International Journal of Biology Research
www.biologyjournal.in
ISSN: 2455-6548
Received: 28-05-2021, Accepted: 12-06-2021, Published 29-06-2021
Volume 6, Issue 2, 2021, Page No. 48-52

Comparing the energy levels of myricetin nanocomposite model structures with copper and cadmium by computational method

Soumalya Chatterjee, Debraj Hazra, Rajat Pal*
Department of Microbiology and Biotechnology, Sister Nivedita University, Kolkata, West Bengal, India

Abstract

As our civilization is developing with more and more advanced technologies and inventions, plant and animal kingdom both has started suffering from various complicated diseases and physiological disorders. Hence, new mode of treatment as well as new mode of drug delivery has to be evolved. Here nanoparticles have come to play an important role to be used as a vehicle for drug molecules, nanoparticles first must interact with them and the interaction is very much important in case of metal nanoparticles. Every metal nanoparticle will not be able to interact with equal efficiency to all drug molecules. For that reason the study of interaction is quite worthy. In our present study, we tried to formulate metal nanoparticles with two different metal atoms (Copper and Cadmium) and the formulated nanoparticles were interacted with Myricetin, a bioflavonoid, in several ways. The model structures for all drug metal nanocomposites were subjected for energy minimization to form the most stable structure. After energy minimization, it was observed that Cadmium can make more stable nanocomposite structure with Myricetin as its energy level is lower than that of Copper. Hence we can suggest that Cadmium could be more suitable to formulate nanocomposites with Myricetin rather than Copper.

Keywords: myricetin, metal nanoparticles, avogadro software, nanocomposite

Introduction

Nanoparticles are the most talked about subject for research in various fields nowadays. These are very small particles having size ranges between 1 to 100 nm by at least one dimension. Humans can't see it with bare eyes. All Nanoparticles show various physical and chemical properties which differs from their larger material counterparts. Mostly the nanoparticles contain few hundreds of atoms. The material's properties change as the size of nanoparticles approaches to the atomic scale, this only happens due to the increase in surface area to volume ratio when compared to bulk materials, like powder, plate and sheet, paper etc. For this reason, the surface atoms of the materials dominate the material performance. Because of this feature, all nanoparticles show unexpected optical, physical and chemical properties as they are very small enough to confine the electrons and produce Quantum effects (TWI, 2021) [30]. The vast applications of nanoparticles in various fields have drawn the focus on its research. In the sector of biomedicine and agriculture, nanoparticles perform the most important role. Some metals are found to be very good ingredient for synthesis of nanoparticles. Many metals have already been reported for being used as precursor for nanoparticle synthesis, among them some mostly common are Gold (Au) (Duncan *et al*., 2010) [5], Silver (Ag) (Santos *et al*., 2014) [27], Copper (Cu) (Kruk *et al*., 2015) [12], Iron (Mahdy *et al*., 2012) [15], Zinc (Zn) (Rojas *et al*., 2016) [25], Nickel (Ni) (Guo *et al*., 2009) [7], Platinum (Pt) (Kim *et al*., 2010) [5], Palladium (Pd) (Adams *et al*., 2014) [1], Ruthenium (Ru) (Xu *et al*., 2019) [34], Rhodium (Rh) (Viau *et al*., 2003) [31], cadmium (Cd) (Qi *et al*., 2001) [22] and antimony (Sb) (Yin *et al*., 2019) [35]. The nanoparticles which are made from these metals are widely used as a vehicle for drug molecules to be administered during the treatment against several diseases. All that kind of supports of such vehicle makes this drug - nanoparticle composites very useful mode of drug delivery system in medical and agricultural science. Free drug molecules generally dissociate and metabolize very easily in animal body due to the presence of different metabolic pathways. But if these drug molecules are administered with a vehicle like nanoparticle, the slow release will occur in physiological condition and the drug will get more time to show its activity in the body. Hence this process becomes very useful for scientists who are working on drug - nanoparticles composite formulation and their application in various fields.

Metal nanoparticles possess physical, chemical, electronic, electrical, mechanical, thermal, optical and biological characteristic features (Schmid, 1992; Daniel and Astruc, 2004) [28, 4]. For having these properties, nanoparticles are being used in a variety of areas in biology and medicine such as fluorescent labeling (Bruchez *et al*., 1998; Chan and Nie, 1998; Wang *et al*., 2002) [2, 3, 32] drug and gene delivery (Mah *et al*., 2000; Panatarotto *et al*., 2003) [14, 20] detection of pathogens (Edelstein *et al*., 2000) [6] and proteins (Nam *et al*., 2003) [18], probing of DNA structure (Mahtab *et al*., 1995) [17], tissue engineering (Ma *et al*., 2003; Isla *et al*., 2003) [13, 9] MRI contrast enhancement (Weissleder *et al*., 1990), phagokinetic studies (Parak *et al*., 2002) [1] and many more. Nanoparticles must interact with drug molecules or any other Ligand for their application.

For the treatment against various diseases, flavonoids stand in a strong position among different biomolecules having medicinal activity. So the composite structure of metal nanoparticles with different flavonoid molecules play key role in the field of biomedical research (Riaz *et al*., 2020). According to many reports, the metal nanoparticles are synthesized by using the extracts of different parts of several plants. This method is commonly known as green synthesis (Shafey, 2020) [29].

In this present study, we have selected Myricetin as a flavonoid molecule. This flavonoid has major array of applications in various fields and can act as antimicrobial (Ong *et al*., 1997) [19], anti-inflammatory (Mahjoub *et al*., 2010) [16], antioxidant (Qu *et al*., 2006) [23] and anticancer (Ha *et al*., 2017) agent. We selected this bioflavonoid because it contains six -OH groups which are well-distributed throughout its surface. As metal, we chose copper (Khalid *et al*., 2015), and cadmium (Salam *et al*., 2018) as because they both can be synthesized by reduction method with borohydrate. So the computer generated model structure could be done with the metal and boron atoms and its interaction with Myricetin bioflavnoid. From this study we can have a better and clear idea about the formation and development of metal nanocomposite structures.

Methods

In this present study, we tried to compare two metals for its better binding capacity with the drug myricetin. The chemical structure of myricetin is shown in figure 1. In the structure of this drug molecule, six OH groups are present that means there are six probable binding sites for metal nanoparticles for the formation of nanocomposite structures. We have chosen here copper and cadmium as metals for the synthesis of metal nanoparticles. As reported by many research groups (Khalid *et al*., 2015; Salam *et al*., 2018) [10, 26], both nanoparticles (Cu and Cd) can be synthesized by borohydrate reduction method of their individual salts. Hence for the construction of metal nanoparticle drug composite model structure, we will attach metal atoms to drug molecule through boron atom. As, a nanoparticle consists of many metal atoms and that much of metal atoms can con be accommodated in our computational model structure, we are taking one single metal atom associated with one single boron atom as a representation of the nanoparticle. To formulate the model structures, we are using the Avogadro software for windows here (Hanwell *et al*., 2012) [8].

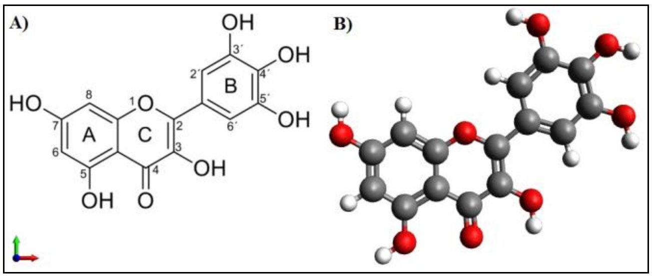

Fig 1: A) Chemical structure of Myricetin, B) Model structure of Myricetin constructed by Avogadro software.

At first we tagged the boron atom of the representative nanoparticle (for both Copper and Cadmium) with all -OH groups on Myricetin molecule. The compounds generated were given names as Cu_M_1/ Cd_M_1, Cu_M_2/ Cd_M_2, Cu_M_3/ Cd_M_3, Cu_M_4/ Cd_M_4, Cu_M_5 / Cd_M_5 and Cu_M_6 / Cd_M_6 respectively when metal atoms were attached through Boron to OH groups present at 7, 5, 3, 5', 4' and 3' positions of Myricetin. All these nanocomposite model structures were subjected for energy minimization after their construction and the calculation of their energy levels were listed in tabular form.

After binding with individual -OH groups, the representative metal nanoparticles (a metal atom and a Boron atom) were attached at every -OH groups of Myricetin as probable binding sites together. These compounds are named as Cu_M_7 and Cd_M_7 respectively for Cu and Cd metal drug nanocomposite model structures. Energy minimization was done with these structures to get the most stable structure. The energy levels for both structures were recorded in tabular form.

Among all the composite structures where boron atom was attached with different -OH groups individually, it was observed that the composite where nanoparticle is attached to the -OH group present at 7 position, possess lowest energy level. Hence we consider this position as the most suitable position as nanoparticle binding site in Myricetin molecule. So we constructed nanocomposite structure where one metal atom (Cu or Cd) was attached with two drug molecules.

At last we formulated a model structure where a single metal atom (Cu / Cd) was attached with two drug molecules through Boron atom at -OH groups which is present at 7 positions of both drug molecules. In addition to that all other -OH groups were also tagged with metal atoms through Boron atoms. Hence a structure was formulated where one metal is attached with two drug molecules and those two drug molecules were again attached with several representative nanoparticle structures which actually mimics the probable structure of drug nanoparticle composites formed in vitro. These structures we also allowed for energy minimization and the energy levels calculated were listed in table. To characterize these structures, we calculated the Boron – Metal – Boron bond angles and length of the bonds involved in the interaction. The bond angle and lengths were also listed in the table along with corresponding energy levels. Further, space fill model with Van der Waal's sphere were made for both the nanocomposite structures (Cu and Cd).

Results

At first we attached one copper atom to each and every -OH group of Myricetin through Boron atom separately. As six -OH groups are present in the structure of Myricetin, six nanocomposite structures were formed. All these structures are depicted in figure 2. As discussed in method section, the Boron atom will be attached at 7, 5, 3, 5', 4' and 3' positions of Myricetin in six different nanocomposite structures. These structures are named as Cu_M_1, Cu_M_2, Cu_M_3, Cu_M_4, Cu_M_5 and Cu_M_6. The energy levels of all these structures are listed in table 1.

Table 1: The list of energy levels of different nanocomposite structures of Myricetin with Copper and Cadmium when attached at different -OH groups separately.

Metal	Compound	Energy (KJ/Mol)
Copper (Cu)	Cu_M_1	262.953
	Cu_M_2	266.032
	Cu_M_3	283.803
	Cu_M_4	265.23
	Cu_M_5	280.731
	Cu_M_6	263.98
Cadmium (Cd)	Cd_M_1	262.347
	Cd_M_2	264.688
	Cd_M_3	293.518
	Cd_M_4	264.824
	Cd_M_5	280.329
	Cd_M_6	263.61

By comparing the energy levels, we can observe that the nanocomposite structure where the Cu and Boron atom was attached at -OH group present at 7 position of Myricetin was having lowest energy level suggesting most stable nanocomposite structure among all of these.

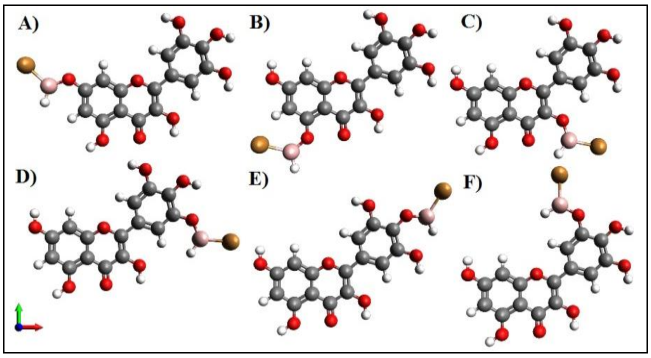

Fig 2: Myricetin nanocomposite structures with Copper through Boron. A) Cu_M_1, B) Cu_M_2, C) Cu_M_3, D) Cu_M_4, E) Cu_M_5 and F) Cu_M_6.

Same experiment was also performed with Cadmium (Cd). One Cd atom was interacted with each and every -OH groups of Myricetin through Boron atom. Similar to Copper, Cadmium also made six nanocomposite model structures when attached with different -OH groups of Myricetin separately. All these structures have been shown in figure 3 and named as Cd_M_1, Cd_M_2, Cd_M_3, Cd-M_4, Cd_M_5 and Cd_M_6. The energy levels of all these model structures are listed in table 1. Similar to Cu, in case of Cd also, the nanocomposite structure where the Cd atom is attached with -OH group present at 7 position of Myricetin was found to have lowest energy level among all other structures.

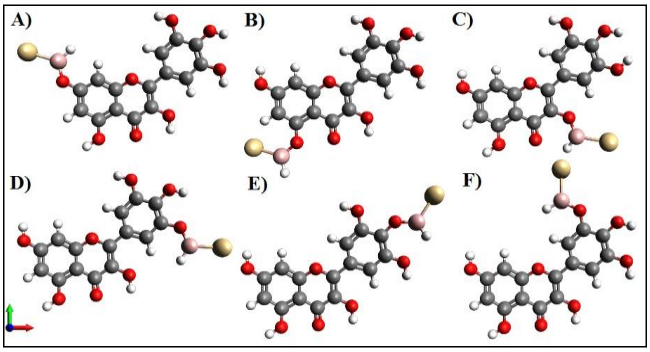

Fig 3: Myricetin nanocomposite structures with Copper through Boron. A) Cd_M_1, B) Cd_M_2, C) Cd_M_3, D) Cd_M_4, E) Cd_M_5 and F) Cd_M_6.

As myricetin has six -OH groups, so in our next step, we attached six Cu/Cd atoms through Boron atom with all -OH groups present at a time. Likewise two structures were developed for myricetin, one with Cu and the other with Cd. For Cu, the composite is named as Cu_M_7 (figure 4A), similarly for Cd, the composite is termed at Cd_M_7 (figure 4C).

After formation of the model structures, the energy levels were calculated and listed in table 2. If we observe at the energy levels of both composites, Cd exhibited less energy (434.393 KJ/ Mol) with respect to that of Cu (442.935 KJ/ Mol).

Table 2: List of energy levels of Copper and Cadmium nanocomposites named Cu_M_7, Cu_M_8, Cd_M_7 and Cd_M_8.

Metal	Compound	Energy (KJ/Mol)
Copper (Cu)	Cu_M_7	442.935
	Cu_M_8	524.3
Cadmium (Cd)	Cd_M_7	434.393
	Cd_M_8	517.324

In a nanoparticle, as one drug molecule may interact with more than one nanoparticles, reverse is also true. That means, one nanoparticle may also interact with more than one drug molecules. To make a representative model structure of this phenomenon, we constructed a nanocomposite where one Cupper or Cadmium atom was attached with two Myricetin molecules through Boron atoms. The nanocomposite of Cu is depicted in figure 4B and that of Cd has been shown in figure 4D. The compounds were named as Cu_M_8 and Cd_M_8 respectively. Their energy levels are also listed in table 2. From comparison of their energy levels, it was observe that aging Cd showed less energy when attached with two molecules of Myricetin that means, in this case also Cd make more stable composite with Myricetin rather than Cu.

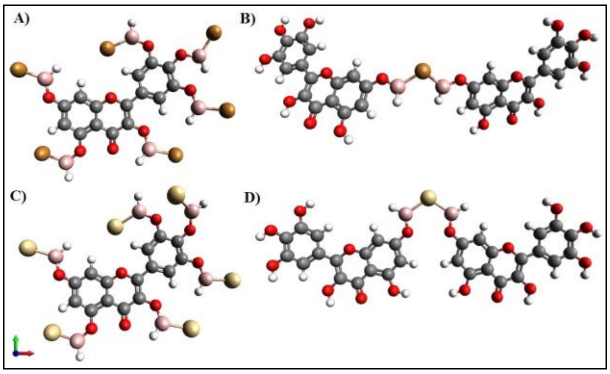

Fig 4: Model structure of A) Cu_M_7, B) Cu_M_8, C) Cd_M_7 and D) Cd_M_8.

Finally we constructed such a nanocomposite model structure with both metals (Cu and Cd) so that each metal may interact with two Myricetin molecules at -OH groups present on 7 position and the other -OH groups of these two Myricetin molecules were also engaged in interaction with metal atoms through Boron. This structure could be the actual probable representative structure of nanocomposites when synthesized in vitro. After the construction of the structures, minimization of energy levels was performed and the energy levels are listed in table 3. To characterize these structures, we also calculated the bond angles between one Boron atom, interacted metal atom and the other Boron atom. The same is also presented in table 3.

Table 3: List of energy levels of nanocomposite structures Cu_M_9 and Cd_M_9 along with the B – Metal – B bond angles.

Metal	Compound	Energy (KJ/Mol)	B – Metal – B bond angle (Å)
Copper (Cu)	Cu_M_9	897.22	107.3
Cadmium (Cd)	Cd_M_9	887.333	105.1

The model structures are named as Cu_M_9 and Cd_M_9 when constructed with Copper and Cadmium respectively. Both the structures are shown in figure 5. Just to see their actual structure, we also made the space filled model of these composite structures. They are presented in the figure 5. These space filled models are actually showing the Van der wall's spheres on the composite structures.

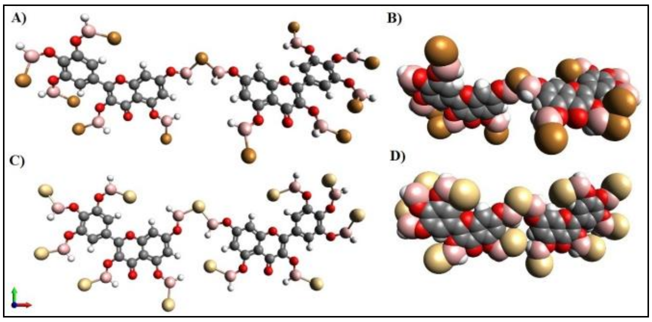

Fig 5: A) Model structure of the composite Cu_M_9, B) Space filled Van der Waal's sphere structure of Cu_M_9, C) Model structure of the composite Cd_M_9 and D) Space filled Van der Waal's sphere structure of Cd_M_9.

Conclusion

Myricetin is a drug which contains six -OH groups hence can form six different nanocomposite structures with any metal when attached to different -OH groups separately. Among all these -OH groups, the -OH present at 7 position of the drug molecule showed lowest energy when interacted with metal through Boron. This suggests that -OH at carbon number 7 might be the most suitable position for nanoparticle attachment. When we constructed the final composite model structure of Myricetin with both Copper and Cadmium, Cadmium exhibited lower energy level than the Copper. From this study it can be concluded that Cadmium could be the suitable metal to form an energetically favorable nanocomposite structure with Myricetin. Our previous studies on this area with several drug molecules and many metal atoms also support this result.

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