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Exploring molecular flexibility and the interactions of Quercetin derivatives in the active site of α-glucosidase using molecular docking and charge density analysis

Y.J. Qi [a,*], Y.M. Zhao [a], H.N. Lu [b], X.E. Wang [a], N.Z. Jin [c]

[a] Department of Chemical Engineering, Northwest University for Nationalities, Lanzhou 730124, PR China
[b] Department of Life Sciences and Biological Engineering, Northwest University for Nationalities, Lanzhou 730124, PR China
[c] Gansu Province Computing Center, Lanzhou 730000, PR China

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ABSTRACT

Molecular docking and charge density analysis were carried out to understand the geometry, charge density distribution and the electrostatic properties of Quercetin and its derivatives and for the same present in the active site of the α-glucosidase of *S. cerevisiae*. By using molecular docking, the binding energies and nearest amino acids were calculated. Due to absence of the bioactive conformation from experimental data, conformations were elected in this text from the docking procedure based on chemometric techniques in order to represent the set of the promising configurations. The optimized geometries of these molecules were performed using Hartree-Fork and Density Functional Theory (DFT-B3LYP) combined with the theory of atoms in molecules (AIM). It is observed that the geometrical, bond topological and the electrostatic properties of the molecules are significantly altered in the active site. The introduced substituent groups with different volume and polarity have some influence on the variations of charge and polarization when the molecules present in the active site. All of the dipole moments of the three molecules are changed in the active site on compared with the gas phase, especially the one introduced large polar substituent group. Comparing with the parent Quercetin molecule, the two derivatives have lower energy gaps between highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) in the active site, which illustrates their lower stability and higher inhibition activity. The comparative study on the geometrical and electrostatic properties of these synthetic or natural molecules is useful for further designing new drugs for the better treatment of diabetes disease.

1. Introduction

Diabetes is a chronic metabolic disorder whose prevalence has been increasing steadily all over the world. WHO proposed that diabetes will be the 7th major disease responsible for most of the deaths by 2030. Type 2 diabetes is the most common form of diabetes, affecting 85–90% of all diabetic population. In fact, the number of diabetes patients has become more than double since 1980–2008 [1], and the Type 2 diabetes mellitus will increment by 53% due to increase in ageing population in the next two decades [2,3]. To cure diabetes, the hyperglycemia condition is needed to be controlled well, which may be achieved with a healthy lifestyle and appropriate pharmacological therapies [4]. Several categories of drugs, including sulfonylureas, biguanids, thiazolidinediones, meglitinides and α-glucosidase inhibitors are used for the type 2 diabetes [5]. α-glucosidase inhibitors decrease the postprandial hyperglycemia by inhibiting carbohydrate hydrolyzing enzymes, such as acarbose and miglitol [6,7]. Although these synthesized drugs can decrease the absorption of glucose into the blood stream and reduce plasma glucose levels, the deleterious side effects are appeared simultaneously, such as liver toxicity and harmful gastrointestinal symptoms [8,9]. Therefore, the efforts for finding and synthesis of new effective and safer inhibitors have continued [10–14].

In recent years, the presence of phytochemicals in plant products gives a great potential for balancing metabolic disturbances. Effective α-glucosidase inhibitors that come from medicinal plants achieved wide attention due to their high effectivities and low toxicities. For example, leaf extract of Moringa stenopetala, which was approved to be a potent inhibitor of α-glucosidase, have some effect on pancreatic and intestinal enzymes that related to

* Corresponding author.
E-mail address: qiajiao@163.com (Y.J. Qi).

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antihyperglycemic and antihyperlipidemic activities [12]. The main components that derived from Chinese traditional medicine *Jinqi Jiangtang Tablet* were approved to have inhibitory activity of enzymes related with diabetes [13]. Quercetin is a polyphenolic compound that can be found in a variety of plant-based foods and beverages. Possessing both antioxidant and inhibitory of α-glucosidase properties [14,15], Quercetin is regarded as a lead compound in the design of anti-diabetic drugs. It was approved that the relatively planar and phenolic structures of Quercetin derivatives have more pronounced α-glucosidase inhibitory activity than the parent Quercetin itself [16]. For example, Quercetin-3-O-glucoside was synthesized from rutin was confirmed more effective than rutin and even Quercetin because of its enhanced solubility and inhibitory properties [17]. Recently, it was reported that the compound Quercetin-3-O-(6″-benzoyl)-β-galactoside (named Quercetin-I) [18] from the aerial parts of *V. corymbosa*, and the synthetic compound 1-geranyl Quercetin (named Quercetin-II) have the yeast α-glucosidase inhibitory activity [19]. Both of the two compounds have the common Quercetin structure, whereas the hydrogen of the hydroxyl group on the C ring is replaced by the benzoyl-β-galactoside on the Quercetin-I molecule, and the hydrogen on the A ring of Quercetin-II is replaced by a geranyl group. The planar structures are shown in Fig. 1(a–c).

At present, various studies are committed to understand the structure and properties of inhibitors, and to design new derivatives with enhanced efficiencies and lower toxicities. Actually, the main purpose is to excavate its binding affinity, mode of binding in the active site, molecular flexibility, variation of the charge density distribution and the electrostatic potential (ESP) of the molecule in the active site [20,21]. Combined with quantum chemical calculations [22,23], Bader's theory [24] of atoms in molecules (AIM) and molecular docking [25,26], in this study, the molecular conformation, the charge density and the electrostatic properties of the Quercetin and its derivatives were comparatively analyzed in gas phase and in the active site of α-glucosidase. The geometrical and the bond topological parameters of both forms of the molecules have been compared, which are very important to understand the molecular flexibility and intermolecular interactions [27]. The dipole moment and the ESP of the molecules are significantly changed, which are related to the charge redistribution on the different substituent groups of the parent structure.

2. Computational methods

The structures of the molecules (I–III) were prepared by ChemDraw software. Using Gaussian 09 software [28], the geometry and energy were then optimized with 6-311G (d, p) basis set using Hartree–Fock (HF) [29] and DFT (B3LYP) [30,31] methods in the gas phase calculations, whereas the single point energy calculations of the active site were performed by DFT method. Molecular electrostatic potential surfaces were created with GaussView 5.0.8. Topology analysis of electron density and the deformation density map were performed by the Multiwfn program [32]. AutoDock 4.2 [33] was used to identify the binding modes of molecules responsible for the activity. The docking grid box was set at $60 \times 60 \times 60$ points with a spacing value of 0.375 Å. Genetic Algorithm with default settings was employed in the search parameter, and the number of runs was set at 100. The proteins of the *Saccrhromyces cerevisiae* isomaltase (PDBID: 3A4A) and human serum albumin (PDBID: 1H9Z) were download from the PDB website (http://www.rcsb.org), and the crystal structure of *Saccrhromyces cerevisiae* isomaltase was used as the template. Protein sequence for Baker's yeast α-glucosidase (MAL12) was obtained from uniprot (http://www.uniprot.org). Homology modeling was used to construct a 3D model of a-glucosidase by using SWISSMODEL [34–36], which is an automated protein modeling server. The developed structure was subjected to energy minimization up to 0.05 RMS gradients. The final refine structure was then used for the molecular docking purpose.

3. Results and disscussion

3.1. Selection of the molecular conformations

The molecular docking procedure generates many system configurations, because the lowest energy conformations rarely represent bioactive conformations in the active site, they can't be used for the investigation of the reaction mechanism and further quantum chemistry analysis [37–39]. As reported by Willian E.A., chemometric techniques based on the principal component analysis (PCA) were used to select the active conformation, and good results were obtained [40–42]. In this text, eight variables (Binding_energy, ligand_efficiency, intermol_energy, vdw_hb_desolv_energy, electrostatic_energy, unbounded_energy, cIRMS, refRMS, named VAR00001-9) generated in the docking analysis (Fig. 2) were evaluated by PCA in order to investigate the influence of the interaction energy values. As a result, the percentage of explained variance by each PC (PC1, PC2 and PC3) for Quercetin-I, Quercetin-II and Quercetin-III are (41.4%, 12.3% and 14.6%), (46.6%, 12.9% and 11.2%) and (55.5%, 19.9% and 11.7%), respectively. These values are regarded as well-known indexes of goodness of fit in multivariate data analysis [40]. It is necessary to select conformation from the docking procedure that can represent the set of the promising configurations because of the absence of the bioactive conformation from experimental data. Fig. 2 displays the PCA results for the Quercetin-I, Quercetin-II and Quercetin-III with the presence of three principal components with a representativity of 68.3%, 70.7% and 87.1%, respectively. Based on the occupancy frequency, configurations that contribute less to the

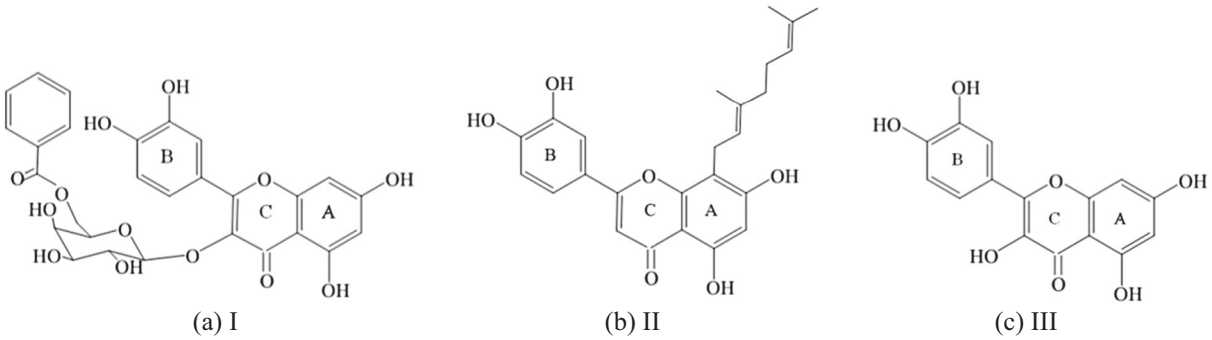

Fig. 1. Chemical structures of (a) Quercetin-I, (b) Quercetin-II and (c) Quercetin-III molecules.