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Designing of Nanocomposite model structure using Gallic acid and Ellagic acid with four different metals

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ABSTRACT

Bioflavonoids are now being an attraction of research for a couple of decades due to its immense application in therapeutics. To apply these flavonoids as a potential therapeutic drug in medical field, a vehicle is required to increase their retention in physiological conditions. Nanoparticles have come up with several unique properties to act as medium for drug delivery system. Hence, the formulation of nanoparticle – drug composite and their study has become mandatory today. Here we selected Gallic acid and its dimer Ellagic acid as drug molecules for having several applications in therapeutics that can be interacted with a metal nanoparticle. Twelve metals have been considered for study of interaction with mentioned drug molecules to construct nanoparticle–drug nanocomposite model structure by computational approach. All structures were subjected to energy minimization for reaching most stable structure. By considering all structures, cadmium (Cd) exhibited the most stable nanocomposite structure with Gallic acid and Ellagic acid as the composites contained lowest energy levels. It was also found that *meta* positioned –OH of Gallic acid is preferably the best suitable attachement site for metal atom and the same for Ellagic acid was found to be at corresponding 2 and 7 positioned –OH groups.

Keywords: Flavonoids, Nanoparticles, Gallic acid, Ellagic acid and Avogadro software.

INTRODUCTION

Since technology is evolving every hour, the doors of various subjects are also opening. One of them, which has deviated the attention for most of the researchers towards itself, is mainly these tiny entities, very well known as nanoparticles. In context to this, the groundwork has led to finding all the answers regarding nanoparticle-mediated drug delivery. These are basically of two types; the first one is the polymeric nanoparticles (Bolhassani *et al.*, 2014) which entrap drug molecules inside their core whereas the metallic nanoparticles (Mody *et al.*, 2010) attach drug

molecules to their surface. These metal nanoparticle–drug composites hold greater status than that of polymeric nanoparticle – drug formulations, which can be used as a carrier of drug molecules to combat various ailments because it attaches the drug molecule directly to its surface. The metals which have already been reported for having the potency to synthesize nanoparticles, such as gold (Au) (Duncan *et al.*, 2010), silver (Ag) (Santos *et al.*, 2014; Mandal, 2017), copper (Cu) (Kruk *et al.*, 2015), iron (Fe) (Mahdy *et al.*, 2012), zinc (Zn) (Rojas *et al.*, 2016), nickel (Ni) (Guo *et al.*, 2009), platinum (Pt) (Kim *et al.*, 2010), palladium (Pd) (Adams *et al.*, 2014), ruthenium (Ru) (Viau *et al.*, 2003), rhodium (Rh) (Xu *et al.*, 2019), cadmium (Cd) (Qi *et al.*, 2001) and antimony (Sb) (Yin *et al.*, 2019). Amongst all the metals selectively were reported to be heavy as well as a toxic substance, although these can be minimized via accurate treatment in the proper dose. Nevertheless, the selection of proper metallic nanoparticle is a prime necessity as one needs to be familiar with the interaction between nanoparticle and drug molecules.

The ubiquitous, polyphenolic compounds–Flavonoids exhibit various therapeutic applications such as antioxidants (Anjaneyulu and Chopra, 2004), anti-inflammatory (Guardia *et al.*, 2001), anticancer (Ren *et al.*, 2003) and many more. In our recent study, Gallic acid and its dimer Ellagic acid have been selected – in consideration of all its extensive availability in food supplements and the potentiality to be applied in various medical and research fields. The study on the interaction among eight metals (Au, Ag, Cu, Fe, Ni, Zn, Pt, and Pd) with Gallic acid and Ellagic acid has previously been reported by us (Hazra and Pal, 2020). Therefore in this research article, we reported the interaction between Gallic acid and its dimer Ellagic acid along with four metals which also can synthesize nanoparticles, these are cadmium (Cd), rhodium (Rh), ruthenium (Ru) and antimony (Sb). Hence our study will help in the selection of the most suitable metal for synthesizing nanoparticle – drug composite structures that are to be used as a carrier in association with the presence of above-mentioned drug molecules.

MATERIALS AND METHODS

To study the interaction between metal Nanoparticles and the drug molecule, we began with constructing the structures of Gallic acid and Ellagic acid in Avogadro – software for windows (Hanwell *et al.*, 2012). The molecule of Gallic acid has 3 -OH groups that serve its position for binding sites and similarly for Ellagic acid, it has 4 -OH groups present in its structure. The constructed structures are shown in Figure 1 in comparison with their diagrammatic structures.

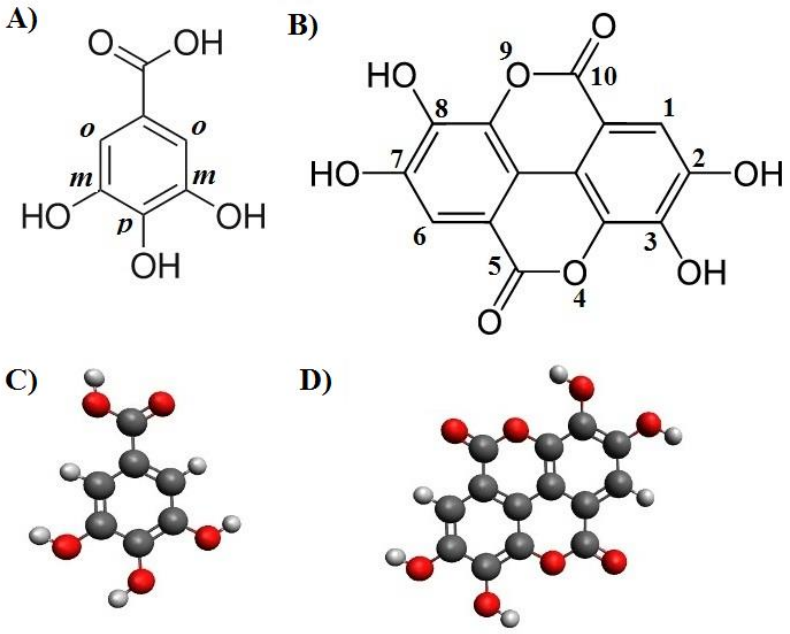

Figure 1: Diagrammatic chemical structure of A) Gallic acid and B) Ellagic acid. Avogadro software-generated structure of C) Gallic acid and D) Ellagic acid.

As we know one nanoparticle contains a large number of metal atoms, and though it is not possible to mimic *in silico,* we selected only one metal atom instead of many to study the interaction between metal and drug. The four metals (Cd, Ru, Rh, and Sb) were selected based on their potentiality towards the capability to synthesize nanoparticles well as the formation of a complex with drug molecule to be applied in a wide range of applications. With Gallic acid and Ellagic acid, three and four nanocomposite structures were being constructed respectively. In this case, each of the hydrogen atoms of the –OH group was replaced by metal atom from their specific positions one at a time to form the nanocomposite. After completion of structures, the energy was being minimized. Along with energy levels, C–O, O–metal bond length, and C–O–metal bond angles were also measured. All these parameters are listed in tabular form (Table 1 and 2). From the lowest energy level, the most stable structure and susceptible position for nanoparticle binding were in view.

RESULTS AND DISCUSSIONS

Interaction of Gallic acid with metal nanoparticle:

Firstly the selected four metal atoms such as Cd, Rh, Ru, and Sb were used to form the nanocomposite model structures with gallic acid. There are two –OH groups present at *meta* position (*m*) and one at the *para* position (*p*) of gallic acid. The four atoms were interacted with the same and after the energy minimization of this nanocomposite; the result has been listed in table–1. From the energy level, it is clear that the metal when interacts with the –OH group present at *meta* position posses lower energy than that of *para*. To be noted that both *meta* positions exhibit similar energy levels with minimal energy difference in few. Hence it can be taken into consideration that binding at *meta* position could be more suitable in comparison to the *para* position concerning the metal atom binding ability. Nanocomposite model structures of gallic acid with all four metal atoms at their different attachment sites have been depicted in Figure 2.

For the following, in the case of cadmium (Cd), the nanocomposite structure showed minimum energy in comparison with the other three metals; out of which antimony (Sb) proclaimed to have the highest energy among them when associated with gallic acid molecule. Abiding by the statement *para* positioned -OH group having higher energy levels than *meta* position. Though the ruthenium nanocomposite structure can be taken into consideration by looking at its energy levels at *meta* position, there is a little difference in the corresponding levels. By considering all structures, Cd nanocomposite structure exhibited the least energy level which was found the same for both *meta* positioned –OH groups. Hence it can be taken as the best suitable metal for the synthesis of the nanocomposite, with gallic acid later for therapeutic applications too.

Table 1: List of energy levels of all Gallic acid – nanoparticle nanocomposite model structures along with metal – O – C bond angles, metal – O bond lengths, and O – C bond lengths.

Metal	Nanocomposite	Energy (KJ/Mol)	Metal – O – C bond angle	Bond length (Å)	
				Metal – O	O – C
Cadmium	Cd-GA_1	70.5048	121.2°	2.002	1.346
	Cd-GA_2	71.4648	123.7°	2.004	1.348
	Cd-GA_3	70.547	121.2°	2.003	1.346
Rhodium	Rh-GA_1	71.5246	120.5°	1.894	1.346
	Rh-GA_2	72.393	121.7°	1.895	1.348
	Rh-GA_3	71.5438	120.5°	1.894	1.346
Ruthenium	Ru-GA_1	71.3543	120.5°	2.014	1.346
	Ru-GA_2	72.0936	121.8°	2.015	1.348
	Ru-GA_3	71.3786	120.5°	2.014	1.346
Antimony	Sb-GA_1	85.5551	127.4°	2.015	1.355
	Sb-GA_2	97.493	130.7°	2.016	1.358
	Sb-GA_3	85.4541	127.3°	2.015	1.355

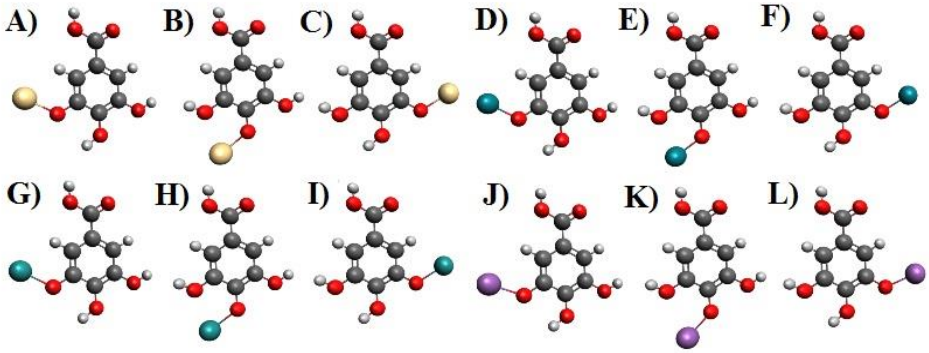

Figure 2: Nanocomposite model structures of Gallic acid with Cadmium [A) Cd-GA_1, B) Cd-GA_2, C) Cd-GA_3], Rhodium [D) Rh-GA_1, E) Rh-GA_2, F) Rh-GA_3], Ruthenium [G) Ru-GA_1, H) Ru-GA_2, I) Ru-GA_3] and Antimony [J) Sb-GA_1, K) Sb-GA_2, L) Sb-GA_3].

Although the formation of nano-complex of gallic acid with metallic nanoparticles like gold (Moreno-Alvarez *et al.*, 2010), silver (Ghodake *et al.*, 2020; Lakshmipathy and Nanda, 2015; Farrokhnia *et al.*, 2019), palladium (Can *et al.*, 2012) and iron (Zeng *et al.*, 2016) had been reported previously their interaction between the metal and drug molecule has not been vividly studied yet.

Interaction of Ellagic acid with metal nanoparticle:

Ellagic acid is a dimer of gallic acid having various/many therapeutic potentials. The structure contains four –OH groups present at 2, 3, 7, and 8 positions (as shown in Figure 1B). Hence these are four susceptible locations for binding of metal atoms. Therefore here we endeavored to search some metal atoms having the most stable and minimal energy level which may bind with Ellagic acid to form a nanocomposite. These nanocomposite formulations would later fulfill the requirements for being applied in therapeutics. The calculated energy levels for all metal nanocomposite structures have been listed in table–2. Due to the sharing of similar chemical environments amid 3 and 8 positioned -OH groups, we noticed when they interacted with metal, gave out similar energy levels which were also noticed in –OH groups positioned at 2 and 7 which corresponds to *meta* positions in Gallic acid.

Table 2: of energy levels of all Ellagic acid – nanoparticle nanocomposite model structures along with metal – O – C bond angles, metal – O bond lengths, and O – C bond lengths.

Metal	Nanocomposite	Energy (KJ/Mol)	Metal – O – C bond angle	Bond length (Å)	
				Metal – O	O – C
Cadmium	Cd-EA_1	207.218	122.2°	2.002	1.346
	Cd-EA_2	207.589	123.4°	2.004	1.348
	Cd-EA_3	207.218	121.2°	2.002	1.346
	Cd-EA_4	207.589	123.4°	2.004	1.348
Rhodium	Rh-EA_1	208.834	120.5°	1.894	1.346
	Rh-EA_2	208.853	121.5°	1.895	1.348
	Rh-EA_3	208.234	120.5°	1.894	1.346
	Rh-EA_4	208.854	121.5°	1.895	1.348
Ruthenium	Ru-EA_1	208.07	120.5°	2.014	1.346
	Ru-EA_2	208.548	121.6°	2.015	1.348
	Ru-EA_3	208.07	120.5°	2.014	1.346
	Ru-EA_4	208.548	121.6°	2.015	1.348
Antimony	Sb-EA_1	221.956	127.3°	2.015	1.355
	Sb-EA_2	231.947	130.5°	2.016	1.358
	Sb-EA_3	221.956	127.3°	2.015	1.355
	Sb-EA_4	231.948	130.5°	2.016	1.358

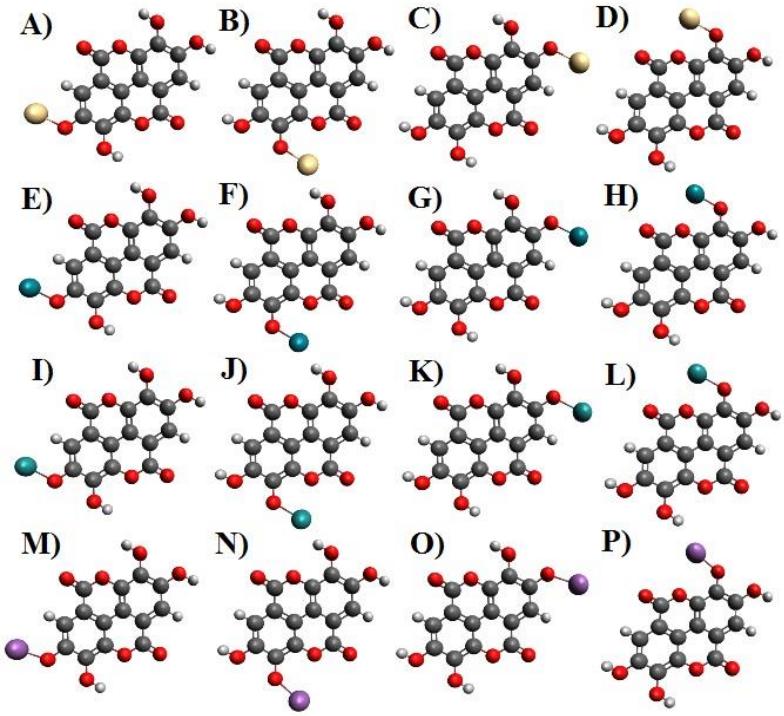

Figure 3: Nanocomposite model structures of Ellagic acid with Cadmium [A) Cd-EA_1, B) Cd-EA_2, C) Cd-EA_3, D) Cd-EA_4], Rhodium [E) Rh-EA_1, F) Rh-EA_2, G) Rh-EA_3, H) Rh-EA_4], Ruthenium [I) Ru-EA_1, J) Ru-EA_2, K) Ru-EA_3, L) Ru-EA_4] and Antimony [M) Sb-EA_1, N) Sb-EA_2, O) Sb-EA_3, P) Sb-EA_4].

Alike Gallic acid, the metals namely cadmium, rhodium, ruthenium, and antimony were also interacted with Ellagic acid and showed an almost similar trend of energy levels. In interacting with Ellagic acid, cadmium was found to have the lowest energy level in comparison to other metal atoms and amongst them, antimony showed the highest. Considering the atoms when placed at 2 and 7 positions showed the same energy content and even when positioned at 3 and 8 gave almost identical results.

Hence from observation, it can be said that 2 and 7 positioned –OH groups showed similar energy levels as 3 and 8 positioned –OH groups also do. Moreover, composites with –OH groups of 2 and 7 position contained less energy than that of 3 and 8 positions. As 2 and 7 position of Ellagic acid corresponds to *meta* position in Gallic acid, the results in an agreement for both the flavonoid molecules.

The result is inclined towards Cadmium possessing the least energy level and most suited to form a nanocomposite structure with Ellagic acid for remedial.

Very few metals like silver (Barnaby *et al*., 2011) and copper (Affrose *et al*., 2014) have been reported to form nanocomposite along with Ellagic acid. In those cases, the interaction study between drugs and nanoparticles has not been emphasized so well. Consequently, here we tried to study the mode of interaction thoroughly which may help researchers in their upcoming future researches in this field.

CONCLUSION

In Gallic acid, both –OH groups present at its *meta* position may be considered as the best site for binding with metal atoms instead of *para* positioning –OH group. Whereas in the case of Ellagic acid, -OH groups present at 2 and 7 positions can interact with metal atoms possess lower energy in contrast to 3 and 8 positioned -OH groups. Taking into consideration all these above-mentioned results, Cadmium was found to be the most suitable metal atom to construct the nanocomposite with both Gallic as well as Ellagic acid.

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Conflict of Interest

The author declares that there is no conflict of interest.

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