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A First-Principles Study on Interaction between Carbon Nanotubes (10,10) and Gallates Derivatives as Vehicles for Drug Delivery

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First principles calculations, based on density functional theory (DFT), were performed for investigating the novel 7-hydroxycoumarinyl gallates derivatives in gas and liquid phases. Computational chemistry simulations were performed to compare calculated quantum chemical parameters for gallates derivatives. All calculations were done using DMol3 code which is based on DFT. The double numerical basis set with double numerical plus d-function was employed. Calculations were carried out to study the interaction of covalently binding gallates derivatives to the armchair single-walled carbon nanotube (10,10). The local reactivity was studied via the Fukui indices to predict the reactive centers as well as the practicable sites of nucleophilic and electrophilic attacks. The adsorption energies, quantum molecular descriptors analysis and structural changes at the adsorption site are indicative of chemisorption on the armchair single-walled carbon nanotube (10,10) surface. The HOMO and LUMO are witnesses to the substantial changes in the electronic properties of the SWCNT systems. Adsorption energies indicate that 7-hydroxycoumarinyl gallates derivatives are physicosorbed on carbon nanotube (10,10). This property enables the delivery of these derivatives with anti-cancer potential from the nanotube at the targeted sites. These results are extremely relevant to diagnose the potential applications of carbon nanotubes as efficient boats for targeted drug delivery.

Keywords: Single-walled carbon nanotubes, 7-Hydroxycoumarinyl gallates derivative, Adsorption energy, Density functional theory (DFT)

INTRODUCTION

Gallic acid is a phenolic acid that is widely distributed in foods like blueberries, gallnuts, apples, flax seed and sumac herbs which are well known of being powerful antioxidants [1]. It contains antioxidant, antiviral, anti-inflammatory and antibacterial properties. Also, this compound is a well-known chemopreventive and anticancer agent [2]. GA and its derivatives may be evaluated as a powerful medicine for cancer treatment as well as in combination with other anticancer drugs to enhance the sufficiency of chemotherapy [3]. Studies have revealed that GA has anti-cancer properties against certain colon, prostate, leukemia and lung cancer cells [4]. Moreover, coumarin derivatives display a wide range of biological activity, and its role as *vitro* antiproliferative activity against human neoplasms is important and significant. Therefore, combination of gallic acid derivatives with coumarin components can provide compounds that potentially inhibit the growth of cancer cells [5]. Recently, the novel 7-hydroxycoumarinyl gallates derivatives, having anticancer activity, have been synthesized by Hejchman *et al*. [6].

Carbon nanotubes, due to their fantastic structure, high surface area, high thermal conductivity, stability, electronic properties, and unique physical properties are significant particularly for molecular transport, drug delivery and new therapeutic mechanisms [7]. In the scope of drug delivery, CNTs have gained opulent consideration as good nanocarriers owing to their special properties, such as enhanced cellular uptake and the feasibility to be easily

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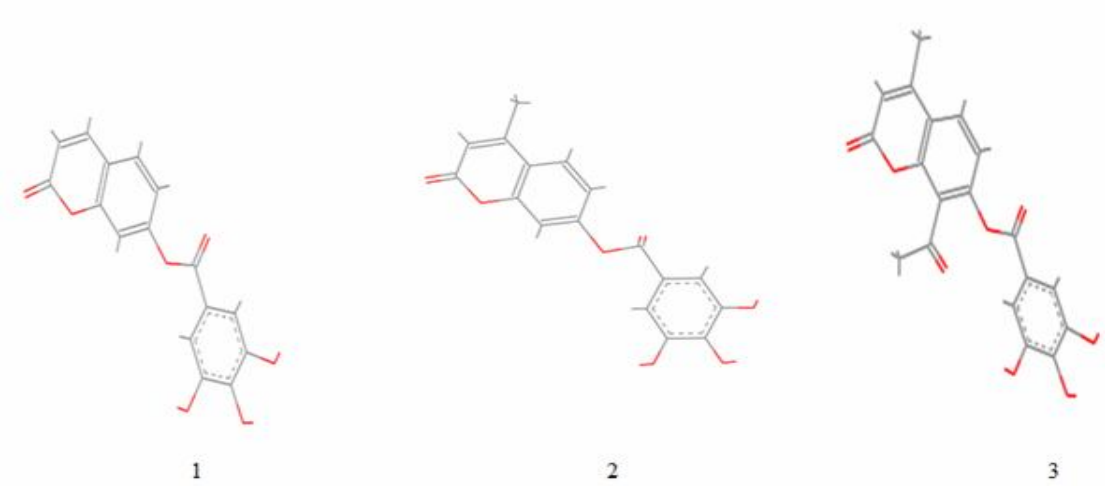
conjugated with much therapeutics, avoiding solvent usage and reducing side effects [8].

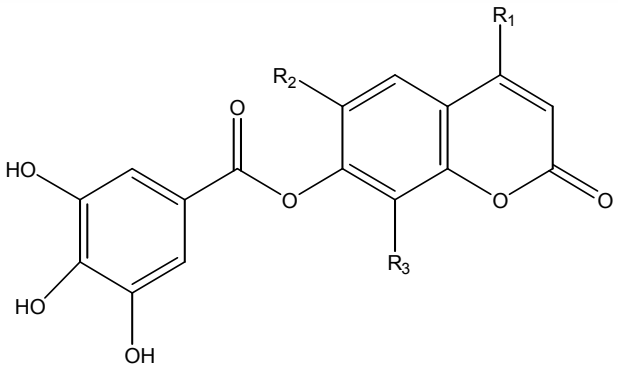
Recently, the interaction of folic acid as carriers in drug delivery systems with (5,0) zigzag and (5,5) armchair single-walled carbon nanotube (SWCNT) has been investigated through density functional theory (DFT) at the B3LYP/6-31G* level [9]. Theoretical investigations by Lu *et al*. revealed that SWCNTs are the most reactive species because of their small diameter which is an important parameter in nanotubes reactivity [10]. A first-principles study of functionalized carbon nanotubes with 5-Aminolevulinic acid as vehicles for drug delivery has been carried out by ab initio density functional calculations [11]. Interaction of anticancer drug molecules such as cisplatin [12], carboplatin [13], paclitaxel [14], methotrexate [15] and doxorubicin [16,17] with carbon nanotubes have been investigated. Computational characterization of interactions between CNT and papain for expanding a biosensor was investigated by Athira *et al.* [18]. In another research activity, Hamedani et al. investigated the interaction of folic acid drug on CNT using DFT method [19]. Computational and experimental investigation of the interaction between single-walled carbon nanotubes and folic acid was studied by Castillo *et al.* [20]. Shojaee *et al.* investigated the interaction of functionalized SWCNT (5,5) with Mitoxantrone drug using DMol3 code and the double numerical basis set with polarization functions (DNP) [21]. Also, DFT/NBO analysis of interaction between a CNT and anti-cancer drugs have been studied [22]. The adsorption of drug cisplatin onto CNT by DFT method have been studied [23].

Systemic toxicity may extend because of lack of selectivity of the GA derivatives and coumarins for cancer cells in chemotherapies. For improved influence of these compounds, carbon nanotubes can be used as target carriers in drug delivery systems for cancer therapies. In this work, the interacting capability of armchair single walled carbon nanotube (10,10) with the novel gallates derivatives is investigated. Thus far, the probability of covalent interaction occurring between the gallates derivatives and carbon nanotube (10,10) has not been reported. The specification of the properties of adsorbed novel 7-hydroxycoumarinyl gallates derivatives on SWCNT surface is important for comprehending its reactivity and bonding in carbon nanotube-based drug delivery systems. This chemical interaction is studied as a new approach to drug delivery.

COMPUTATIONAL METHODS

All calculations were carried out using DMol3 code [24] which is based on DFT. Accordingly, the electronic wave functions are extended in numerical atomic basis sets explained as an atomic-centered spherical polar mesh. The electron density in DMol3 is extended in terms of multipolar, atomic-centered partial densities, and can perform all electron or pseudo-potential calculations. The double numerical plus d-function of all electron basis set was used for all calculations. The DND basis set involves one numerical function for each occupied atomic orbital and a second set of functions for valence atomic orbitals, plus a polarization d-function on all atoms. This basis set is comparable with the 6-31G* gaussian basis set. The high quality of these basis sets minimizes basis set superposition effects and allows an improved description of molecular polarizabilities. The density function is treated within the generalized gradient approximation with exchange correlation potential represented by Wang and Perdew method (GGA-PW91) [25]. The gamma centered k-point is employed to represent the Brillouin zone. We considered single-wall armchair (10,10) nanotube with open edges. The diameter of the nanotube is 13.56 Å, and the average bond length is 1.42 Å. Five layers of carbon rings along the tube axis (z axis) are modeled, where the bottom hanging bonds are saturated by hydrogen atoms to simulate the bulk properties. Full geometry optimization was performed for three of 7-hydroxycoumarinyl gallates in both gas and solvent phases. The effect of solvent was computed by the Conductor-like Screening Model [26]. The dielectric constant of water was taken as 78.54 in this model. In simulation studies, the three gallates derivatives were attached covalently to CNT. The (10,10) pristine carbon nanotubes employed in the carbon nanotube functionalization contain 200 carbon atoms and 40 hydrogen atoms. In this COSMO model, the three gallates derivatives are also attached to functionalized nanotubes. We define the attaching sites of the drugs to the CNT based on Fukui indices analysis of electrophilic sites. This study





1	R1=R2=R3=H
2	R1=CH3, R2=R3=H
3	R1=CH3 ,R2=COCH3 ,R3=H

Fig. 1. Derivatives of 7-hydroxycoumarinyl gallates.

focuses on adsorption of 7-hydroxycoumarinyl gallates onto the CNTs.

RESULTS AND DISCUSSION

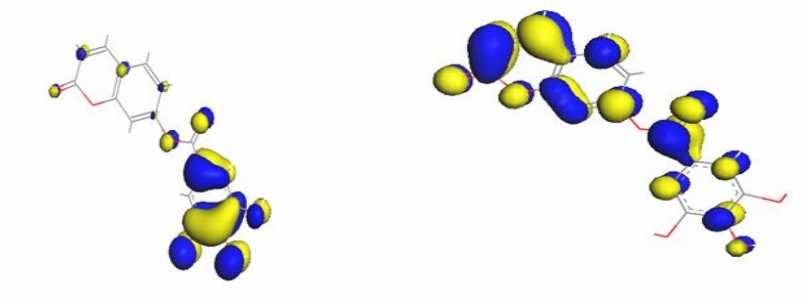
The structures and the optimized configurations of three gallates derivatives are illustrated in Fig. 1. IC_{50} values (IC_{50} is the concentration of an inhibitor where the response is reduced by half) after incubation with these compounds toward prostate cancer DU145 cell are 280, 300 and 305 μM, respectively [6]. Using the optimized geometries, the energy of the highest occupied molecular orbital (E_{HOMO}), energy of the lowest unoccupied molecular orbital (E_{LUMO}), total energy, binding energy, enthalpy, entropy, Gibbs free energy, heat capacity, energy gap (E), and total negative charge (TNC) [27,28] were calculated for three gallates derivative molecules (see Table 1).

The Fukui indices permit the recognition of the reactive regions and the electrophilic and nucleophilic behavior of a molecule, as well as its chemical reactivity. For a limited system, when a molecule is accepting electrons, it has the Fukui index for nucleophilic attack (f^+), and when the

Table 1. Quantum Chemical Descriptors for Three Gallates Derivatives

	1		2		3	
Molecular descriptor	Gas	Solvent	Gas	Solvent	Gas	Solvent
Total charge negative	-3.536	-4.652	-4.654	-5.019	-5.342	-5.719
HOMO (eV)	-5.618	-5.605	-5.594	-5.604	-5.415	-5.603
LUMO (eV)	-2.986	-3.026	-2.861	-2.94	-3.107	-3.099
Total energy (hartree)	-1141.968	-1142.001	-1181.258	-1181.302	-1333.848	-1333.897
Binding energy (kcal mol^{-1})	-4080.148	-4101.152	-4376.097	-4404.132	-4941.166	-4971.969
Dipole magnitude (debye)	6.2313	8.7595	6.7568	9.5039	7.5465	10.9066
Gap (eV)	2.632	2.579	2.733	2.664	2.308	2.504

HOMO **LUMO**



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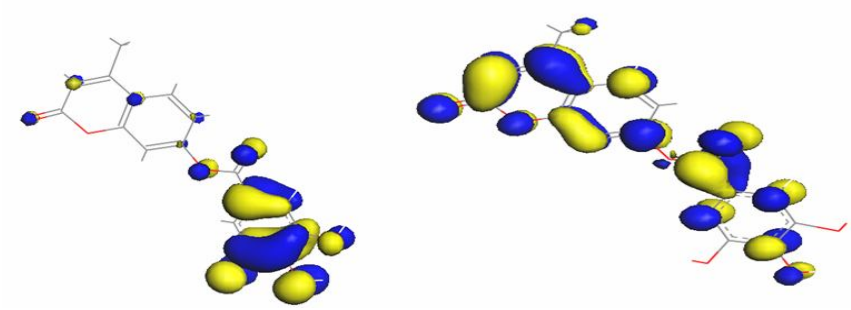

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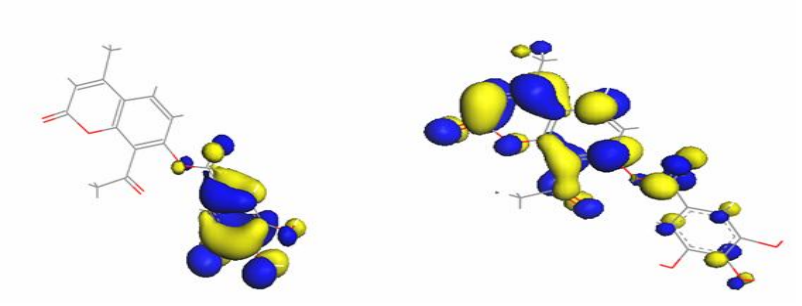

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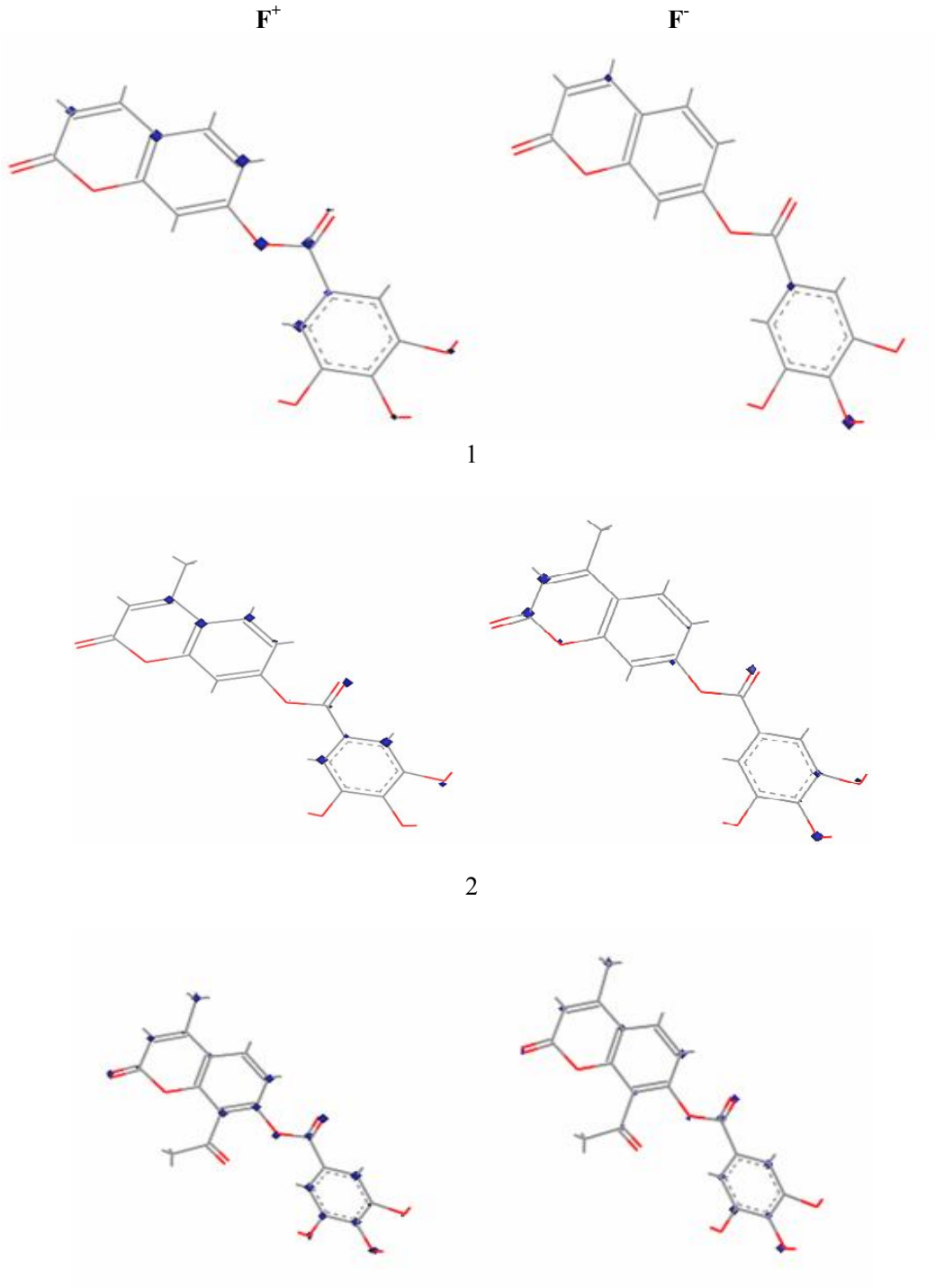

Fig. 3. The Fukui functions for the studied drugs in gas.

Table 2. Quantum Chemical Descriptors for CNT (10,10)

Molecular descriptor	Gas	Solvent
Total charge negative	-5.495	-9.636
HOMO (eV)	-4.300	-4.516
LUMO (eV)	-3.053	-3.293
Total energy (hartree)	-7644.211	-7646.355
Binding energy (kcal mol^{-1})	-37907.29	-4101.152
Dipole magnitude (debye)	0.000	0.009
Gap (eV)	1.247	1.223

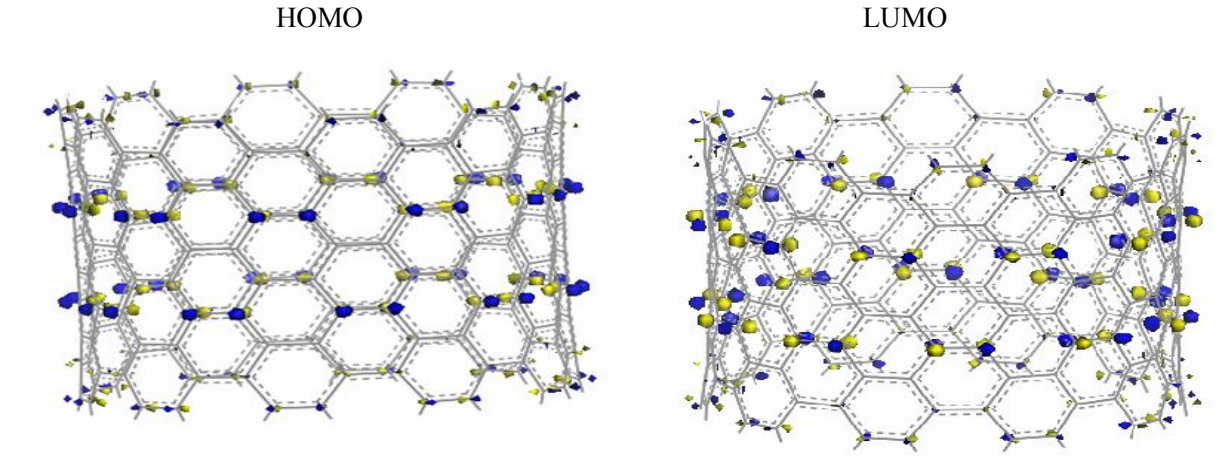

Fig. 4. The HOMO and the LUMO for the CNT (10,10) in gas.

molecule is donating electrons, it has the Fukui index for electrophilic attack (f^-). Therefore, HOMO and LUMO are related to negative and positive Fukui indices, respectively. The Fukui functions permit forecast where the most electrophilic and nucleophilic sites of the drug molecules are situated. The HOMO, LUMO and the Fukui functions for the studied drugs in the gas phase are shown in Figs. 2 and 3, respectively. Figure 2 reveals that the LUMO is almost distributed throughout the molecule 1, while the HOMO is distributed across this molecule. In Fig. 3, the O atom is the nucleophilic site of the molecule 1 in gas phase and the Fukui indices (f^-) are almost throughout the entire molecule 1. This figure shows that the Fukui indices (f^+) are almost throughout the entire molecule 1. The N1 and C2 atoms have the highest nucleophilic electron density and the highest electrophilic electron density in gas phase. The N2 and C2 atoms have the highest nucleophilic electron density and the highest electrophilic electron density in solvent phase. The HOMO and LUMO energy distributions depend on the drug's chemical structure. Many electronic properties of chemical structures are directly related to the HOMO and LUMO levels, thus the energy gap depends on the energy geometric structure of the molecule. A high LUMO-HOMO energy gap represents greater stability and low reactivity of

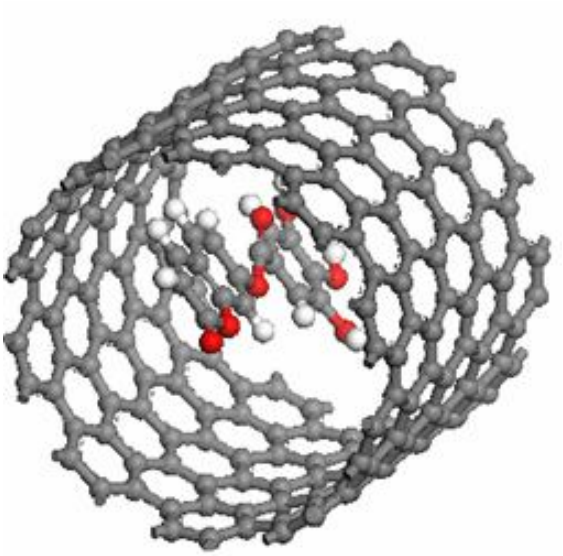

Fig. 5. Model for adsorption state for 1 molecule on the inner surface of a (10,10) single-walled CNT.

the chemical species. An increase in hardness leads to increase in stability and decrease in reactivity of the system. The calculations depict that Molecule 3 has the highest value of the total negative charge when compared to 1 and 2. This property expresses the capability of a molecule's donating electrons as confirmed by Fukui indexes (f). The adsorption of the drugs onto the SWNT surface is enhanced at higher TNC values. The TNC of the molecule 3 is higher in water solution than in the gas phase. The polarity of a molecule describes its dipole moment. Table 1 shows that molecule 3 has the highest value of dipole moment in gas and solvent phases. The quantum chemical descriptors for CNT (10,10) are listed in Table 2. The total negative charge of CNT (10,10) in solvent phase is more than that in gas phase. The HOMO and LUMO for the CNT (10,10) in gas phase are shown in Fig. 4.

To evaluate the stability of the three gallates derivatives/CNT complexes, we first optimized the structures of a complex between the three gallates derivatives and CNT by Dmol3 program, and then the adsorption energy (E_{ads}) of the considered systems was calculated using the equation:

$$E_{ads} = E_{CNT\text{-}drug} - (E_{CNT} + E_{drug})$$

Where $E_{CNT\text{-}drug}$ denotes the total energy of the CNT with a adsorbed drug molecule, E_{CNT} is the total energy of the CNT and E_{drug} is the total energy of the drug. Adsorption locator module was used to find minimal energy of interaction. In this module, Monte Carlo simulation of a substrate-adsorbate was carried out and the best configuration among possible configurations was achieved. With adsorption locator module, the most stable adsorption site and adsorption energies can be predicted. The SWCNTs consist of delocalized electrons. The distribution and character of these electrons depend on the curvature of the CNTs. In the case of (10,10) SWCNT, the curvature on outer surface is lesser than that in the inner wall [29]. Therefore, this situation introduces extra π-π character to the inner wall. In the 7-hydroxycoumarinyl gallates derivatives, the active site of binding is essentially determined by the unpaired electrons in oxygen atoms. In a non-covalent interaction of gallates derivatives with (10,10) SWCNT, the π-π stacking interaction plays a major role. In the present case, there is a strong π-π interaction between the unpaired electrons in 7-hydroxycoumarinyl gallates derivatives and electrons with extra π character present inside the CNT. In general, drug molecules are aligned along the inner tube wall of CNTs having an average diameter less than 20 Å [29]. In the interaction of SWCNT (10,10) with gallates derivatives, gallates derivatives are loaded inside the nanotube. Drug molecules are attached covalently and noncovalently as well

onto the side walls and interiors of CNTs [30]. Interaction of SWCNT (10,10) with gallates derivatives concentrates on non-covalent adsorption of gallates derivatives molecules inside SWCNT. The adsorption energy (E_{ads}) of 1, 2 and 3 compounds on the inner surface of SWCNT are -23.6567, -28.3586 and -31.877 kcal mol^{-1}, respectively, and compound 3 has the most adsorption energy (Fig. 5). The negative adsorption energies of gallates derivatives on the surface of (10,10) CNT demonstrated a more favorable interaction between the drug and the CNT. In addition, adsorption process is physisorption process due to weak Van der Waals interaction between the nanotube and the gallates derivatives.

CONCLUSIONS

The interaction between the gallates derivatives as anticancer drug and SWCNT was investigated with DFT approach using DMol3 code, a widely used first principles approach. Drug molecules are attached covalently and noncovalently onto the side walls and interiors of CNTs. This work concentrates on non-covalent adsorption of gallates derivatives inside SWCNT. The quantum chemical parameters of pristine SWCNT and interaction demonstrated that reactivity of complexes increases compared to pristine nanotube. The negative adsorption energies showed a more favorable interaction between the drug and the CNT. It can be concluded that SWCNT as pharmaceutical nanocarriers (large diameter) are efficient drug carrier and delivery boats.

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