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ONIOM studies of interaction between single-walled carbon nanotube and gallates derivatives as anticancer agents

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ABSTRACT

Objective(s): The novel 7-hydroxycoumarinyl gallates derivatives are detected in many pharmaceutical compounds like anticancer and antimicrobial agents. Whereas carbon nanotubes (CNTs) have been discussed for nanomedicine applications and in particular as drug delivery systems. The capability of armchair (5, 5) SWCNT -based drug delivery system in the therapy of anticancer has been investigated by quantum mechanics/molecular mechanics method.

***Materials and Methods*:** Theoretical investigation of the interaction between armchair (5, 5) SWCNT with gallates derivatives has been fulfilled by quantum mechanics/molecular mechanics (QM/MM) method by ONIOM2 (DFT: UFF) using the program of GAUSSIAN 03 suite.

***Results*:** The results derived from this study, demonstrate that armchair (5, 5) SWCNT has weak interaction that these interactions contain Vander Waals interactions and indicated clearly that these systems have relatively low durability and so armchair (5, 5) SWCNT is appropriate drug delivery that have been investigated for anti-cancer drug.

***Conclusion*:** Analysis of ONIOM2 calculations and the interaction energies of the armchair (5, 5) SWCNT and gallates derivatives represented that this carrier can be utilized to improve the biological and anti-cancer activity of gallates derivatives.

Keywords: *Anticancer, Armchair (5, 5) SWCNT, Drug Delivery, Gallates derivatives, ONIOM2, Quantum Mechanics/ Molecular Mechanics*

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INTRODUCTION

Gallic acid (GA) is an organic acid found in a variety of foods such as blueberries, gallnuts, apples, flax seed and sumac herbs that are well known as powerful antioxidants [1]. Also this compound is known as chemopreventive and anticancer agents [2].Types of ester derivatives with distinct pharmacological properties are obtained of Gallic acid because of the existence of three phenolic and one carboxyl substituents [3].

Substituent of coumarins with GA increased antitumor effect in comparison to individual substances. coumarin esters of GA are able to impel tumor cell cycle inhibition [4,5], Recently, the novel 7-hydroxycoumarinyl gallates derivatives have been synthesized by Hejchman and coworkers [6] that have anticancer activity (Fig. 1).

Nano compuonds similar carbon nanotubes (CNTs), quantum dots, and polymeric nanoparticles have essential physicochemical properties that can be used for drug delivery in cancer. CNTs have been actively investigated as multipurpose novel carriers for drug delivery [7].

Their inherent physicochemical features enable covalent and non-covalent binding of several pharmaceutical uses and permit for rational design

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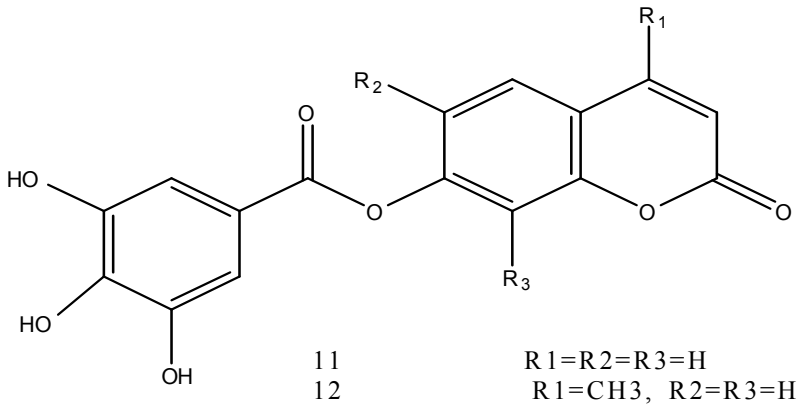

11 R1=R2=R3=H
12 R1=CH3, R2=R3=H
13 R1=CH3 ,R2=COCH3 ,R3=H

Fig. 1. Derivatives of 7-hydroxycoumarinyl gallates

of novel candidate nano materials for drug development [8].

Single wall carbon nanotubes (SWCNTs) with a highly site-selective delivery and sensitivity, are made of a single cylindrical graphene layer covered both ends in a hemispherical arrangement of carbon networks [9].

SWNTs can be clearly linked to biomolecules by adsorption, chemical attachment or encapsulation due to high specific surface areas. These types of bioconjugates on SWNTs have the capability to carry bioactive molecules into the cell nuclei and across cell membranes [10, 11].

Interaction of anticancer drug molecules like cisplatin [12], carboplatin [13], paclitaxel [14], methotrexate [15] and doxorubicin [16, 17] with carbon nanotubes have been investigated. Computational characterization of CNT-papain interactions for developing a biosensor have been investigated by Athira and coworkers [18]. Interaction of folic acid drug on CNT has been studied with DFT method by Hamedani *et al*. [19].

Computational and experimental investigation of the interaction between single-walled carbon nanotubes and folic acid has been studied by Castillo et al. [20]. Shojaee and coworker have been investigated interaction functionalized SWCNT (5, 5) with Mitoxantrone drug [21]. Also, DFT/NBO analysis of interaction between a CNT and anti-cancer drugs have been studied [22].

The Adsorption of Drug Cisplatin onto Carbon Nanotubes by DFT method have been Studied [23]. In this work, the interacting capability of carbon nanotube (5, 5) with the novel 7-hydroxycoumarinyl gallates derivatives is investigated. So far, the probability of occurring covalent interaction between the 7-hydroxy- coumarinyl gallates erivatives and carbon nanotube (5, 5) has not been reported. This chemical interaction is studied as a new approach to drug delivery.

METHODS

An ONIOM (our Own N-layer Integrated Orbital molecular Mechanics) approach was developed to perform a complex geometry optimization. In this method, it together behaves different parts of a system with good accuracy and lower computational cost contrast to pure DFT methods [24].

ONIOM approach, presented by Morokuma et al [25], is a computationally impressive tool for the study of chemical reactions involving large molecular systems. In ONIOM approach, the molecule (real) divided to two or three different regions, where a high-level calculation on a small region (model) is carried out, and the effects of the residue spectator areas are included at a low of theory.

Selection of the atoms in the model and the level of theory in that part of the system (high-level), as well as the level of theory for the real system (low-level), is the limiting factors regarding the accuracy of the results [26].

B3LYP/6-31G at the high-level for gallates derivatives and a unified force field (UFF) approach for the low-level real SWCNT was applied. Binding energies (BE) had to be estimated from the high-level of theory part [27].

The importance of the layers partitioning in the application of ONIOM for the investigation of SWCNTs, was recently pointed out [28, 29]. All calculations were performed using ONIOM2 (B3LYP/ 6-31g: UFF). It is considerable that of these drugs has more than one functional group which can react with CNTs. Also, thermodynamic parameters of interaction are calculated using the two-layered ONIOM Becke3LYP/UFF method.

In our calculations, an armchair (5, 5) SWCNT comprising 110 carbon atoms and end-terminated with hydrogen atoms (Fig. 2). interacting with the gallates derivatives we retaken as the model system. Calculations were carried out using the program of GAUSSIAN 03 suite [30].

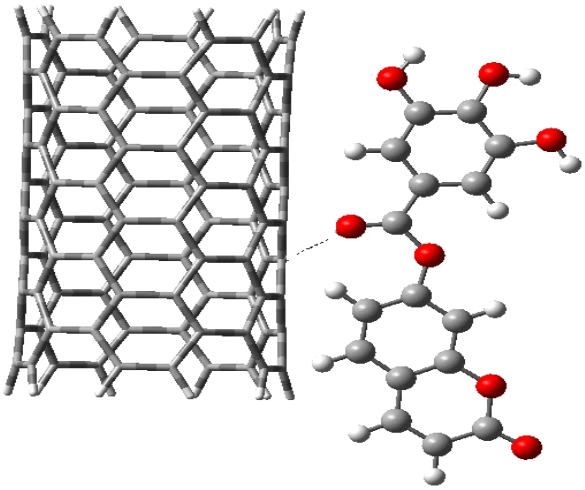

Fig. 2. gallate derivative (11) and armchair (5, 5) SWCNT (ONIOM2)

RESULTS AND DISCUSSION

The optimized configurations and structures and the of the three 7-hydroxycoumarinyl gallates derivatives have been obtained with DFT method. The gallates derivatives conformers were investigated to be minima based on the absence of imaginary frequencies. HOMO and LUMO are related to negative and positive Fukui indices, respectively. The most electrophilic and nucleophilic sites of the drug molecules by the fukui functions predicted.

Table 1 shows the quantum chemical parameters for 7-hydroxycoumarinyl gallates derivatives. These parameters give information on the chemical reactivity of the studied molecules in the gas. The lower the value of E_{LUMO} is, the more probable that the molecule would accept electrons. The binding potential of the 7-hydroxycoumarinyl gallates derivatives to the SWNT increases with increasing HOMO and decreasing LUMO energy values. Based on quantum molecular descriptors, as given in Table 1, compound 12 has a high E_{HOMO} and a low E_{LUMO} compared to other compounds. The gap between the HOMO and LUMO energy levels is a major parameter of reactivity of a molecule. The calculations indicate that the compound 11 has a low energy gap. Thus, moving an electron from the HOMO of the compound 11 to its LUMO is easier than in other two derivatives. This means that this drug could have a better performance.

Absolute hardness, ionization potential, chemical potential and softness are important properties to measure the molecular reactivity and stability. Table 1shows that compound 11 has the lowest hardness and the highest softness. The ability of molecules to accept electrons may be explained by the electrophilicity index. It is a measure of a system's energy stabilization after the system accepts the extra value of electron charge from its surroundings.

Compound 12 has the lowest value of electro-

The polarity of a molecule demonstrates its dipole moment. Compound 12 has the highest value of dipole moment in phase. Here, the combination of gallates derivatives as anticancer drug and armchair (5, 5) carbon nanotube by ONIOM2 is shown in Fig. 2.

Table 1. Quantum chemical descriptors for the studied compounds

Molecular descriptor	11	12	13	CNT 5,5
HOMO(ev)	-6.3810	-6.3487	-6.5623	-4.4352
LUMO(ev)	-2.2471	-2.1342	-2.2286	-2.6724
Gap energy(ev)	4.1339	4.2145	4.3337	1.7627
Ionization Potential(IP)	6.3810	6.3487	6.5623	4.4352
Electron Affinity(EA)	2.2471	2.1342	2.2286	2.6724
Global Hardness(η)	2.0669	2.1072	2.1668	0.8814
Global softness(σ)	0.2418	0.2373	0.2307	0.5672
Electrophilicity(ω)	4.5021	4.2686	4.4581	7.1646

The integrated energy for the two-layer ONIOM approach is defined as:

$$E_{(ONIOM2)} = E_{(HIgh,Molel)} + E_{(Low,Real)} - E_{(Low,Model)} = E_{(High,Model)} + \Delta E_{(Low,Real \rightarrow Model)} \quad (1)$$

Where 'Real' defines the full system, which is behaved d at the 'Low' level, and 'Model' defines the part of the system for which the energy is computed at both 'High' and 'Low' levels. One can see that the method can be as an extrapolation scheme. Beginning at E_{Low} model, the extrapolation to the high-level calculation ($E_{High, Model} - E_{Low, Model}$) and the extrapolation to the real system ($E_{Low,Real} - E_{Low, model}$) are supposed to give an approximation for $E_{High, Real}$. The ONIOM approach enables an extrapolated energy (E_{ONIOM2}) for a system division in this method.

Binding energy (BE) analysis of the appointed complexes allowed the basic aspect of the gallates derivatives as anticancer drug and armchair (5, 5) carbon nanotube interactions to be assigned based on the ONIOM approach. The calculated binding energies at the B3LYP/6–31G (d): UFF level of calculation for the optimal configuration between gallates derivatives as anticancer drug and armchair (5, 5) carbon nanotube are summarised in Table 2. Our results clearly indicated that these complexes have relatively low stability because of low binding energies, so armchair (5, 5) carbon nanotube can be used for drug delivery. Among the gallates derivatives, compound 13 lead to the strongest binding energy. Also, we have obtained the thermodynamic parameters of the interaction of gallates derivatives as anticancer agents and armchair (5, 5) carbon nanotube with ONIOM2 approach. Based on ONIOM2 approach, can be suggested the following relationships for enthalpy and Gibbs free energy of ONIOM2 (QM / MM):

$$G_{ONIOM} = G_{QM(Model)} + G_{MM(Real)} - G_{MM,Model} \quad (2)$$

$$H_{ONIOM} = H_{QM(Model)} + H_{MM(Real)} - H_{MM(Model)} \quad (3)$$

Hence, Enthalpy and gibs free energy of interaction QM/MM between drug and polymer can be obtained as followed [31]:

$$\Delta G_{interaction} = G_{ONIOM} - G_{QM,drug} - G_{MM,polymer} \quad (4)$$

$$\Delta H_{interaction} = H_{ONIOM} - H_{QM,drug} - H_{MM,polymer} \quad (5)$$

Table 2. Values of enthalpy, Gibbs free energy, $E_{binding}$, and LnK of interaction gallates derivatives as anticancer and carbon nanotube with ONIOM2 (B3LYP/6-31G: UFF) method

compound	ΔH^0 (kJ/mol)	ΔG^0 (kJ/mol)	$E_{binding}$ (kJ/mol)	LnK
11	-16.0608	-12.0292	-8.5612	20.3768
12	-22.4073	-18.2790	-11.8696	30.9638
13	-29.0928	-24.4662	-15.6568	41.4445

The constituents values of the enthalpy and Gibbs free energy of gallates derivatives as anticancer agents and armchair (5, 5) carbon nanotube as drug delivery evaluated from the ONOIM2 output results are listed in Table 2.

The standard Gibbs free energy tell us about whether the reaction takes place or not, but also it is used to efficiency the stability constant of the reaction.

The results obtained from frequency study reveal that, Gibbs free energy of complexes formed from gallates derivatives and mentioned nanotube are negative. This means that the complex formations are exothermic and are done thermodynamically. The calculated stability constants are shown in Table 2. According to the results, the stability constant for formation of complex 13 is much more than that of complex 11 and 12.

Results suggest that interaction between drug and carbon nanotube is relatively weak and carbon nanotube can be used as a carrier of drug in the cancerous patients.

CONCLUSION

In this work, calculations were performed to study gallates derivatives as anticancer agents in gas phase using density functional theory (DFT). Then calculations were carried out to study the interaction of gallates derivatives to single wall carbon nanotube (5, 5).

The binding energy between gallates derivatives and carbon nanotube (5, 5), showed that this energy decreases from -8.5612 kcal/mol to -15.6568 kcal/ mol in gas phase.

The quantum chemical descriptors of pristine CNT and CNT- gallates derivatives showed that reactivity of CNT- gallates derivatives increased comparison to pristine nanotube. According to the results, all gallates derivatives under study can be thermodynamically formed in 298 K. The stability

constants are calculated thereby showing a considerably large amount.

Values of enthalpy, Gibbs free energy and $E_{binding}$ of interaction gallates derivatives and carbon nanotube with ONIOM2 method are almost low and less than -40kJ/mol.

So the nanotube can be a useful container to release this drug in the special cells without showing side effects as a result of damaging healthy cells. In all complexes, the hyperconjugation effect can be observed.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interests regarding the publication of this manuscript.

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