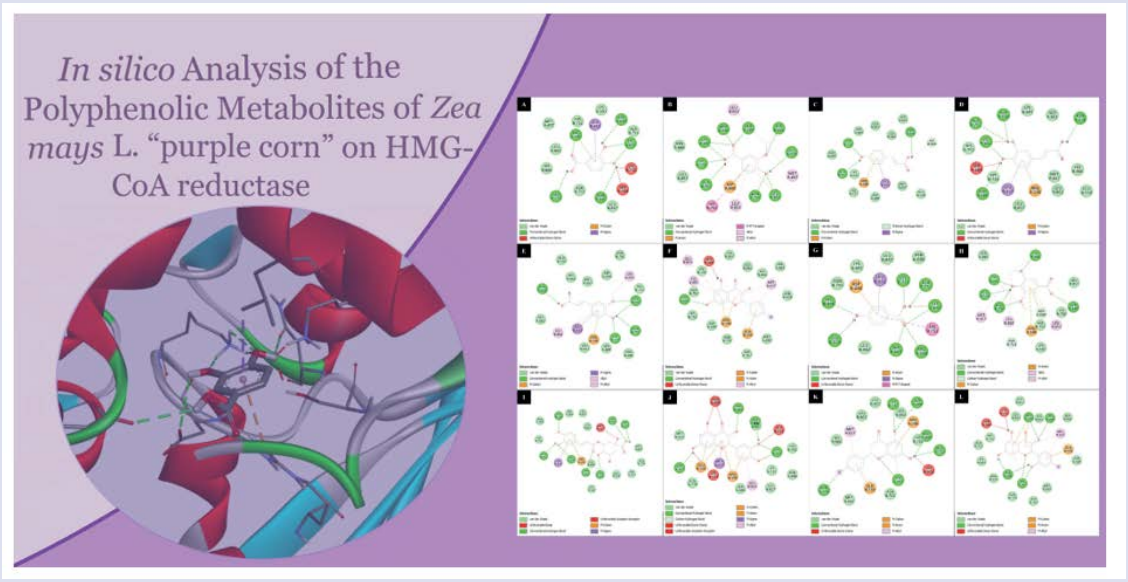
## GRAPHICAL ABSTRACT



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