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# Molecular Docking study of the flavonoids quercetin and artemetin front the angiotensin-converting enzyme

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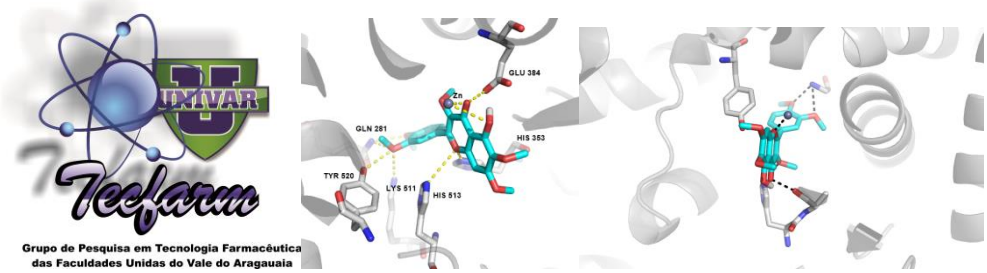
**Abstract:** Phenolic compounds, such as flavonoids, have aroused great scientific interest due to their diverse pharmacological activities, such as antioxidant, anti-inflammatory, anticancer and antihypertensive, among others. Several studies suggest the mechanisms responsible for the antihypertensive activity of flavonoids, and among them is the inhibitory activity of the angiotensin-converting enzyme (ACE). Thus, the objective of the present study was to perform a molecular docking study of flavonoids quercetin and artemetin against ACE, aiming at a better understanding of the interaction of these flavonoids with the enzyme. The crystallographic structure of the enzymatic target ACE was obtained from the Protein Data Bank database [PDB: 1UZE]. The molecular docking study was performed using Autodock 4.0 software. Gasteiger charge and polar hydrogens needed for the power calculations were added to the enzyme, with the water molecules removed. The grid was positioned in the catalytic region of the enzyme with dimensions on the X-, Y- and Z-axis at 32 Å 30 Å and 38 Å, respectively, spacing 0.375 Å. The Lamarckian Genetic algorithm was chosen to search for the best conformations with 100 runs for each binder. During the search, the enzyme was held rigid and the ligands were kept flexible. Both artemetin and quercetin interacted with the active site of the enzyme attractively. With docking energy at -6.89 kcal/mol, artemetin was more stable in complex with the active site of the enzyme ACE, whereas quercetin presented docking energy at - 6.63 kcal/mol. Both ligands interacted by hydrogen bonds with amino acids GLU 384, TYR 520, HIS 513, HIS 353, GLN 281, LYS 511 and the Zn ion. The study showed that the methodology used in the present study can be well used for the understanding of the interaction of pharmacologically active compounds with target enzymes, saving time and resources.

**Keywords:** Molecular docking; flavonoides; angiotensin-converting enzyme

**Graphical Abstract:**



**Introduction:**

Flavonoids are phenolic compounds that can be found in various plant foods such as fruits, teas, wine, chocolates and others. Flavonoids have gained great interest due to their diverse pharmacological effects, such as antioxidant, anti-inflammatory, anticancer and antihypertensive action, among others [1].

There are several studies suggesting the mechanisms responsible for the antihypertensive activity of flavonoids. Recent studies have shown that flavonoids have antihypertensive activity due to the inhibitory action of the angiotensin converting enzyme (ACE) [2]. ACE inhibitors prevent the formation of angiotensin II.

In a study by Häckl et al. (2012) [3] it was observed that quercetin (**Figure 1-a**) satisfactorily inhibited the angiotensin-converting enzyme, through a mechanism similar to that of captopril. In a study by Souza et al. (2010) [2] it was observed that artemetin (**Figure 1-b**), another flavonoid, has been shown to be effective in reducing blood pressure through inhibition of angiotensin converting enzyme.

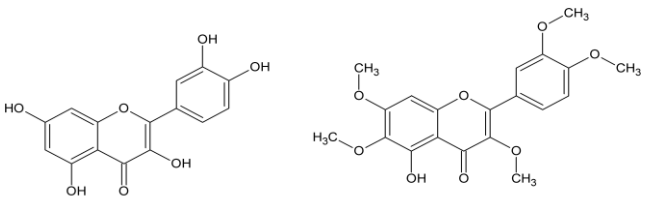



**Figure 1.** Molecular structure of the binders. A) quercetin; B) artemetin.

In this perspective, the objective of the present work was to perform a molecular docking study of the flavonoids quercetin and artemetin against the angiotensin converting enzyme in order to verify the interaction energy of the flavonoids with the active site of the enzyme and the functional groups of the ligands Responsible for interacting with ACE.

**Materials and Methods:**

The crystallographic structure of the enzymatic target ACE was obtained from the Protein Data Bank database [PDB: 1UZE]. The structures of the ligands were obtained through the PubChem base data and optimized by quantum chemistry calculations using the DFT (Density Function Theory) method, with B3LYP and base set 6-31G, through GAMESS software. The molecular docking study was performed using Autodock 4.0 software. Gasteiger and polar hydrogens needed for the power calculations were added to the enzyme, with the water molecules removed. The grid was positioned in the catalytic region of the enzyme with dimensions on the X-, Y- and Z-axis at 32 Å 30 Å and 38 Å, respectively, spacing 0.375 Å. The Lamarckian Genetic algorithm was chosen to search for the best conformations with 100 runs for each binder. During the search, the enzyme was held rigid and the binders were kept flexible. The method was validated by RMSD (Root-Mean-Square-Deviation), obtained through molecular re-docking of enalapril.

**Results and Discussion:**

Both artemetin and quercetin interacted with the active site of the enzyme attractively. With docking energy at -6.89 kcal / mol, artemetin was more stable in complex with the active site of the enzyme ACE, while quercetin presented docking energy at -6.63 kcal / mol. Both ligands interacted by hydrogen bonds with amino acids GLU 384, TYR 520, HIS 513, HIS 353, GLN 281, LYS 511 and the $Zn^{+}$ ion, as shown in **Figure 2**.

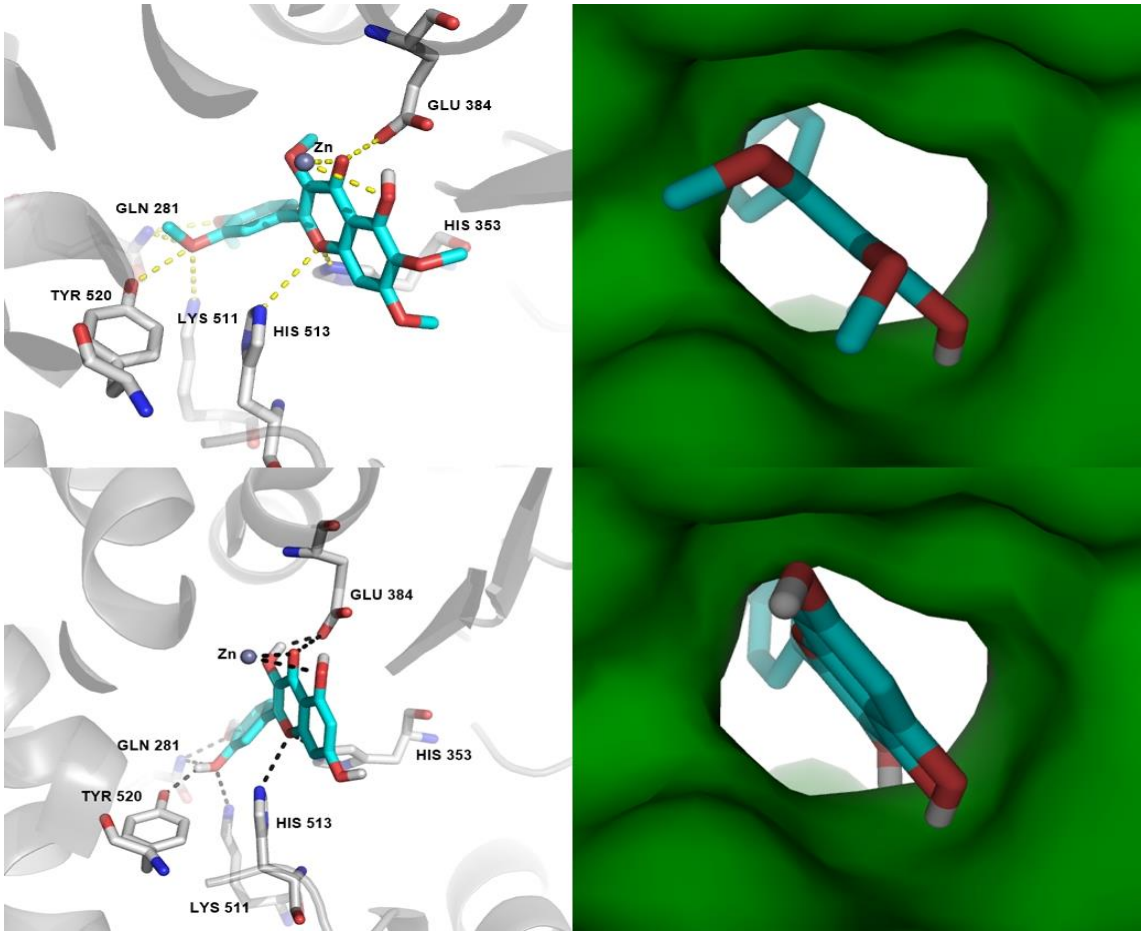



**Figure 2.** Flavonoid-Enzyme Complex. A) artemetin; B) quercetin

It is worth noting that hydrogen bonds were predominant in the interactions between the ligands and the amino acids of the active site of the enzyme, which shows that the phenolic hydroxyls of quercetin and the methoxyl groups of artemetin are of extreme importance for the activity of the ligands.

The redocking presented RMSD value = 0.89 Å, considering the most stable pose of the most populous cluster. This result is considered satisfactory when the RMSD (which measures the deviation) between the best pose and the complexed crystallographic ligand is less than 2.0 Å [4].

**Conclusions:**

It was observed that the interaction of flavonoids quercetin and artemetin with ACE occurred favorably, in accordance with the experimental studies. These interactions occurred mainly through the polar groups of the ligands. The study showed that the methodology used in the present study can be well used for the understanding of the interaction of pharmacologically active compounds with target enzymes, saving time and resources.

**References:**

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