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Formulation of nano-composite model structures using apigenin with several metals using *in silico* approach

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Abstract
The research on Metal nanocomposite formulations is very enthusiastic and attractive point of interest for recent researchers and scientific communities. Due to its noticeable drug vehicle properties, it has been used vividly in medical research now a day. Flavonoids have capacity to fight against different and huge ranges of diseases. Different metals have the ability to from nano-composites which is useful in core research in drug deliveries. To understand the attachment of drug on nanoparticle, it is very much important to study the interaction between drug and the nanoparticles. On this point of view, here we are reporting the interaction between 12 metal atoms (Gold, Silver, Copper, Iron, Zinc, Nickel, Platinum, Palladium, Rhodium, Ruthenium, Antimony, and Cadmium) with one flavonoid (Apigenin). Throughout the demonstration, we used Avogadro software for formulating all the metal nanocomposite model structures with energy minimisation. There are three -OH groups in apigenin chemical structure where one metal atom was attached at a time. From this study we can conclude that zinc metal can formulate most suitable nanocomposite structure with apigenin having the lowest energy level of 202.854 KJ/mol.

Keywords: flavonoids, Apigenin, nanocomposite, avogadro software

Introduction

Nanotechnology refers to the branch of science and engineering dedicated to materials, having any one dimensions of 100 nm or less (Salata, 2004) [19]. In the present arena of nanoparticle research, metal nanoparticles have grabbed the attention of many groups of scientists. These tiny particles are used vividly in the industry over the past few decades with usages varying from food additives (Weir *et al*., 2012) [25] to drug administration (Singh and Lillard, 2009) [22]. The small particle size of these nanoparticles imparts the large surface area to volume ratio which makes them a good vehicle for drug molecules to be retained for a longer time in the physiological condition. There are mainly two types of nanoparticles that are being synthesized for application in drug delivery (Jong and Borm, 2008) [10]; these particles are mainly made of either polymer (Crucho and Barros, 2017) [4] or metal (Kumar *et al*., 2018) [13]. A variety of metallic nanoparticles are being used as a drug delivery system as well as an antimicrobial agent. Among these metals, the most widely used and applied are gold (Au) (Duncan *et al*., 2010) [6], silver (Ag) (Santos *et al*., 2014; Mandal, 2017) [21, 15], iron (Fe) (Mahdy *et al*., 2012) [14], copper (Cu) (Kruk *et al*., 2015) [12], nickel (Ni) (Guo *et al*., 2009) [8], zinc (Zn) (Rojas *et al*., 2016) [18], platinum (Pt) (Kim *et al*., 2010) [11] and palladium (Pd) (Adams *et al*., 2014) [1]. These metals have lots of roles in the field of medical and therapeutics. Among the various uses of gold nanoparticles, therapeutic (Aziz *et al*., 2012) [3] and biomedical applications (Zhang, 2015) [27] are much renowned. Silver nanoparticles have a broad area in the application of herbicide detection (Dubas and Pimpan, 2008) [5], biosensor (Kumar *et al*., 2018) [13], cancer treatment (Ren *et al*., 2003) [17], protein sensing arrays (Thapa *et al*., 2017) [23], degradation of environmental pollutants (Mody *et al*., 2009) [16] etc.

Flavonoids are characterized by broad biological activities, demonstrated in numerous mammalian systems *in vitro* and *in vivo*. These compounds are polyphenolic in nature and found abundantly in many plant products including fruits and vegetables. They act as free-radical scavengers and antioxidants (Anjaneyulu and Chopra, 2004) [2], exhibiting anti-mutagenic, anti-inflammatory (Guardia *et al*., 2001) [7], anticancer, antihyperglycemic (Wu and Yen, 2005) [26], and antiviral (Salehi *et al*., 2019) [20] compound. Apigenin is one type of flavonoid which is found in many fruits and vegetables, but parsley, celery, celeriac, and chamomile tea are the most common sources of it. Apigenin is particularly abundant in the flowers of chamomile plants, constituting 68% of total flavonoids (Venigalla *et al*., 2015) [24].

Here, in present work we tried to construct a computational model of apigenin nanocomposite with twelve different metals. Because the study of drug nanoparticle interaction is very much important to understand the mode of action of the nanocomposite in combating the disease, this research work may help many researchers and scientists who are working in this area.

Methods

Here in this study, we consider only the metal atoms for interaction with flavonoids in the nanoparticle composite graphical representation.

In the chemical structure of apigenin, three –OH groups are present at C7, C5, and C4' positions. Hence there are the 3 probable sites where the metalatoms may be attached. In this study, we use 12 metals which are vividly used in nanoparticle synthesis *in vitro*. Apigenin, which is a flavonoid and the nanoparticles are widely used in the biomedical field as therapeutic units. These metals are Gold (Au), Silver (Ag), Copper (Cu), Iron (Fe), Zinc (Zn), Nickel (Ni), Platinum (Pt), Palladium (Pd), Rhodium (Rh), Ruthenium (Ru), Antimony (Sb), Cadmium (Cd). Here *in silico* study 12 metals were attached with 3 different –OH groups at a time in apigenin structure. Same as we constructed 12 apigenin-metal composite structures and followed by energy minimization and after that, the bond length of metal-O and O-C bonds along with metal-O-C bond angle was calculated. The whole experiment was performed on Avogadro software (Hanwell *et al*., 2012) [9] compatible in windows.

Results

By using Avogadro software, 12 metal-flavonoid nanocomposite compounds are developed with an energy minimization approach. At first, the structure of apigenin was constructed in the software, and after that energy minimization oh that structure was calculated and found to be 204.614 KJ/mol. The formulated structure is shown in the Figure 1.

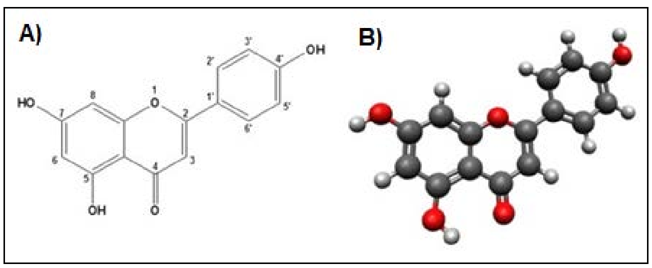

Fig 1: A) Chemical structure of Apigenin, B) Model structure of Apigenin formulated by Avogadro software with energy minimization.

Each metal was attached with all the three -OH groups at a time and developed a metal-apigenin nanocomposite model structure. All twelve metal-apigenin nanocomposites are listed in table 1 along with their calculated energy levels, Metal-O bond lengths, O-C bond lengths and Metal-O-C bond angles.

We can see here that cadmium (Cd), Nickel (Ni), and Iron (Fe) are all at the same energy level acquired after attaching with apigenin (Fe: 204.268 KJ/mol, Cd: 204.490 KJ/mol, Ni: 204.713 KJ/mol). Silver (Ag) and Platinum (Pt) nanocomposite structures are showing almost the same energy level i.e. 210.238 KJ/mol and 210.827 KJ/mol respectively. Copper (Cu) exhibited energy of 209.811 KJ/mol which is very much close to that of Silver and platinum nano composites. Palladium (Pd), Rhodium (Rh) and Ruthenium (Ru) possessed more or less the same energy level but higher than previous metals. Palladium (Pd) showed energy of 213.237 KJ/mol where as Ruthenium (Ru) and Rhodium (Rh) showed 214.421 KJ/mol and 216.299 KJ/mol of energy respectively. So, these three metals lie between the 213-216 KJ/mol ranges of energy. Gold (Ag)-apigenin nanocomposite developed with an energy level of 224.102 KJ/mol which is quite higher than previous nanocomposite model structures. As a result, among all twelve metals, Zinc (Zn) showed lowest energy level whereas antimony (Sb) possesses the highest energy level (299.233 KJ/mol). Hence it suggests that the Zinc-apigenin nanocomposite structure could be the most stable nanocomposite among the above and Sb will form quite a bit unstable nanocomposite with Apigenin. All the apigenin-metal nanocomposite model structures are illustrated in Figure 2.

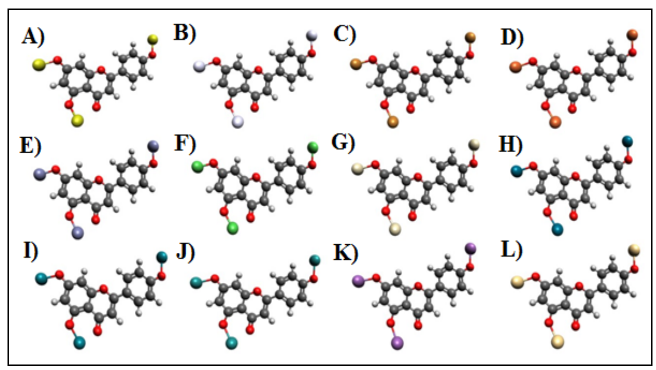

Fig 2: Nanocomposite model structures of Apigenin with A) Gold, B) Silver, C) Copper, D) Iron, E) Zinc, F) Nickel, G) Platinum, H) Palladium, I) Rhodium, J) Ruthenium, K) Antimony, L) Cadmium.

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

Metals	Total Energy (KJ/mol)	-OH position	Bond Angle (˚)	Bond length (Å)	
				Metal – O Bond	O – C Bond
Gold (Au)	224.102	7	121.2	1.860	1.346
		5	132.5	1.861	1.358
		4’	121.1	1.860	1.346
Silver (Ag)	210.238	7	121.0	1.967	1.345
		5	135.0	1.972	1.335
		4’	121.0	1.967	1.345
Copper (Cu)	209.811	7	121.1	1.876	1.345
		5	134.2	1.879	1.335
		4’	121.0	1.876	1.345
Iron (Fe)	204.268	7	120.4	1.886	1.345
		5	130.3	1.888	1.335
		4’	120.3	1.886	1.345
Zinc (Zn)	202.854	7	121.1	1.797	1.345
		5	135.9	1.799	1.354

		4’	121.0	1.797	1.345
Nickel (Ni)	204.713	7	120.4	1.749	1.345
		5	128.8	1.748	1.335
		4’	120.3	1.749	1.345
Platinum (Pt)	210.827	7	120.3	1.956	1.345
		5	129.9	1.958	1.357
		4’	120.3	1.956	1.345
Palladium (Pd)	213.237	7	120.4	1.915	1.345
		5	130.0	1.916	1.357
		4’	120.4	1.914	1.344
Rhodium (Rh)	216.299	7	120.5	1.894	1.345
		5	128.3	1.895	1.357
		4’	120.4	1.894	1.345
Ruthenium (Ru)	214.421	7	120.5	2.014	1.345
		5	130.7	2.017	1.358
		4’	120.4	2.014	1.345
Antimony (Sb)	299.233	7	127.2	2.015	1.345
		5	143.3	2.018	1.363
		4’	126.9	2.015	1.354
Cadmium (Cd)	204.496	7	121.1	2.002	1.345
		5	137.4	2.010	1.354
		4’	121.0	2.002	1.345

Conclusion

From the above study we can conclude that Apigenin has the ability to make a nanocomposite structure with the association of many metal atoms with three -OH groups which are present in 7, 5 and 4’ positions in its chemical structure. In this study among the 12 metals, zinc (Zn) was found to be the most suitable metal atom to formulate the nanocomposite with Apigenin. The most unstable nano-composite formulation was shown by antimony (Sb) due to its highest energy level. If we arrange rest of the metals in descending order in the form of stability for nano-composite formulation, that would be iron (Fe), cadmium (Cd), nickel (Ni), copper (Cu), silver (Ag), platinum (Pt), palladium (Pd), ruthenium (Ru), rhodium (Rh), gold (Au). From this study we can suggest that zinc metal may formulation a stable apigenin nanocomposite structure.

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