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RESEARCH ARTICLE

SPECULATION OF METAL FOR SUITABLE LUTEOLIN – METAL NANOCOMPOSITE FORMULATION THROUGH *IN SILICO* APPROACH

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Abstract

Nanocomposite formulation has an impact on therapeutics and medical research as we are moving forward in these fields. During the formation of nanocomposite, the most important part is the mode of interaction between drug and nanoparticle. Hence the study about this interaction is necessary for understanding their binding nature. In our present study we selected luteolin as drug molecule because of its remarkable application in combating several diseases. To form nanocomposite, we choose metals which are widely used for nanoparticles synthesis such as gold, silver, copper, iron, zinc, nickel, palladium, platinum, ruthenium, rhodium, cadmium and antimony. Here we used Avogadro software for the formation of model structures and energy minimization of these nanocomposites. From the results, cadmium was found to be most suitable metal to form nanocomposite in association with luteolin having lowest energy level and antimony possesses highest energy level amongst all metals under consideration.

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Introduction:-

The study of nanoparticle is being attractive area of research for last few decades. The increased use of nanoparticle in research and biomedical application is due to its wide range application in food additives (Weir et al., 2012) to drug delivery system (Sing and Lillard, 2009). Polymers (Rao and Geckeler, 2011) and metals (Kumar et al., 2018) are the main constituents that are widely being used in the synthesis of nanoparticle. Before implication of nanoparticles in various fields, it is very much important to know about its synthesis process as well as its characterization. The metals we have used here in the synthesis of nanoparticles are 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), nickel (Ni) (Guo et al., 2009), zinc (Zn) (Rojas et al., 2016), platinum (Pt) (Kim et al., 2010), palladium (Pd) (Adams et al., 2014), rhodium (Rh) (Xu et al., 2019), ruthenium (Ru) (Viau et al., 2003), cadmium (Cd) (Qi et al., 2001) and antimony (Sb) (Yin et al., 2019).

These metals have lots of role in the field of medical and therapeutics. Among the various uses of gold nanoparticles, therapeutic (Aziz et al., 2012) and biomedical applications (Zhang, 2015) are much renowned. Silver nanoparticles have a broad area in the application of herbicide detection (Dubas and Pimpan, 2008), biosensor (Ma et al., 2005), cancer treatment (Thapa et al., 2017), protein sensing arrays (He et al., 2014), degradation of environmental pollutants (Rastogi et al., 2012) etc. Alike silver, the copper nanoparticles have also a variety of applications in antimicrobial activity (Zain et al., 2014), metal ion sensing (Guo et al., 2016) etc. Zinc nanoparticles have a capacity to destroy tumour cells selectively and they have potentiality for drug delivery as well (Rasmussen

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et al., 2010). Ghosh et al. (2015) reported the anticancer and antimicrobial activity of platinum–palladium bimetallic nanoparticles. Cadmium and ruthenium nanoparticles also act as fluorescence probe (Wang et al., 2002) and possess catalytic activity (Yoon and Wai, 2015) respectively. Among all these, their application in medical and in the field of drug delivery is remarkable. Hence the study of these nanoparticles with drug molecules has become very important aspects of research.

Flavonoids are widely used drug molecules which are found in many food materials and frequently available in the variety of plant products. Luteolin is a bioflavonoid used for treatment of many diseases and plays a major role in preventing cancer (Lin et al., 2008; Shi et al., 2007). Although Wu et al. (2019) studied the application of luteolin in gloma therapy through folacin-modified nanoparticles, but the study on metal nanoparticle luteolin composite formation has not been done yet. If this drug is capable of binding with metals, they can construct metal nanoparticle – luteolin composite which may work as a drug delivery system to be used in therapeutic applications. In this study we are reporting the interaction of luteolin with several metal atoms.

Methods:-

Metal nanoparticles contain a huge number of metal atoms when synthesized *in vitro*. As a representation of nanoparticle we are considering the metal atom only for this study regarding its interaction with the flavonoid molecule.

The structure of luteolin was constructed first using Avogadro software for window (Hanwell et al., 2012) and subjected for energy minimization. This drug molecule has four –OH groups at 3', 4' 5 and 7 position of its chemical structure. Hence there are four probable sites for metal atom to bind. We used twelve metals here for *in silico* study of their interaction with luteolin. All these metals are widely used for nanoparticle synthesis and have remarkable application in biomedical and therapeutic. Those metals are gold, silver, copper, iron, zinc, nickel, palladium, platinum, ruthenium, rhodium, cadmium and antimony. The metal atoms were attached to four different –OH groups present in luteolin structure and allowed for energy minimization of every nanocomposite model structure. Subsequently, four metal atoms were attached at a time with four different –OH groups present on each luteolin model structure. Likewise we constructed twelve luteolin–metal nanocomposite structures and allowed for energy minimization then we calculated the bond lengths of metal–O and O–C bonds along with metal–O–C bond angle.

Results and Discussions:-

At first the structure of luteolin was constructed using Avogadro and optimized its energy level (shown in Figure 1B). After energy minimization, the structure of drug molecule was found to possess 190.631 KJ/mol of energy. Then different metal atoms were interacted at all –OH groups present on its surface to form the luteolin – metal nanocomposite.

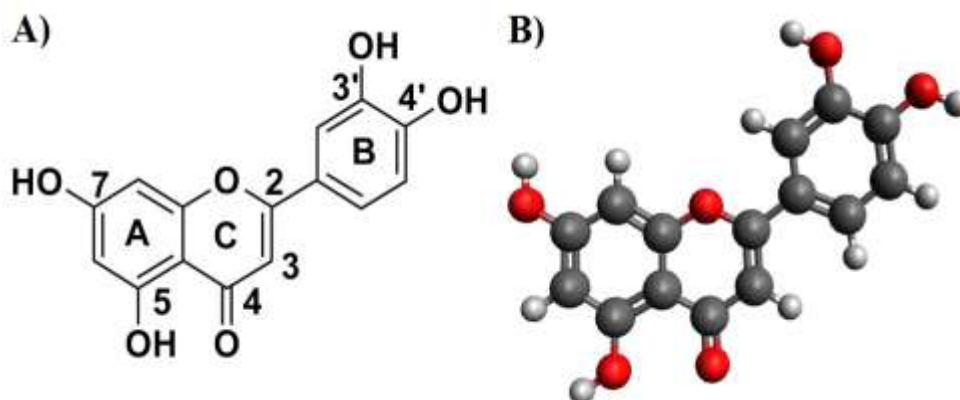


Figure 1:- A) chemical structure of luteolin. B) Model structure of luteolin formulated by Avogadro with energy minimization.

In our previous study (Hazra and Pal, 2020), we performed the attachment of the metal atoms separately at only one position of –OH group at a time, here in this study we are attaching metal atoms to all the –OH groups present in luteolin structure. As nanoparticle is available on the surface of the drug molecule (in vitro), that is why we made this kind of model. Surprisingly when metal atoms were attached with the -OH groups present on the drug molecule, the energy got lower down suggesting more stable structure. The model structures of luteolin with all metal atoms are depicted in Figure 2. The energy levels of all luteolin – metal nanocomposite are listed in table 1. From table 1, we can see gold and copper acted very closely with respect to their energy levels when attached with luteolin (180.910 and 180.414 KJ/mol respectively). Silver and nickel showed very similar energy levels i.e. 177.575 and 177.124 KJ/mol respectively; same trend was followed by iron, palladium and rhodium to have almost similar energy levels of 176.964, 176.036 and 176.327 KJ/mol respectively. Zinc and platinum exhibited similar to each other but lesser amount of energy levels (174.423 and 174.399 KJ/mol respectively) than the previous metals. Ruthenium showed 176.327 KJ/mol of energy, which was not similar to any other metals when bound with luteolin. Highest energy level was observed in case of antimony – luteolin nanocomposite i.e. 230.676 KJ/mol. Cadmium is one of the metals which supported the minimum energy level among all these metals under consideration. Cadmium–luteolin nanocomposite showed 172.265 KJ/mol of energy which suggests the most stable nanocomposite structure among all above.

Although several research groups has already reported the nanocomposite formulation with different metals such as silver (Niu et al., 2009), gold (Wu et al., 2015), zinc and copper (Jing-fen, 2006) etc, but the study of molecular interaction between the drug molecules along with the metal is not vividly studied. Here we have created a nanoparticle-surrounded environment for the drug molecule which will mimic the actual circumference of the drug in nanocomposite. Though we attached each metal atoms at every probable positions in the luteolin structure (all the –OH groups as depicted in Figure 1A), it represents the nanocomposite structure *in vivo*. From the results of energy level calculations, it was found that few metal atoms bind with the drug molecule having the lower energy while some other possess a bit higher energy level. As this is now known to all that lower energy supports more stable structure to form and higher energy provide an unfavourable condition for its stability. Hence we will consider the nanocomposite with lowest energy level for having the ability to form most stable nanocomposite model structure. In this study we found cadmium to have the lowest energy level when conjugated with luteolin supporting the most stable nanocomposite structure. On the other hand, antimony exhibited quite higher energy level in comparable to the other metal atoms in the formulation of nanocomposite that suggested the most unfavourable nanocomposite structure among all the selected metals.

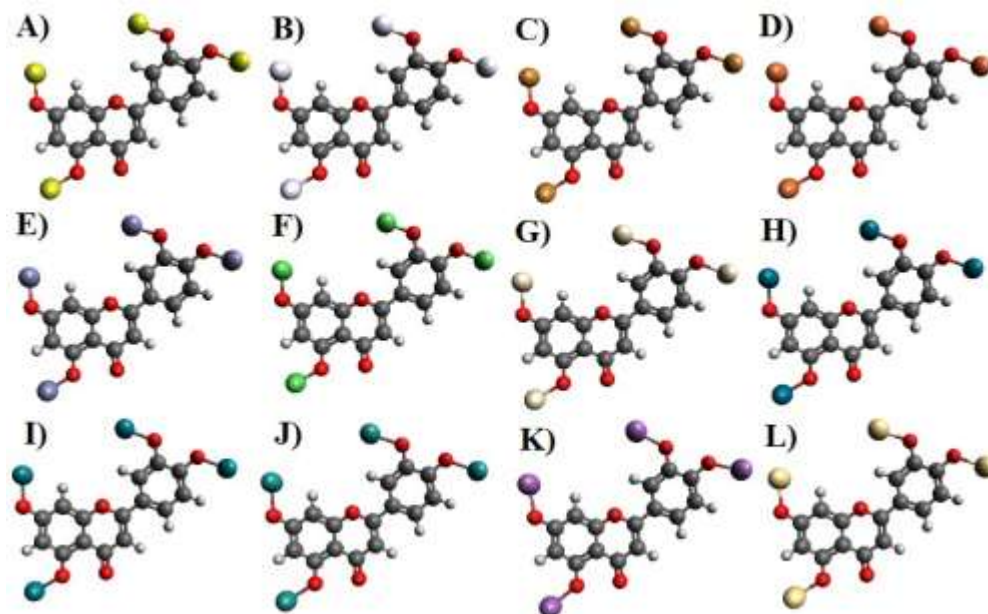


Figure 2:- Nanocomposite model structures of luteolin with A) gold, B) silver, C) copper, D) iron, E) zinc, F) nickel, G) platinum, H) palladium, I) Rhodium, J) Ruthenium, K) antimony and L) Cadmium.

Table 1:- List of energy levels of different metal – luteolin nanocomposite with metal–O bond length, O–C bond length and metal–O–C bond angle.

Metal	Compound	Total Energy (KJ/mol)	-OH position	Bond Angle ($^{\circ}$)	Bond Length (\AA)	
					Metal – O Bond	O – C Bond
Gold (Au)	Au_L	180.91	7	121.0	1.967	1.345
			5	121.2	1.967	1.347
			4'	121.0	1.967	1.346
			3'	121.1	1.967	1.346
Silver (Ag)	Ag_L	177.575	7	121.2	1.860	1.346
			5	121.4	1.860	1.348
			4'	121.2	1.860	1.347
			3'	121.3	1.860	1.347
Copper (Cu)	Cu_L	180.414	7	121.0	1.876	1.345
			5	121.2	1.876	1.347
			4'	121.1	1.876	1.346
			3'	121.1	1.876	1.346
Iron (Fe)	Fe_L	176.964	7	120.4	1.886	1.345
			5	120.4	1.886	1.346
			4'	120.3	1.886	1.345
			3'	120.4	1.886	1.345
Zinc (Zn)	Zn_L	174.423	7	121.1	1.797	1.345
			5	121.3	1.797	1.347
			4'	121.1	1.797	1.346
			3'	121.2	1.797	1.346
Nickel (Ni)	Ni_L	177.124	7	120.3	1.749	1.345
			5	120.4	1.750	1.347
			4'	120.3	1.749	1.345
			3'	120.4	1.750	1.346
Platinum (Pt)	Pt_L	174.399	7	120.3	1.956	1.345
			5	120.4	1.956	1.346
			4'	120.3	1.956	1.345
			3'	120.3	1.956	1.345
Palladium (Pd)	Pd_L	176.036	7	120.4	1.915	1.345
			5	120.5	1.915	1.347
			4'	120.4	1.915	1.346
			3'	120.5	1.915	1.346
Rhodium (Rh)	Rh_L	176.327	7	120.5	1.894	1.345
			5	120.6	1.894	1.347
			4'	120.5	1.894	1.346
			3'	120.5	1.894	1.346
Ruthenium (Ru)	Ru_L	175.679	7	120.4	2.014	1.345
			5	120.6	2.014	1.347
			4'	120.5	2.014	1.346
			3'	120.5	2.014	1.346
Antimony (Sb)	Sb_L	230.676	7	127.0	2.015	1.354
			5	127.7	2.015	1.356
			4'	127.2	2.015	1.355
			3'	127.4	2.015	1.355
Cadmium (Cd)	Cd_L	172.265	7	121.0	2.002	1.345
			5	121.3	2.002	1.347
			4'	121.1	2.002	1.346
			3'	121.2	2.002	1.346

Conclusion:-

From this study we can conclude that many metal atoms have the ability to make a composite structure in association with the luteolin as it contains four –OH groups. Among the metals under our study, cadmium was found to be the most suitable metal atom to formulate the nanocomposite with luteolin. If we arrange rest of the metals in descending order, in the order of suitable to unsuitable metals for nanocomposite formulation, the that would be platinum, zinc, ruthenium, palladium, rhodium, iron, nickel, silver, copper and gold. Among all these metals, antimony possesses highest energy in its composite form with luteolin, suggesting less suitable metal to be selected for luteolin metal nanocomposite formulation.

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