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# Formulation of Metal Nanocomposite Model Structures with Gallic acid and Ellagic acid by Computational Method

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***Abstract:*** Nanoparticles are very attractive concern for scientists in recent years. Their different physical and chemical properties make them a very good vehicle for drug molecules for that reason their application in therapeutics and drug delivery research is remarkable. Many metals are already being used to formulate nanoparticles for this purpose. The flavonoids have also grabbed attention of many research groups for their tremendous efficiency for combating a huge variety of diseases. Hence, Metal nanoparticle drug composite formulation is one of the prime concerns in today's research. To understand the attachment of drug on nanoparticle, it is very much important to study the interaction between drug and the nanoparticle. That is why; here we are reporting the interaction between two flavonoids (Gallic acid and Ellagic acid) with eight metal atoms (gold, silver, iron, copper, nickel, zinc, platinum and palladium). We used Avogadro software to formulate the nanocomposite model structures and to minimize the energy level. From the results it can be concluded that the –OH groups present at the *meta* positions of Gallic acid are most suitable site for binding of metal atom and in case of Ellagic acid the binding site would be the -OH groups present at 2 and 7 positions. For both Gallic acid and Ellagic acid, platinum was found to be most suitable nanocomposite having lowest energy level.

***Keywords:*** **Nanoparticle, Nanocluster, Gallic acid, Ellagic acid and Avogadro Software.**

## 1. INTRODUCTION:

Nanoparticle mediated drug delivery is one of the major interested area of research nowadays. There are mainly two types of nanoparticles are being synthesized for application in drug delivery (Jong and Borm, 2008); they are polymeric (Crucho and Barros, 2017) and metallic (Kumar et al., 2018). The polymeric nanoparticles entrap drug molecules inside their core (Vrignaud et al., 2011) whereas metallic nanoparticles attach drug molecules on their surface (Levin et al., 2009). A huge variety of metallic nanoparticles are being used as a carrier of drug molecules for the treatment against many diseases and antimicrobial agents. Among these metals the most widely used and applied metals are gold (Au) (Duncan et al., 2010), silver (Ag) (Santos et al., 2014; Mandal, 2017), iron (Fe) (Mahdy et al., 2012), cupper (Cu) (Kruk et al., 2015), nickel (Ni) (Guo et al., 2009), zinc (Zn) (Rojas et al., 2016), platinum (Pt) (Kim et al., 2010) and palladium (Pd) (Adams et al., 2014). Although amongst them, many have been recognized as heavy metals and reported to have toxic effects on living entity though the dose for treatment can be adjusted to minimize the adverse effect. To use the metallic nanoparticles as a vehicle for drug molecules, they must be attached to the surface of the nanoparticles, and to do so, the metal should be interacted with the drug molecule. So, before selecting a proper nanoparticle for a specific drug, it is necessary to have the idea about interaction pattern between the nanoparticle and the drug molecule.

Flavonoids are polyphenolic compounds having many therapeutic activities including antioxidant (Anjaneyulu and Chopra, 2004), anti-inflammatory (Guardia et al., 2001), anticancer (Ren et al., 2003), antihyperglycemic (Wu and Yen, 2005) and many more. Here we have taken Gallic acid and its dimer Ellagic acid for their extensive availability in daily diet and food materials. These two drug molecules have a variety of therapeutic applications as other flavonoids do possess (Soong and Barlow, 2006; Chen et al., 2007; Singh et al., 2014; Perchellet et al., 1992). Many research groups have worked on the Gallic acid – metal nanoparticle complex formation and their activity. In this research article, we are reporting the interaction study between Gallic acid and Ellagic acid along with eight metals as mentioned above to formulate nanocomposite model structures. This study will help us to select the best suitable metal nanoparticle for being used as carrier for Gallic acid and Ellagic acid.

## 2. METHODS:

To study the interaction pattern between metal nanoparticle and the drug molecules, at the very beginning we formulated the chemical structure of Gallic acid and Ellagic acid using Avogadro software for windows (Hanwell et al., 2012). The molecule of Gallic acid contain three –OH groups (structure of Gallic acid is shown in Fig. 1A) and its dimer Ellagic acid has four –OH groups (structure of Ellagic acid is shown in Fig. 1B) in it. Hence in Gallic acid, there are three probable positions for the nanoparticle binding and in case of Ellagic acid, there are four binding site. At all these positions where –OH groups are present, we attached the metal atoms for the study of their interaction. One nanoparticle contains a large number of metal atoms which is not possible to mimic *in silico*. That is why we studied the interaction between the drug molecules with a selected single metal atom. Although a single atom does not represent a nanoparticle, to minimize the structural complexity we are considering the metal atom as a nanoparticle mimetic entity. The drug molecule attached with a single metal atom is called a drug nanocomposite and all these composites are given a unique name to identify the position of metal atom binding site. The metals have been chosen according to their potentiality towards the application in drug delivery as nanoparticle. Here we selected gold, silver, iron, copper, zinc, nickel, platinum and palladium. Among them, gold, silver, iron and copper are maximally used as their nanoparticulate form for drug delivery. Rests are also in use but in lesser extent. With Gallic acid and Ellagic acid, we constructed three and four nanocomposite model structures respectively for each metal atom. After the formulation of nanocomposite structures, the energy minimization was also done. Then the levels of energy were calculated for each model structure and listed along with the 'metal–O–C' bond angle, 'metal–O bond length' and O–C bond length. From the lowest energy level, the most stable structure was found and the most susceptible position for nanoparticle binding was also pointed out.

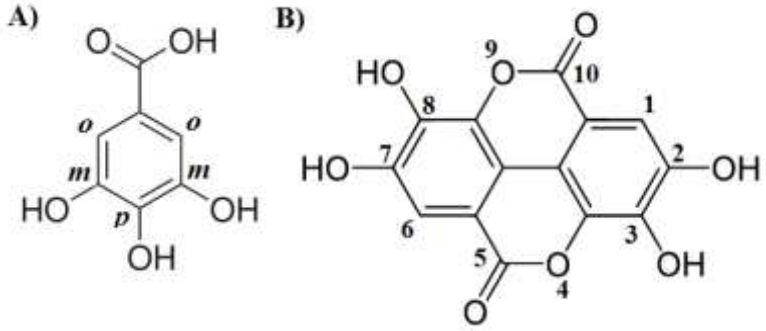


**Figure 1: Chemical structures of A) Gallic acid [*o* – *ortho*; *m* – *meta*; *p* – *para*] and B) Ellagic acid.**

## 3. RESULTS AND DISCUSSIONS:

### 3.1. Interaction of Gallic acid with metal atoms:

Gold, silver, iron and copper are the metals widely used to form nanoparticles and for the application in therapeutics. Hence, at the beginning, we used these metal atoms to form Gallic acid nanocomposite. There are two –OH groups present at *meta* position and one –OH group is present in *para* position in Gallic acid (structure shown in Fig. 1A). The presence of –OH groups at *meta* and *para* positions are interacted with gold, silver, iron and copper metal atoms correspondingly. After energy minimization, the calculated minimum energy levels were listed in table 1. From the minimum energy levels, it can be clearly shown that in both the nanocomposite structures where metal atom binds with –OH present at *meta* positions possess lower energy than that of its corresponding *para* position. Iron does not show the same feature like gold, silver and copper. It binds to the *para* –OH group having quite low energy, although the energy difference from *meta* position is negligible. Surprisingly both *meta* positions exhibited almost same energy level when bound with corresponding metal atoms. Hence it can be suggested that *meta* positions are suitable for the binding of metal atoms but not the *para* position.

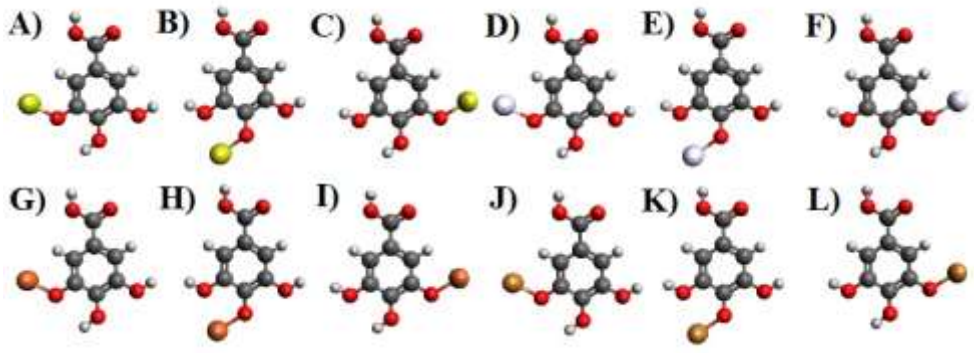


**Figure 2: Gallic acid nanocomposite model structures with different metal atoms namely Gold [A) Au-GA_1, B) Au-GA_2, C) Au-GA_3], Silver [D) Ag-GA_1, E) Ag-GA_2, F) Ag-GA_3], Iron [G) Fe-GA_1, H) Fe-GA_2, I) Fe-GA_3] and Copper [J) Cu-GA_1, K) Cu-GA_2, L) Cu-GA_3].**

Though the above mentioned metals are most widely used for nanoparticle formulation, beside that zinc, nickel, platinum and palladium are also used quite often as the metal for nanoparticle synthesis and subsequently used as a vehicle for drug delivery. Similar to the previous metal atoms, these metal atoms can also bind at three probable –OH groups present in *meta* (two positions) and *para* (one position) with Gallic acid. Like iron, nickel also exhibited almost similar energy level for the three positions with

the energy of *para* –OH little less than both *meta* positions. In case of platinum, the nanocomposite structures possess the energy levels exactly similar to gold, silver and copper, i.e. *para* position contains higher energy level than both *meta* positions. Zinc and platinum have similar energy levels when bind with all three –OH groups present in Gallic acid but –OH group present at *para* position has little higher energy level which is also supportive to gold, silver, copper and platinum results.

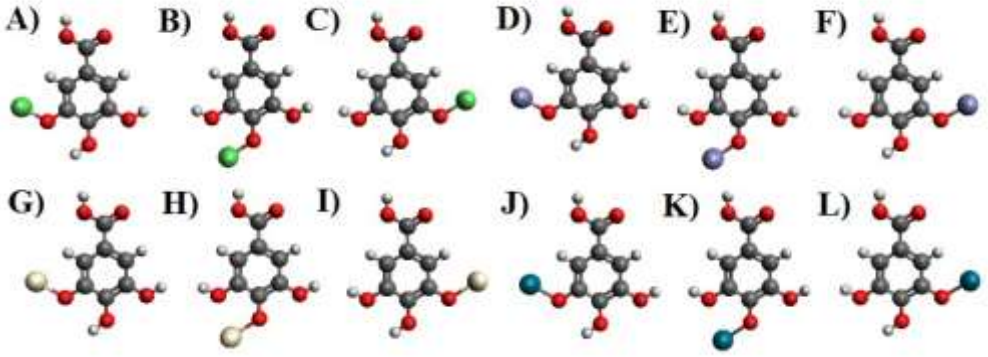


**Figure 3: Gallic acid nanocomposite model structures with metal atoms namely Nickel [3A) Ni-GA_1, B) Ni-GA_2, C) Ni-GA_3], Zinc [D) Zn-GA_1, E) Zn-GA_2, F) Zn-GA_3] Platinum [G) Pt-GA_1, H) Pt-GA_2, I) Pt-GA_3] and Palladium [J) Pd-GA_1, K) Pd-GA_2, L) Pd-GA_3].**

So from all these structures, it can be said that gold, silver, copper and palladium have similar energy level to form nanocomposite with Gallic acid. In all cases, –OH group present at *para* position exhibited higher energy than both *meta* positioning –OH groups. Zinc and platinum are also in agreement with above mentioned metals that means they also bind stably with both *meta* positioned –OH groups than *para* positioned –OH group, but their energy levels were lower than that of gold, silver, copper and palladium. On the other hand, iron and nickel have little higher energy level when they bind with *para* positioned –OH group than binding with–OH groups at *meta* position in Gallic acid structure, though the difference in their energy level is very low. By observing all the respective results, zinc and platinum were found to have less amount of energy levels than other metal atoms. Therefore, we can suggest that zinc and platinum both could be the best choice over other selected metals (8 metals here in this study) for the synthesis of nanocomposite with Gallic acid, and this can be applied in therapeutic applications also.

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

| Metal | Compound | Energy (KJ/mol) | Bond Angle ($^{O}$) | Bond Length (Å) | |
|---|---|---|---|---|---|
| | | | | Metal–O Bond | O–C Bond |
| Gold (Au) | Au-GA_1 | 72.7214 | 121.3 | 1.860 | 1.347 |
| | Au-GA_2 | 74.9091 | 123.0 | 1.861 | 1.350 |
| | Au-GA_3 | 72.7118 | 121.3 | 1.860 | 1.347 |
| Silver (Ag) | Ag-GA_1 | 71.8442 | 121.2 | 1.967 | 1.346 |
| | Ag-GA_2 | 72.8084 | 123.1 | 1.968 | 1.348 |
| | Ag-GA_3 | 71.8581 | 121.1 | 1.967 | 1.346 |
| Iron (Fe) | Fe-GA_1 | 71.6597 | 120.4 | 1.886 | 1.346 |
| | Fe-GA_2 | 71.4353 | 121.4 | 1.887 | 1.347 |
| | Fe-GA_3 | 71.6822 | 120.4 | 1.886 | 1.346 |
| Cupper (Cu) | Cu-GA_1 | 72.5594 | 121.2 | 1.876 | 1.346 |
| | Cu-GA_2 | 73.2884 | 122.9 | 1.877 | 1.348 |
| | Cu-GA_3 | 72.5594 | 121.1 | 1.876 | 1.346 |
| Nickel (Ni) | Ni-GA_1 | 71.7044 | 120.4 | 1.750 | 1.346 |
| | Ni-GA_2 | 71.5066 | 121.2 | 1.750 | 1.347 |
| | Ni-GA_3 | 71.7253 | 120.4 | 1.750 | 1.346 |
| Zinc (Zn) | Zn-GA_1 | 71.0429 | 121.3 | 1.797 | 1.346 |
| | Zn-GA_2 | 71.6053 | 123.3 | 1.798 | 1.348 |
| | Zn-GA_3 | 71.0747 | 121.2 | 1.797 | 1.346 |
| Platinum (Pt) | Pt-GA_1 | 71.0207 | 120.4 | 1.956 | 1.346 |
| | Pt-GA_2 | 71.3107 | 121.4 | 1.957 | 1.348 |
| | Pt-GA_3 | 71.0535 | 120.3 | 1.956 | 1.346 |
| Palladium (Pd) | Pd-GA_1 | 71.4435 | 120.5 | 1.915 | 1.346 |
| | Pd-GA_2 | 72.0269 | 121.6 | 1.915 | 1.348 |
| | Pd-GA_3 | 71.4660 | 120.5 | 1.915 | 1.346 |

The metals which have been used for the synthesis of nanocomposite with Gallic acid mostly is silver (Ghodake et al., 2020; Lakshmipathy and Nanda, 2015; Farrokhnia et al., 2019). Nanocomposite formulation of Gallic acid with iron (Zeng et al., 2016), gold (Moreno-Alvarez et al., 2010) and palladium (Can et al., 2012) have been reported but other metals are not very much studied in the field of nanocomposite formulation with Gallic acid.

**3.2. Interaction of Ellagic acid with metal atoms:**

Ellagic acid is the dimer of gallic acid, having different therapeutic potentials (Edderkaoui et al., 2008). This structure contains four –OH groups at 2, 3, 7 and 8 positions (structure shown in Fig. 1B). Therefore these are the susceptible locations for binding of metal atoms. Here we will find the best suitable metal which could be bound most stably having minimum energy level (i.e.) with the drug to form Ellagic acid–metal nanocomposite, so that these composites can have the application in drug delivery also. Since gold, silver, iron and copper are being used most frequently as metal for synthesis of nanocomposite in drug delivery, hence these metals are studied first for their suitability of binding with different –OH groups present in the structural conformation of Ellagic acid. In case of gold, silver and copper, the energy level varies when the metal atoms are attached with –OH groups present at their different positions. As the Gallic acid structure resembles, –OH groups present at 2 and 7 positions of its structure possess similar chemical environment. That is why, when they interact with metal atoms, they exhibited almost similar level of energy. The same result was noticed for the –OH groups present at 3 and 8 positions also. Only Iron showed almost equal energy levels (difference in energy levels are very less) when attached with any of the four –OH groups present at different positions (i.e; 2, 3, 7 or 8) in Ellagic acid. Not only that, iron has lower energy levels when attached with any –OH groups present in Ellagic acid with respect to gold, silver and copper.

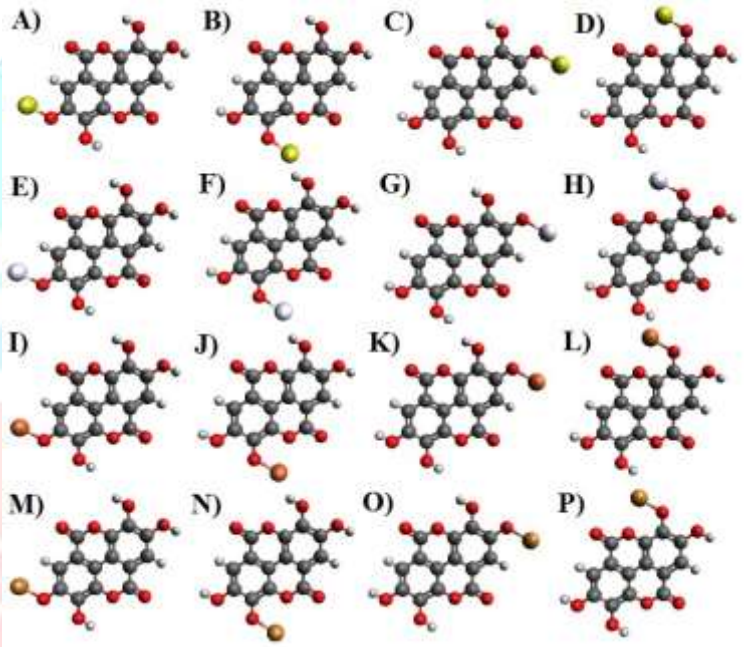


**Figure 4: Ellagic acid nanocomposite model structures with different metal atoms, namely Gold [A) Au-EA_1, B) Au-EA_2, C) Au-EA_3, D) Au-EA_4], Silver [E) AG-EA_1, F) Ag-EA_2, G) Ag-EA_3, H) Ag-EA_4], Iron [I) Fe-EA_1, J) Fe-EA_2, K) Fe-EA_3, L) Fe-EA_4] and Copper [M) Cu-EA_1, N) Cu-EA_2, O) Cu-EA_3, P) Cu-EA_4].**

Alike Gallic acid, we performed the interaction study of Ellagic acid with nickel, zinc, platinum and palladium (Fig. 5). Although they are less attractive for the synthesis of nanoparticle, still they have potentiality to form nanocomposite with drug molecules. Among these metals, platinum exhibited uniformly low energy content as compared to nickel, zinc and palladium atoms, when interacted with different –OH groups of Ellagic acid. Here also similar trend of energy levels were observed. Considering every metal, 2 and 7 positions of –OH groups were found to have almost same energy levels after binding with metal atoms. This pattern was followed in case of 3 and 8 positions also, but the variation in energy level was minimum in platinum with respect to nickel, zinc and palladium.

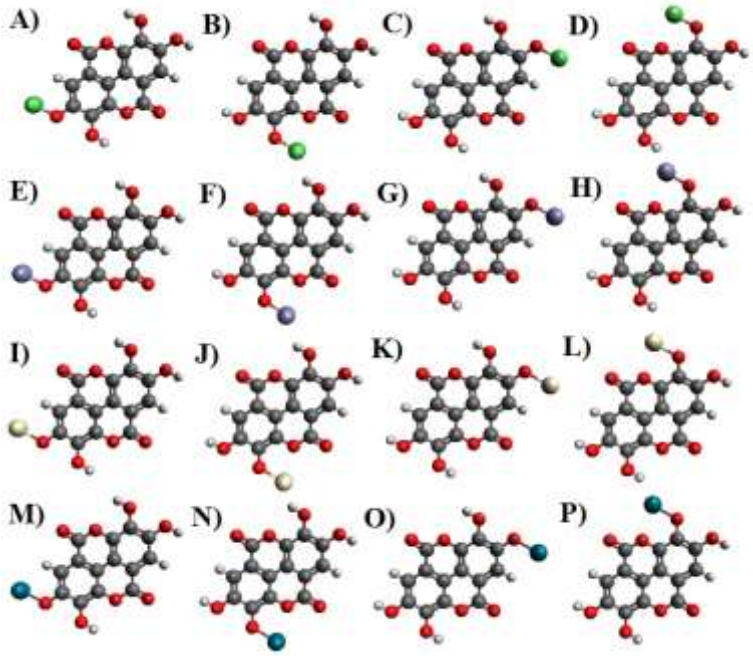


**Figure 5: acid nanocomposite model structures with different metal atoms, such as Nickel [A) Ni-EA_1, B) Ni-EA_2, C) Ni-EA_3, D) Ni-EA_4], Zinc [E) Zn-EA_1, F) Zn-EA_2, G) Zn-EA_3, H) Zn-EA_4], Platinum [I) Pt-EA_1, J) Pt-EA_2, K) Pt-EA_3, L) Pt-EA_4] and Palladium [M) Pd-EA_1, N) Pd-EA_2, O) Pd-EA_3, P) Pd-EA_4].**

Hence from the observations, we can say that –OH groups present at 2 and 7 positions as well as at 3 and 8 positions in Ellagic acid structure exhibited similar energy levels when bound with different metal atoms. Though, 2 and 7 positioned –OH groups possess lower energy levels than –OH groups present at 3 and 8 positions. Among all these eight metals, Platinum possesses the lowest energy levels when bind with all –OH positions. Hence it can be suggested that Platinum could be the best metal for constructing the Ellagic acid–metal nanocomposite formulation.

**Table 2: List of calculated energy levels of different Ellagic acid–metal nanocomposite model structures, metal–O–C bond angles, metal–O bond length and O–C bond lengths of all nanocomposite model structures with Gallic acid.**

| Metal | Compound | Energy (KJ/mol) | Bond Angle ($^{O}$) | Bond Length (Å) | |
|---|---|---|---|---|---|
| | | | | Metal – O Bond | O – C Bond |
| Gold (Au) | Au-EA_1 | 209.404 | 121.3 | 1.860 | 1.347 |
| | Au-EA_2 | 211.242 | 122.8 | 1.861 | 1.349 |
| | Au-EA_3 | 209.394 | 121.3 | 1.860 | 1.347 |
| | Au-EA_4 | 211.242 | 122.8 | 1.861 | 1.349 |
| Silver (Ag) | Ag-EA_1 | 208.549 | 121.1 | 1.967 | 1.346 |
| | Ag-EA_2 | 209.312 | 122.8 | 1.968 | 1.348 |
| | Ag-EA_3 | 208.554 | 121.1 | 1.967 | 1.346 |
| | Ag-EA_4 | 209.312 | 122.8 | 1.968 | 1.348 |
| Iron (Fe) | Fe-EA_1 | 208.387 | 120.4 | 1.886 | 1.345 |
| | Fe-EA_2 | 208.235 | 121.2 | 1.887 | 1.347 |
| | Fe-EA_3 | 208.387 | 120.4 | 1.886 | 1.345 |
| | Fe-EA_4 | 208.235 | 121.2 | 1.887 | 1.347 |
| Cupper (Cu) | Cu-EA_1 | 209.261 | 121.1 | 1.876 | 1.346 |
| | Cu-EA_2 | 210.029 | 122.7 | 1.877 | 1.348 |
| | Cu-EA_3 | 209.262 | 121.1 | 1.876 | 1.346 |
| | Cu-EA_4 | 210.029 | 122.7 | 1.877 | 1.348 |
| Nickel (Ni) | Ni-EA_1 | 208.428 | 120.4 | 1.749 | 1.346 |
| | Ni-EA_2 | 208.299 | 121.1 | 1.750 | 1.347 |
| | Ni-EA_3 | 208.428 | 120.4 | 1.749 | 1.346 |
| | Ni-EA_4 | 208.299 | 121.1 | 1.750 | 1.347 |
| Zinc (Zn) | Zn-EA_1 | 207.752 | 121.2 | 1.797 | 1.346 |
| | Zn-EA_2 | 208.001 | 123.0 | 1.798 | 1.348 |
| | Zn-EA_3 | 207.756 | 121.2 | 1.797 | 1.346 |
| | Zn-EA_4 | 208.001 | 123.0 | 1.798 | 1.348 |
| Platinum (Pt) | Pt-EA_1 | 207.745 | 120.3 | 1.956 | 1.345 |
| | Pt-EA_2 | 207.794 | 121.3 | 1.957 | 1.347 |

| | | | | | |
|---|---|---|---|---|---|
| | Pt-EA_3 | 207.745 | 120.3 | 1.956 | 1.345 |
| | Pt-EA_4 | 207.794 | 121.3 | 1.957 | 1.347 |
| Palladium (Pd) | Pd-EA_1 | 208.159 | 120.5 | 1.915 | 1.346 |
| | Pd-EA_2 | 208.546 | 121.5 | 1.915 | 1.348 |
| | Pd-EA_3 | 208.159 | 120.5 | 1.915 | 1.346 |
| | Pd-EA_4 | 208.546 | 121.5 | 1.915 | 1.348 |

Nanocomposite formation of Ellagic acid with metal has not been studied very much. Although Silver (Barnaby et al., 2011) and Copper (Affrose et al., 2014) have been reported for the formulation of nanocomposite with Ellagic acid, but still the interaction study was very much less in the literature.

## 4. CONCLUSION:

In Gallic acid, both –OH groups present at *meta* positions are more suitable for binding with metal atoms than *para* positioning –OH groups. But in case of Ellagic acid, –OH groups of 2 and 7 positions can interact with metal atoms with lower energy than that of 3 and 8 positions –OH groups. Most importantly it was found that Platinum could be the best suitable metal to form a nanocomposite with both Gallic acid and Ellagic acid.

We can see that the interaction of Gallic acid and Ellagic acid have not yet been studied vividly so far. Therefore, in this circumstance, the interaction study of metal nanocomposite with Gallic acid and Ellagic acid become an important aspect and we hope this study will help us along with other research groups who are engaged with research on metal nanoparticle formation as a drug delivery system.

## 5. ACKNOWLEDGEMENTS:

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