STRUCTURAL PROPERTIES OF QUERCETIN BY MOLECULAR DYNAMICS SIMULATION

*N. Baloochzadeh, M. Housaindokht and F. Moosavi**

Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran

Abstract - One of the most important types of antioxidants are flavonoids which contain flavonols, flavonones, isoflavones, etc. Because of the importance of quercetin as an antioxidant, the present study pays special attention to this compound of flavonols. The main focus of this investigation is to explore structural properties of quercetin by molecular dynamics simulation. The results show that intermolecular hydrogen bonds between quercetin and water are stronger than water-water interactions. In addition, intramolecular hydrogen bond in quercetin is observed. Hydrogen bond interaction of water contains an enormous number, 930 hydrogen bonds in average though the number of hydrogen bonds between water and considered antioxidant is in average three. From dynamical point of view, RMSD of the system witnesses stability after a nanosecond of simulation which indicates the structure of quercetin finds its stable form and no conformational change is observed. However, R_g fluctuates around 0.37 nm that is also a sing of structural stability. The results of pair atomic correlations also designate that the interaction of alcoholic oxygen and hydrogen of target antioxidant with water are stronger than the interatomic interactions between etheric oxygen and corresponding carbon that confirms strong interaction between quercetin and water.

1. Introduction

Drugs can be divided into different categories from diverse points of view. One division is those which their source is chemical, no obtained from dietary sources; the other group contains drugs that have natural resources obtained through dietary (found in plants, fruits, vegetables, etc.). In the present study, a particular group that are taken from natural resources were examined. Some of the main characteristics of this class are anticancer, antivirus, antioxidant, etc.; in the meantime, we chose a particular category of antioxidants. Another property is free radical scavenging; it also reduces oxidative stress and can effect on the macromolecules, such as, DNA, lipid, and proteins [1-3]. Antioxidants can also act as anti-tumorigenic and anti-proliferative [2]. Flavonoids are one of the most important types of antioxidants which include flavonols, flavonones, and isoflavones, as a very large series of compounds. Here, we consider one antioxidant flavonol, the most common category. Interestingly, all flavonoids have the same overall structure and differ only at some certain substituent groups. For example, quercetin and kaempferol are unsimilar just only in a hydroxyl group. Fig. 1 shows their molecular structure.

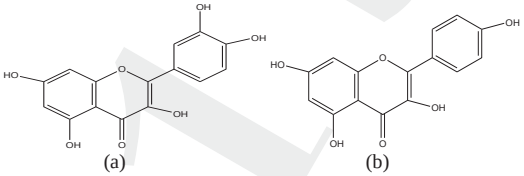

Fig. 1. (a) Quercetin molecular structure, (b) kaempferol molecular structure.

The main focus of this investigation is to compute quercetin structural properties including hydrogen bond (H-bond) interaction, root mean square deviation (RMSD), radial distribution function (RDF), and radius of gyration (R_g) by molecular dynamics simulation.

2. Method

Molecular dynamics simulations were performed using GROMACS 4.5.4 software [4] and force field gromos 53a6 [5] was selected for quercetin. The antioxidant was solved in water; the water model was SPC [6] and the number of water molecules is 1024. All simulations were solved using leapfrog integration method with time step of 2 fs. Symmetric cubic periodic boundary conditions were applied on the system and total time of simulation was 10 ns. Geometries and energies were saved every 2 ps. Lennard-Jones and Coulomb interactions were used with a cut-off distance of 1.5 nm. The simulation was performed first at 300 K in NVT ensemble and then final structure was applied to perform NPT simulation at 1.0 bar. The pressure and temperature were controlled by Parrinello-Rahman barostat and v-rescale, respectively. To be ensure that equilibration has achieved, some thermophysical properties including temperature, pressure, and density were evaluated.

3. Results and discussion

Current study investigates RDF, H-bond, RMSD, and R_g of the system. RDF of liquid phase is between a solid and a gas phase in which there are a few peaks at short distances. The height of peaks reduces

* Corresponding author Email: moosavibaigi@um.ac.ir

continually until it reaches constant value at large distances. Notice that the results of interactions between several groups were considered: 1. Interaction of alcohol oxygen of antioxidant with water; 2. Interaction between corresponding alcohol hydrogen with water; 3. Interaction of etheric oxygen with water; 4. Interaction between corresponding etheric carbons with water. All studied interactions, RDFs, are shown in Fig. 2.

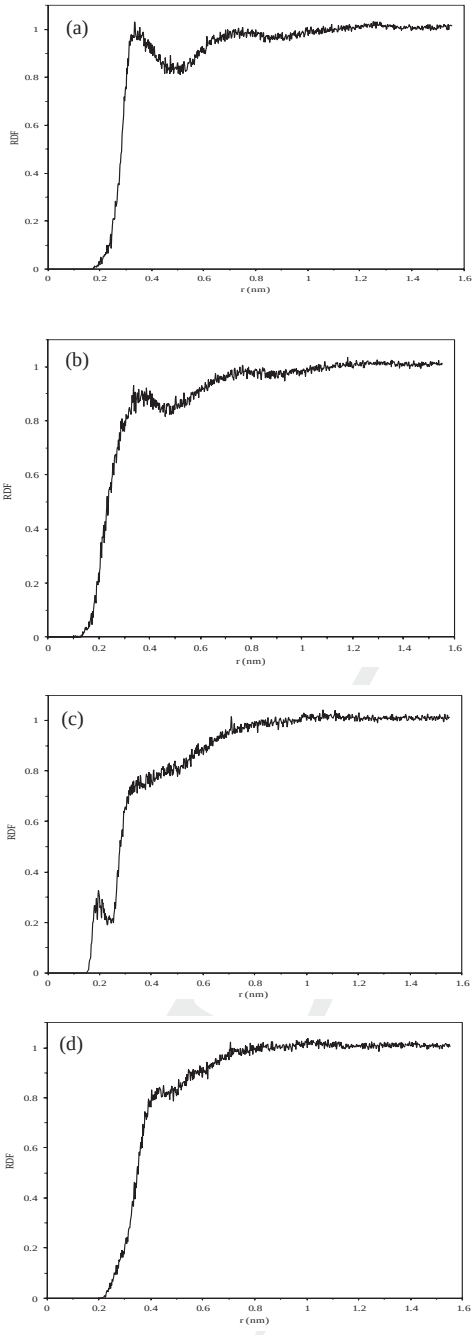

Fig. 2. RDF of different groups of antioxidant with water (a) alcoholic oxygen, (b) alcoholic hydrogen, (c) etheric oxygen, and (d) etheric carbon.

The results indicate that the interaction of alcoholic oxygen and hydrogen of quercetin with water is stronger than the interaction between etheric oxygen/carbon and water. In other words, it can be expected that the interactions are hydrogen bonding type. To confirm this point of structural view, H-bond analysis was performed.

Analysis by H-bond was carried out between the two groups of atoms (which can be identical or non-identical). These groups are hydrogen bond donor and hydrogen bond acceptor which are studied by using their distance and angle criteria [7, 8]. H-bond study was performed on three groups: water-water, quercetin-water, and quercetin-quercetin; the two first ones are intermolecular type and the last is intramolecular. The results are shown in Fig. 3.

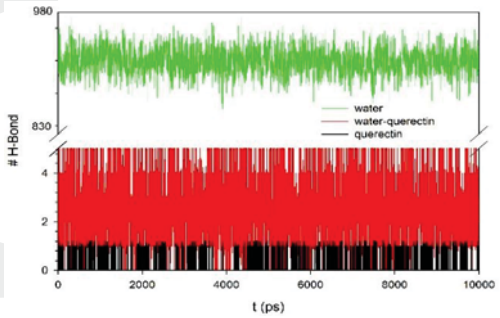

Fig. 3. H-bond number for three groups including water-water (Green), water-quercetin (red), and quercetin-quercetin (black).

As can be seen in Fig. 3, H-bond interaction of water with water contains an enormous number of H-bond, 930 in average. The number of H-bond between water and considered antioxidant is in average three while intramolecular H-bond in the quercetin is just only one H-bond which looking at Fig. 1 shows that this type of interaction can be related to the interaction of adjacent carbonyl oxygen and hydrogen.

Dynamic character can be provided from simulation information that shows how the system reaches equilibrium and becomes stable over time of simulation. The characteristics can be studied by RMSD.

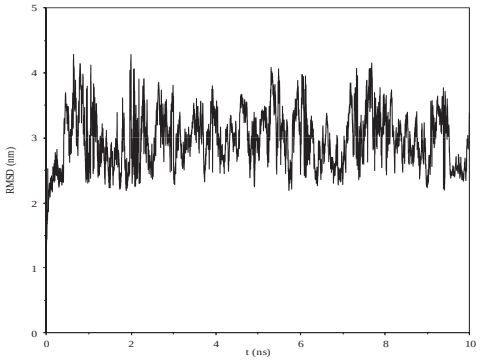

Fig. 4. The variation of RMSD with time of simulation.

As Fig. 4 demonstrates, the RMSD fluctuation is high and after 1 ns quercetin finds its stable form; on the other hand, the target compound does not witness any conformational change.

Radius of gyration measures the size of the molecule and the radii of gyration is measured about x-, y-, and z-axes as a function of time. Though it can be determined by experiment, the result is not accurate. As a result, it is essential to find out distance of interactions. Fig. 5 shows R_g of the target system with configuration number.

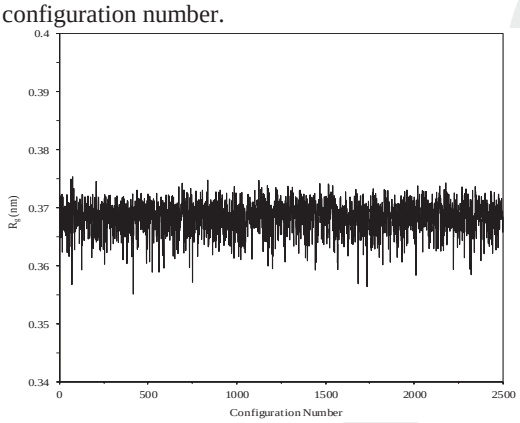

Fig. 5. The fluctuation of R_g with configuration number.

As the figure illustrates R_g value for studies system is constant at 0.37 nm that demonstrates the size of the system is constant over the time evolution.

4. Conclusion

Because of the importance of quercetin as a medicine, it is important to gather information on its structural and dynamical features to be able to predict its antioxidant power (IC_{50}). In this study, as a first step of investigation, some structural and dynamical properties such as RDF, RMSD, H-bond, and R_g were obtained from molecular dynamics simulations. It is proposed that these characteristics have direct influence on their correlations with macromolecules such as DNA. The results of RDF specify that the interactions of alcoholic oxygen and hydrogen of quercetin with water are stronger than its etheric oxygen/carbon and water. The number of H-bond calculated shows that the interaction of antioxidant with water is due to non-coulomb forces and strong vdW interaction leads the compound to be solved in solvent and simplify its interaction with macromolecules. In addition, the results of RMSD and R_g shed light on the stability of the structure and that the configuration does not show any change.

5. References

[1] F. Di Meo, E. Anouar, P. Podloucká, G. Fabre and P. Trouillas, J. Serb. Soc. Comput. Mech. 7 (2013) 58-70.
[2] A. Tawani and A. Kumar, Sci. Rep. 5 (2015) 1-13.
[3] P. Chhetri, C. Lee and L. Rakesh, J. Cancer Sci. Ther. 3 (2011) 220-227.
[4] B. Hess, D. van Der Spoel and E. Lindahl, University of Groningen, Netherland (2010).
[5] C. Oostenbrink, A. Villa, A. E. Mark and W. F. Van Gunsteren, J. Comput. Chem. 25 (2004) 1656-1676.
[6] Y. Wu, H. L. Tepper and G. A. Voth, J. Chem. Phys. 124 (2006) 024503.
[7] A. Gubskaya and P. Kusalik, J. Phys. Chem. A 108 (2004) 7151-7164.
[8] G.-c. Tian, J. Li and Y.-x. Hua, Chin. J. Chem. Phys. 22 (2009) 460-466.