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# Quantum Chemical Computations, Molecular Docking, and ADMET Predictions of Cynarin

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**Abstract**

Cynarin (1,3-o-dicaffeoylquinic acid) is one of the biologically active functional food components which is the most well-known caffeoylquinic acid derivative found in artichoke. The structural and electronic features of cynarin compound were investigated theoretically using density functional theory (DFT). The highest occupied molecular orbital (HOMO) and the least occupied molecular orbital (LUMO) are the most significant orbitals in molecules, these orbitals are quite helpful to know several molecular features such as the chemical reactivity, kinetic stability, electronegativity, chemical potential, electrophilicity index, chemical hardness and softness and electronegativity. Molecular orbital analysis HOMO-LUMO was used to explore the stability of the molecule. Moreover, physicochemical properties, drug-likeness, and toxicity estimation of the cynarin compound were appraised owing to ADMET (including absorption, distribution, metabolism, excretion, and toxicology). Molecular docking was carried out to examine the biological activity of the cynarin compound. 5A19, a liver cancer biomarker, is human methionine adenosyl-transferase enzymes (MATs). Cynarin-MAT enzyme binding energy value was calculated as -7.9 kcal/mol. As a result, this in silico study confirmed that cynarin has the potential to be a drug by revealing its protective effect against liver diseases.

## 1. Introduction

Studies conducted in different disease groups have reported that a diet rich in vegetables and fruits has a significant protective potential effect against the risk of illnesses such as hypertension, diabetes, cardiovascular diseases and cancer [1]. Artichoke (Cynara Scolymus), a vegetable known and consumed for centuries, has been accepted as a potential phytotherapeutic agent for various conditions such as cardiovascular, hepatic, liver and gastric diseases [2], [3]. It is known that artichoke leaf extract contains saponins, caffeic acid derivatives, flavonoid derivatives, fatty acids and various polyphenolic components [4], [5]. It is stated that many phytochemical substances in the composition of artichoke can inhibit cancer-related angiogenesis by preventing the secretion of cancer agents. At the same time, in artichoke; It has been reported that there are many powerful polyphenol-type antioxidants that may contribute to the protection and therapy of prostate cancer, breast cancer, and leukemia [6]. The composition of artichoke contains basic phenolic substances such as cinnamic acids, chlorogenic acid, cynarin, 1,5-o-dicaffeoylquinic acid, 3,4-o-dicaffeoylquinic acid, and basic flavonoid substances such as apigenin and luteolin [7], [8]. Cynarin is one of the active biological chemicals found in artichoke and is found in high levels in the leaves of the plant. Therefore, most of the natural drugs acquired from this plants are made ready from the leaves. Cynarin is a caffeolquinic acid and is largely concentrated in the leaves [9]. Cynarin is a phenolic acid compound that is liable for its cholagogue and choleretic features. Due to these functions, it is quite significant for liver health. In addition to its liver-protective effect,

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cynarin has been observed to inhibits cholesterol biosynthesis and provides low-density lipoprotein (LDL) oxidation [10]. The chemical structure of cynarin is shown in Figure 1.

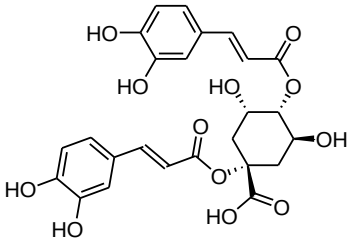

**Figure 1.** Chemical structure of cynarin.

MATs catalyze the formation of S-adenosylmethionine, the major biological methyl donor, and these enzymes play a significant act in the protection of life. Their dysregulation is significantly linked to liver and colon cancers [11].

In computer-aided drug design (CADD) studies, theoretical computational methods are used to simulate drug-receptor interactions. CADD studies enable the design and accurate evaluation of molecules that have the potential to become drugs in the discovery phase [12]. Thanks to computational approaches, the logic of designing natural pharmacologically active molecules that can target proteins of interest by using bioactive natural compounds of plant origin, such as cynarin, for potential drug development has improved significantly.

Many studies have been conducted by researchers for cynarin, which has a wide range of biological activities: Some of these include janus kinase (JAK) inhibition [13], matrix metalloproteinase-9 (MMP-9) inhibition [14], spike (S) glycoprotein inhibition [15], inhibition on human colon cancer HT-29 and RKO. Cells [16], effects on inflammatory response in EA.hy926 human endothelial cells [17], and effects on amelanotic melanoma C32 and renal adenocarcinoma ACHN [18] have been reported.

The main objective of this study is to review the available knowledge regarding the specifically related to liver and colon cancer prevention potency of the cynarin, and to summarise its mechanism of action. In this study, it was aimed to examine the inhibition of cynarin with MATs using in silico methods. Further, ADMET analysis of cynarin natural compound was done. Molecular reactivity analysis (HOMO-LUMO) of the cynarin compound and other electronic parameters acquired from this analysis, molecular electrostatic potential (MEP) analysis, and geometry optimization were computed with the DFT/B3LYP theory and 6-311G* basis set, and the results were displayed.

## 2. Material and Method

### 2.1. Computational methods

Quantum mechanical computations were carried out for the compound cynarin with DFT using B3LYP standard of principle and 6-311G* as the basis set in Spartan '10 software [19]. The acquired outcomes were visualized by the same program. SwissADME (http://www.swissadme.ch/) online tool was used to predict drug-like attributes, and ADMETlab 2.0 (https://admetmesh.scbdd.com/) and Pro Tox-II (https://tox-new.charite.de/protox_II/) online tools were used to predict ADMET properties such as druggability and toxicity risk. AutoDock Vina (in UCSF [University of California, San Francisco] Chimera) [20] is one of the most right programs used in docking analysis. Molecular docking analysis was realized to estimate the binding locations, using AutoDock Vina in UCSF Chimera software (version 1.16) [21], and the crystal structure of target was provided from the protein data bank (https://www.rcsb.org) in the pdb format. The target protein contains human MATs (PDB ID: 5A19). The chemical structure of cynarin compound was received at 3D SDF format from the PubChem site (https://pubchem.ncbi.nlm.nih.gov/).

## 3. Results and Discussion

### 3.1. Computational structural analysis

Frontier orbitals, that is, HOMO and LUMO, are display an important role to estimate the chemical reactivity and stability of molecules [22]. The energy range (ΔE) of these orbitals is a useful method for determining chemical reactivity, kinetic stability, and predicting the softness (σ) and hardness (η) of a molecule. It is also used to predict some the electronic structure-based descriptor such as electronegativity (χ), chemical potential (μ), and electrophilicity index (ω). The HOMO and LUMO representations for the cynarin compound were given in Figure 2. The HOMO, LUMO, and HOMO-LUMO gap energies for cynarin are -5.6382, -1.7769, and 3.8613 eV, respectively, as display in Table 1.

**Table 1.** The HOMO, LUMO energies and ΔE energy ranges of cynarin compound in the gaseous media

| | Cynarin | | | |
|---|---|---|---|---|
| Medium | $E_{HOMO(a.u.)}$ | $E_{LUMO(a.u.)}$ | $\Delta E_{(a.u.)}$ | $\Delta E_{(eV)}$ |
| gaseous | -0.2072 | -0.0653 | 0.1419 | 3.8613 |

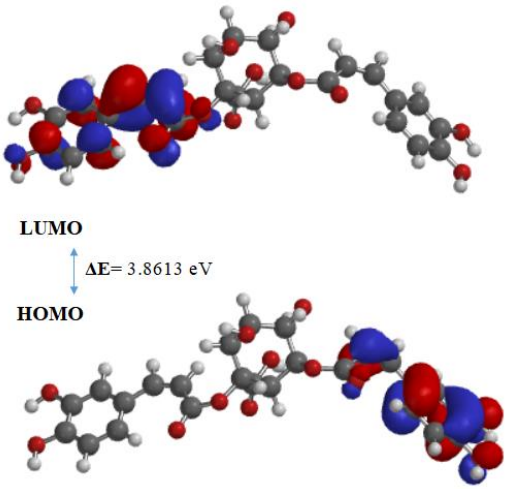


**Figure 2.** HOMO and LUMO energy plots of cynarin compound.

Global chemical reactivity descriptors were calculated from the energies of these orbitals. The ionization potential ($I=-E_{HOMO}$) and electron affinity ($A=-E_{LUMO}$) related immediately to the energies of the HOMO and LUMO orbitals and are computed to be -5.6382 and -1.7769 eV for cynarin, respectively. Hardness ($\eta=(I-A)/2$) and softness ($S=1/2\eta$) provide important information about the reactive behavior of a molecule. Compounds with high chemical reactivity and low stability are described as soft, while hardness is defined as the opposite of softness. The computed electronic structure descriptors of the cynarin compound were given in Table 2. The computed results of chemical hardness and softness for cynarin are 1.9307 eV and 0.2589 eV, respectively. Electronegativity ($\chi=(I+A)/2$), is a relative measure of an atom's ability to attract electrons when creating a chemical bond. It was computed to be 3.7075 eV for cynarin. The electrophilicity index ($\omega=\mu^2/2\eta$) is a descriptor proposed by Parr and Yang and indicates the quantitative expression of the global electrophilic strength of a molecule [23]. The calculated value of the electrophilicity index for cynarin is 3.5597 eV. It was calculated to be -3.7075 eV the chemical potential ($\mu=-(I+A)/2$) of cynarin. A substance with a low chemical potential also has a low effectiveness against other substances [24]. The maximum charge transfer ΔNmax of the cynarin compound is 1.9202 eV.

HOMO-LUMO energy gap (ΔE) values major than 1.5 eV express that the molecules are thermodynamically steady and resistant [25]. According to the calculation result, the energy difference of 3.8613 eV showed that the cynarin was thermodynamically steady. The high HOMO-LUMO energy difference of the cynarin compound makes it harder and less chemically reactive. There is low electron flow due to the high energy difference. This cause the cynarin compound to be low reactive.

**Table 2.** The calculated electronic structure parameters of the cynarin compound

| Parameters | Value (eV) |
|---|---|
| $E_{HOMO}$ | -5.6382 |
| $E_{LUMO}$ | -1.7769 |
| $\Delta E = E_{LUMO}-E_{HOMO}$ | 3.8613 |
| $I = -E_{HOMO}$ | 5.6382 |
| $A = -E_{LUMO}$) | 1.7769 |
| $\eta = (I-A)/2$ | 1.9307 |
| $S = 1/2\eta$ | 0.2589 |
| $\chi = (I+A)/2$ | 3.7075 |
| $\mu = -(I+A)/2$ | -3.7075 |
| $\omega = \mu^2 /2\eta$ | 3.5597 |
| $\Delta nmax = -\mu/\eta$ | 1.9202 |

Molecular electrostatic potential maps (MEPs) provide a three-dimensional view of the charge distribution within a molecule [26]. The electrostatic potential rises in the order of red < orange < yellow < green < blue [27]. While the most negative potential (the region with high electron density) is shown in red; the color blue is used to show the most positive potential (the region where partial positive charges are located). The yellow colour represents regions with fewer electrons than the other regions and the green colour represents neutral regions with zero potential. Positive regions indicate nucleophilic reactivity and negative regions indicate electrophilic reactivity. Interpretation of MEP maps assumes a vital role in the determination of active sites in the chemical binding of the molecule and the synthesis of new chemicals [28].

In order to understand the charge distribution of the cynarin compound, the calculation results made with the B3LYP/6-311G* level were visualized in three dimensions using the Spartan '10 program. These MEP surface maps obtained for the cynarin compound are shown in Figure 3. As in Figure 3, it can be seen that the highest nucleophilic potential is found on the hydrogen atoms of the –COOH groups, and the highest electrophilic potential is situated on oxygen atoms of hydroxyl groups.

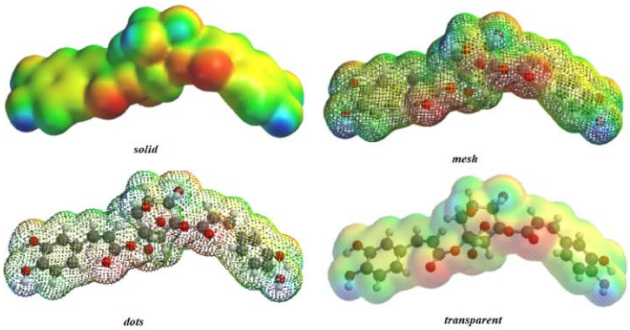


**Figure 3.** Showing the molecular electrostatic potential maps of the cynarin.

### 3.2. Molecular docking studies and ADMET properties

Binding patterns and affinity interactions between small molecules and binding pockets of proteins was able to be examined owing to molecular docking interaction. Cynarin was docked with protein target in liver cancer, specifically the receptors of MATs (PDB ID: 5A19).

There is more than one solved structure information defined for the MATs enzyme in the protein database. The enzyme (PDB code: 5A19) obtained by x-ray crystallization method from the protein data bank (www.rscb.org) was randomly selected as the MAT enzyme. The protein-ligand complex was selected considering the best obtained pose according to binding energy value. The binding free energy of cynarin compound in case of is -7.9 kcal/mol. The good energy value of the docking result for the cynarin compound is given in Table 3. Receptor-ligand interaction to three-dimensional (3D) was visualized using the Biovia Discovery Studio Visualizer program [29]. The receptor was prepared by removing water molecules, ions, and some small molecules for docking analysis.

**Table 3.** Molecular docking results of the cynarin PDB ID: 5A19

| Molecule Name | Binding Energy (kcal/mol) | RMSD | Amino Acid Residues |
|---|---|---|---|
| Cynarin | -7.9 | 1.824 | GLU122, VAL129 LYS133, ARG347, TYR351, GLY355, ARG356 |

The interactions of the conventional hydrogen bond (GLU122, GLY355, ARG347, and ARG356), π-alkyl (VAL129 and LYS133), and π -π T-shaped (TYR351) were observed on cynarin compound with adenosyl-transferase enzyme. Interaction types such as, conventional hydrogen bond, Van der Waals forces, π-alkyl bonds, and π -π T-shaped, also encountered in docking analyses are significant for the structural integrity of many biological molecules with the inclusion of proteins and DNA, and are also very important for drug-receptor interactions.

As a result of the docking process between 5A19 and cynarin, the best binding conformation with a binding energy of -7.9 kcal/mol obtained between 5A19 and the ligand was shown in Figure 4. The binding energy value found in the molecular docking study is a pointer that the docking process is successful.

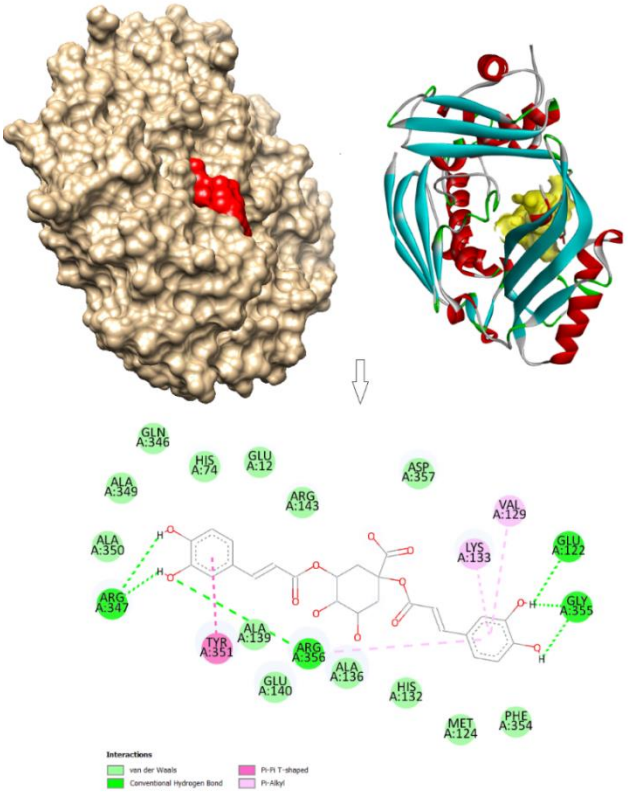


**Figure 4.** The three-dimensional interaction, the 2D structure, and the best binding pose of cynarin compound.

The drug-like features of the cynarin compound were calculated according to Lipinski's five criteria with the relief of the SwissADME web tool, and the relevant parameters were shown in Table 4.

**Table 4.** Estimated physicochemical properties of the cynarin according to the SwissADME program

| | SwissADME Physicochemical Properties |
|---|---|
| Formula | $C_{25}H_{24}O_{12}$ |
| *Molecular weight* | 516.45 g/mol |
| Number heavy atoms | 37 |
| Number aromatic heavy atoms | 12 |
| Fraction $Csp^3$ | 0.24 |
| Number rotatable bonds | 9 |
| *Number hydrogen bond acceptors* | 12 |
| *Number hydrogen bond donors* | 7 |
| *Molar refractivity* | 126.90 |
| TPSA | 211.28 Å$^2$ |
| Lipophilicity | |
| $LogP_{o/w}$ | 1.11 |
| Water Solubility | |
| LogS | -3.65 |
| Solubility | 1.17e-01 mg/ml |
| Absorption | |
| GI absorption | Low |
| Distribution | |
| BBB permeation | No |
| P-gp substrate | Yes |
| Metabolism | |
| CYP1A2 inhibitor | No |
| CYP2C19 inhibitor | No |
| CYP2C9 inhibitor | No |
| CYP2D6 inhibitor | No |
| CYP3A4 inhibitor | No |
| $LogK_p$ (skin permeation) | -8.37 cm/s |
| *(Table 4 devamı)* | |
| Drug-likeness | |
| Lipinski | No; 3 violations: MW>500, NorO>10, NHorOH>5 |
| Ghose | No; 1 violation: MW>480 |
| Veber | No; 1 violation: TPSA>140 |
| Medicinal Chemistry | |
| PAINS | 1 alert: catechol_A |
| Brenk | 3 alerts: catechol, michael_acceptor_1, more_than_2_esters |
| Leadlikeness | No; 2 violations: MW>350, Rotors>7 |
| Synthetic Accessibility | 4.81 |
| Bioavailability Score | 0.11 |

There are some criteria such as Lipinski, Ghose and Veber to establish whether the compounds have a drug-like structure and their activity in living organisms [30].

In this study, the drug similarity properties of the cynarin compound were examined using Lipinski criteria. According to Lipinski's rule, an effective drug taken orally should not cause violations of more than one parameter. According to Lipinski's rule of five, chemical structure limitations are described as molecular weights ≤500, hydrogen bond acceptor numbers ≤10, hydrogen bond donor numbers ≤5, lipophilicity of compounds ≤5, and molar refractivity between 40-130 [31], [32]. According to Lipinski's rule indicates that there is a condition that would prevent the cynarin compound from being an orally active drug in humans (Table 5).

**Table 5.** Drug-like properties of cynarin compound according to Lipinski's five rule

| Lipinski's rule of five | Acceptable range | Cynarin Theoric | Cynarin Result |
|---|---|---|---|
| Molecular weight | ≤500 | 516.45 | + |
| Number hydrogen bond donors | ≤5 | 7 | - |
| Number hydrogen bond acceptors | ≤10 | 12 | - |
| LogP | ≤5 | 1.11 | + |
| Molar refractivity | 40-130 | 126.90 | + |

Toxicity estimation is an important parameter the drug discovery course that helps identify of molecules with the major potential for safe and influential use in humans [33]. The predictive toxicity study was accomplished by Pro-Tox II webserver. The predicted outcome for cynarin compound was demonstrated in Table 6. Accordingly, the cynarin compound did not show hepatotoxic, carcinogenic, mutagenic, and cytotoxic efficiency but it had immunotoxic efficiency. According to Pro Tox-II, the cynarin was categorized as predicted toxicity class 5. Category 5 indicates that it has relatively low acute toxicity. However, it is known that under certain conditions it may pose a danger to some populations.

**Table 6.** The toxicity computation of SDG molecule by Pro-Tox II web tool

| Toxicity Model Report (Predicted Toxicity Class: 5) | | |
|---|---|---|
| Classification | Target | Prediction |
| Organ toxicity | Hepatotoxicity | Inactive |
| Toxicity end points | Carcinogenicity | Inactive |
| Toxicity end points | Immunotoxicity | Active |
| Toxicity end points | Mutagenicity | Inactive |
| Toxicity end points | Cytotoxicity | Inactive |

## 4. Conclusion and Suggestions

The quantum chemical descriptors for the cynarin molecule have been executed by energy minimization, by DFT at the B3LYP level, using the basis set 6-311G*. The HOMO-LUMO energy gap of the cynarin compound has 3.8613 eV, theoretically that it has low chemical reactivity and high kinetic stability. As to the indicated outcomes of MEP computations, the cynarin compound has contained both nucleophilic active regions and electrophilic attack regions. Cynarin compound has low binding energy (-7.9 kcal/mol) which could be regarded as revealing its protective effect against liver diseases. The cynarin compound did not show any cytotoxic, hepatotoxic, mutagenic or carcinogenic efficacy with respect to the Pro Tox II prediction, but had an immunotoxic effect. Therefore, cynarin may be appropriate compound for further analysis drug development in liver cancer with targeted features.

## Acknowledgment

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