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CARBON NANOTUBES AS ELECTROMAGNETICALLY RESPONSIVE GREEN TEA CATECHIN DELIVERY SYSTEMS

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Abstract

Single-walled carbon nanotubes (SWNTs) have emerged as promising drug delivery vehicles due to their exceptional structural and chemical properties. This study employs molecular dynamics (MD) simulations to investigate the adsorption, interaction dynamics, and electrically controlled release of green tea catechin derivatives, epigallocatechin (EGC) and epigallocatechin gallate (EGCG), onto armchair SWNTs with chiralities (10,10), (12,12), and (14,14). Our findings demonstrate that EGC and EGCG exhibit the most stable interactions with SWNTs, primarily driven by enhanced π-π stacking interactions. This is evidenced by lower Root Mean Square Deviation (RMSD) values and closer interaction distances between the catechin derivatives and the SWNTs. Furthermore, we explore the influence of an external electric field on the van der Waals interaction energies between the catechins and SWNTs. Our results indicate that the application of an electric field can effectively modulate these interactions, providing a potential mechanism for controlled drug release. Among the studied SWNTs, the (14,14) SWNT consistently exhibits the strongest interactions with the catechin derivatives and demonstrates the most responsive behavior to electric field modulation. These findings suggest that (14,14) SWNTs may be particularly suitable as electrically controlled drug delivery vehicles for green tea catechins and other molecules with similar structural characteristics.

Keywords: Green tea catechin, Carbon nanotubes, Nanocarrier, Molecular dynamics simulation

ELEKTROMANYETİK DUYARLI YEŞİL ÇAY KATEŞİN TAŞIMA SİSTEMLERİ OLARAK KARBON NANOTÜPLER

Özet

Tek duvarlı karbon nanotüpler (TDKN'ler), üstün yapısal ve kimyasal özellikleri nedeniyle umut verici ilaç taşıma araçları olarak ortaya çıkmıştır. Bu çalışmada, yeşil çay kateşin türevleri olan epigallokateşin (EGK) ve epigallokateşin gallatın (EGKG), (10,10), (12,12) ve (14,14) kiralitelerine sahip koltuk tipi (armchair) TDKN'lere adsorpsiyonunu, etkileşim dinamiklerini ve elektriksel kontrollü salımını incelemek için moleküler dinamik (MD) simülasyonları kullanılmıştır. Elde edilen bulgular, EGK ve EGKG'nin TDKN'lerle en kararlı etkileşimleri sergilediğini göstermiştir; bu etkileşimler öncelikle gelişmiş π-π istifleme etkileşimleriyle yönlendirilmiştir. Bu, kateşin türevleri ve TDKN'ler arasında daha düşük Kök Ortalama Kare Sapması (KOKS) değerleri ve daha yakın etkileşim mesafeleriyle desteklenmiştir. Ayrıca, harici bir elektrik alanının kateşinler ve TDKN'ler arasındaki van der Waals etkileşim enerjileri üzerindeki etkisini araştırılmıştır. Elde edilen sonuçlar, bir elektrik alanı uygulamasının bu etkileşimleri etkili bir şekilde modüle edebildiğini göstermekte ve kontrollü ilaç salımı için potansiyel bir mekanizma sunmuştur. Çalışmada; TDKN'ler arasında, (14,14) TDKN tutarlı bir şekilde kateşin türevleriyle en güçlü etkileşimleri sergilemekte ve elektrik alanı modülasyonuna en duyarlı davranışı göstermektedir. Elde edilen bulgular, (14,14) TDKN'lerin yeşil çay kateşinleri ve benzer yapısal özelliklere sahip diğer moleküller için elektriksel kontrollü ilaç taşıma araçları olarak özellikle uygun olabileceğini göstermektedir.

Anahtar Kelimeler: Yeşil çay kateşini, Karbon nanotüpler, Nanotaşıyıcı, Moleküler dinamik simülasyonu

Cite

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1. Introduction

Green tea is composed primarily of polyphenols, with flavonoids being the predominant class of polyphenols. Epicatechin gallate (ECG) and epigallocatechin gallate (EGCG) are the most abundant polyphenolic compounds present in green tea, with EGCG considered as the most active and significant component [1] (Figure 1). Epigallocatechin-3-gallate (EGCG), has been found to possess a multifaceted mode of action, including powerful antioxidant properties that protect healthy cells from oxidative damage [2]. Additionally, EGCG has been shown to possess antiangiogenic [3, 4], and anti-cancer properties by inhibiting cell growth and inducing cell death by targeting cellular signaling pathways [5–8]. The attachment of pharmaceutical agents to suitable carriers has been demonstrated to enhance their bioavailability through prolongation of circulation time and increased solubility [9]. In general, nanoparticles are effective at carrying drugs, which can be bound to them through covalent conjugation or noncovalent interactions such as van der Waals forces, hydrophobic effects, or electrostatic interactions [10] Carbon nanotubes (CNTs) are cylindrical structures composed of graphene sheets with high aspect ratios, characterized by small diameters (1 nm) and lengths (several micrometers). There are two main types of CNTs: single-walled (SWNTs) and multi-walled (MWNTs). SWNTs are made of a single layer of graphene with a diameter of 0.4-3.0 nm and a length of 20-1000 nm, and are held together by Vander Waals forces, which make them flexible and easily twistable [11]. Carbon nanotubes (CNTs) are suitable for biomedical applications such as drug and gene delivery due to their needle-like shape and ability to efficiently penetrate cell membranes [12, 13]. Their efficiency in transporting drugs into cells through endocytosis is influenced by surface chemistry, size, and type of cell being targeted, and they have the ability to accumulate in tumor tissue due to the enhanced permeability and retention effect. The mechanism of CNTs' cellular uptake depends on various factors such as dimension, cell type, surface functionalization, surface charge, and can occur through direct penetration, passive or active uptake, or endocytosis [10, 14]. Single walled CNTs (SWNTs) are particularly effective drug carriers because they can accumulate near target cells and enhance the permeability and retention (EPR) effect of the drug. Various therapeutic agents, such as small molecules and biologics, can be attached to or encapsulated within CNTs [15]. Carbon nanotubes (CNTs), can facilitate site-selective accumulation of the drug in pathological regions of interest, thereby augmenting their therapeutic efficacy. The unique ability of CNTs to permeate cell membranes further highlights their potential utility as carriers for intracellular delivery of therapeutic agents [9]. In recent decades, interdisciplinary efforts have been devoted to solving the intrinsic defects and maximizing the benefits that are associated with green tea catechins. Delivery of catechins with nanocarriers emerged as a promising strategy to enhance the stability, bioavailability, and bioefficacies (e.g., anticancer, anti-inflammation, and antioxidation effects) of catechins.

Molecular dynamics (MD) simulations have become an indispensable tool for understanding the interactions between drug molecules and SWNTs [16, 17]. These simulations provide detailed insights into the binding mechanisms, stability, and dynamics of drug-SWNT complexes, which are crucial for the development of effective drug delivery systems. Several studies have employed MD simulations to explore the potential of SWNTs in drug delivery. Some studies investigated the adsorption of doxorubicin, an anticancer drug, onto SWNTs or carbon-based nanomaterials using MD simulations [18–22]. The results revealed that doxorubicin molecules interact strongly with SWNTs via π-π stacking interactions, which enhances the drug stability and loading capacity. Similarly, Parlak et al. [23] conducted MD simulations to study the encapsulation and release of ibuprofen from SWNTs. They found that the drug release profile could be controlled by modifying the surface chemistry of the SWNTs, demonstrating the versatility of SWNTs as drug carriers. In another study, Youssef et al. [24] used MD simulations to examine the interaction of curcumin with SWNTs. The simulations showed that curcumin molecules preferentially adsorb onto the surface of SWNTs, forming stable complexes that protect the drug from degradation. This finding is significant as it highlights the potential of SWNTs to enhance the bioavailability and therapeutic efficacy of poorly soluble drugs like curcumin. Further advancements in MD simulation techniques have enabled the study of more complex drug delivery scenarios. For example, a study by Lv et al. [25] utilized MD simulations to investigate the co-delivery of multiple drugs using functionalized SWNTs.

Their simulations demonstrated that functional groups on the SWNTs could be tailored to selectively bind different drugs, facilitating the co-delivery and controlled release of multiple therapeutic agents. Moreover, MD simulations have been instrumental in understanding the biocompatibility and toxicity of SWNTs. Al Qattan et al. [26] performed MD simulations to study the interactions between SWNTs and lipid bilayers, representing cell membranes. Their findings indicated that the functionalization of SWNTs with biocompatible molecules could significantly reduce cytotoxicity while enhancing cellular uptake, which is crucial for the safe application of SWNTs in drug delivery. Overall, the literature underscores the value of MD simulations in elucidating the complex interactions between drugs and SWCNTs. These insights are vital for designing optimized nanocarriers that improve drug stability, bioavailability, and therapeutic efficacy while minimizing adverse effects. The application of MD simulations in drug delivery research continues to

evolve, promising further breakthroughs in the development of SWNT-based therapeutic systems.

In light of the significant potential of carbon nanotubes in drug delivery applications, this study aims to explore the interactions between green tea catechin derivatives and SWNTs using molecular dynamics simulations. We focus on understanding how different catechin compounds—catechin (CA), epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC), and epigallocatechin gallate (EGCG)—bind and interact with SWNTs of different sizes. Our goal is to analyze how stable these interactions are and how they affect the structure and movement of the catechins and SWNTs. This research will help determine if SWNTs can be effective carriers for these compounds, potentially improving their stability, bioavailability, and therapeutic effects.

2. Computational Methods and Details

2.1. Model Setup

In this study, our objective is to investigate the loading of catechin derivatives using three unique armchair single-walled carbon nanotubes (SWNTs) with chiralities of (10, 10), (12, 12), and (14, 14) as carrier systems, employing molecular dynamics simulations. The system was designed to have 15 catechin derivative molecules and one SWNT filled with water molecules in the simulation box. The armchair (10, 10), (12, 12),

(14, 14) SWNTs utilized in this study had lengths of 53.9 Å and diameters of 13.88 Å, 16.27 Å, and 19.40 Å, respectively. The SWNT structures were acquired using the Nanotube Modeler program27, with all carbon atom charges set to zero. Bond, angle, and dihedral types, as well as SWNT parameters, were established according to the OPLS-AA forcefield as reported in previous works28. The initial molecular configurations of green tea catechin derivatives (Figure 1) were determined using the Automated Topology Builder29 (ATB, version 2.0) based on the all-atom Gromos G54A7 forcefield. The interactions between water molecules, both inside the SWNT and in the surrounding environment, were characterized using the rigid, four-site TIP4P/2005 model 30, chosen for its precise prediction of water's bulk viscosity. The SHAKE algorithm31 was employed to constrain angles and bond lengths within water molecules, ensuring accurate representation. Input files, including topology and force field files, were subsequently generated using custom Python codes.

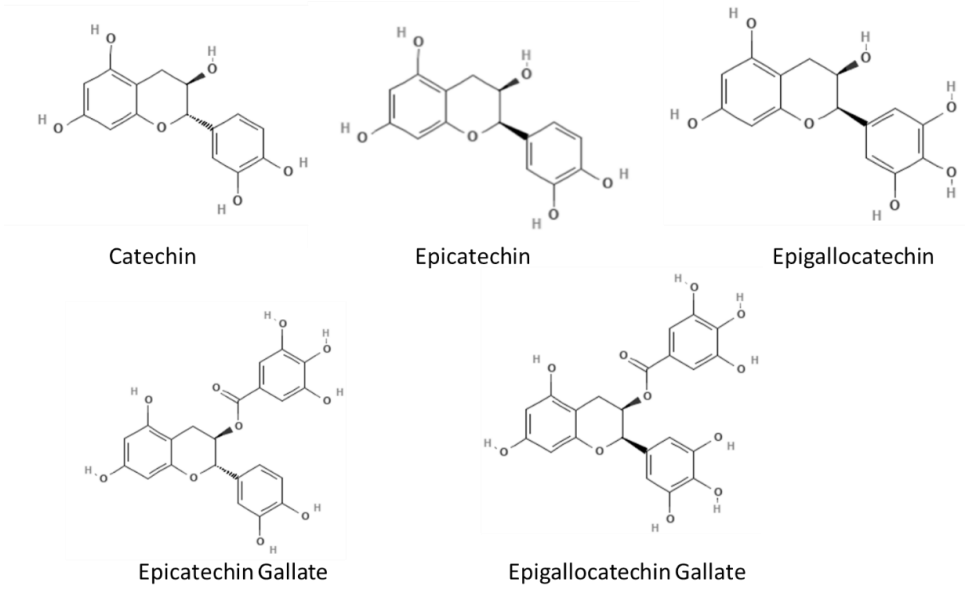

Figure 1: Chemical structures of green tea catechin derivatives used in the MD simulations

2.2. Simulation Details

In this study, classical molecular dynamics (MD) simulations were carried out using the LAMMPS (Large-scale Atomic/Molecular Massively Parallel Simulator). These simulations took place in the NVT ensemble, incorporating a 1 fs timestep at a temperature of 298 K. A total of 30 ns was covered in the production stage, with the system's temperature maintained by the Nose-Hoover thermostat. Our simulation environment was a box measuring 50×50×80 Å, featuring periodic boundary conditions in all orthogonal directions. We modeled van der Waals interactions using the Lennard-Jones (LJ) potential and electrostatic interactions with the Coulomb potential. The LJ potential addressed atom-to-atom van der Waals forces, while the Coulomb potential managed electrostatic forces at charged sites. The particle-particle particle-mesh (PPPM) method in LAMMPS calculated these electrostatic forces, with a set cutoff of 12 Å for both LJ and electrostatic interactions. Lorentz-Berthelot mixing rules were employed to estimate intermolecular potentials for dissimilar molecule pairs. Analytical post-processing was conducted via Python, with visualization of MD outcomes achieved through VMD and OVITO tools. To investigate the effect of an external electric field on the release of catechin derivatives from SWNTs, a uniform electric field with an intensity of 200 V/nm was applied along the central axis of the SWNT.

3. Results

In this section, we offer an in-depth analysis of the efficacy and stability of single-walled carbon nanotubes (SWNTs) as nanocarriers for a range of green tea catechin derivatives. Our research methodically explores the loading/release dynamics of several catechins: Catechin (CA), Epicatechin (EC), Epicatechin Gallate (ECG), Epigallocatechin (EGC), and Epigallocatechin Gallate (EGCG) onto SWNTs with specific chirality indices, (10,10), (12,12), and (14,14). The study encompasses a multifaceted evaluation, including an assessment of complex stability through Root Mean Square Deviation (RMSD) analysis, an investigation of π-π stacking efficiency via distance evolution calculations for the aromatic rings of catechin derivatives and the SWNT surface, and diffusion coefficients. Additionally, we analyze the diameter variations of the three SWNTs during molecular dynamics (MD) simulations, providing insights into the structural adaptability of these nanocarriers in the presence of different catechin molecules. Furthermore, we explore the impact of an external electric field on the release of catechin derivatives from SWNTs through MD simulations. By applying a uniform electric field along the central axis of the SWNT, we investigate the van der Waals interaction during the course of the simulation between catechin derivatives and SWNT.

Figure 2 presents a schematic illustration of the studied SWNTs, including the SWNT (12,12) loaded with 15 catechin derivatives, and a depiction of a catechin-loaded SWNT solvated in an aqueous environment (Figure 2).

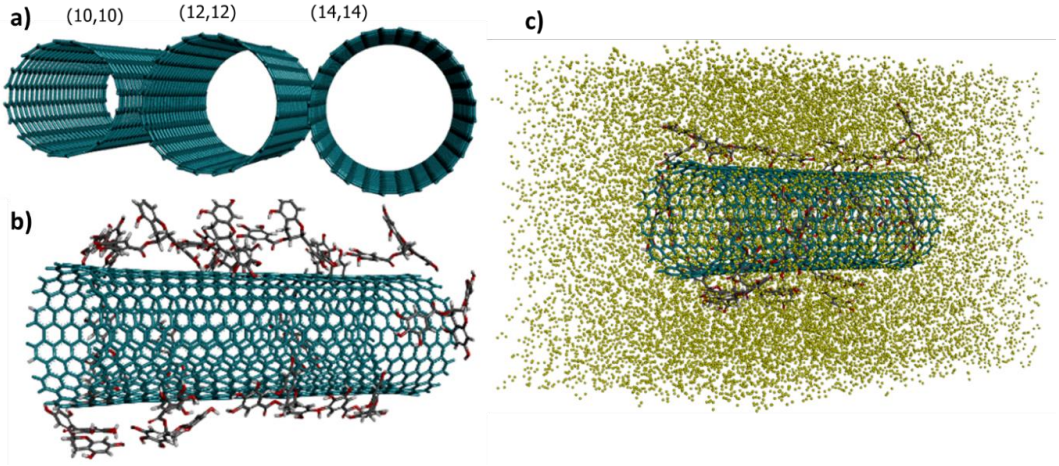

Figure 2: Schematic representation of a) SWNTs with (10,10), (12,12), and (14,14) chiralities b) catechin loaded SWNT c) water solvated catechin loaded SWNT

3.1. Root Mean Square Displacement (RMSD)

Root Mean Square Deviation (RMSD) is a widely used measurement in molecular dynamics (MD) simulations to assess the structural similarity between two conformations [27]. In the context of simulations involving SWNT and catechin derivatives, RMSD calculation can provide valuable insights into the conformational changes and stability of these molecules under various conditions.

Figure 3 illustrates the RMSD profiles for three Armchair Single-Walled Carbon Nanotubes (SWNTs) - SWNT (10,10), SWNT (12,12), and SWNT (14,14) - each externally loaded with five different catechin derivatives. The baseline for RMSD calculations is the initial structure of these nanocarriers at the start of the simulation. Figure 3 display the RMSD results for SWNT nanocarriers complexed with Catechin (CA), Epicatechin (EC), Epicatechin Gallate (ECG), Epigallocatechin (EGC), and Epigallocatechin Gallate (EGCG), with each SWNT carrying 15 molecules of the catechin derivative.

A notable observation is that the RMSD values generally stabilize with minimal fluctuations after 15 to 20 ns in the MD simulations across all complexes, indicating the attainment of structural stability. Interestingly, all SWNTs [(10,10), (12,12), and (14,14)] complexed with EGC and EGCG demonstrate earlier stabilization (~ 17000 ps) and lower RMSD values (~ 3 Å) compared to those loaded with CA, EC, and ECG. This suggests a potentially stronger interaction between EGC and SWNT or EGCG and the SWNT surface, likely due to enhanced π - π stacking interactions, especially given the additional aromatic ring present in these derivatives. This enhanced interaction is consistent with previous studies demonstrating that the presence of multiple aromatic rings in molecules can significantly strengthen π-π stacking interactions with carbon-based nanomaterials [18, 28–30]. Such strong interactions not only stabilize the complex but also potentially enhance the efficiency of SWNTs as drug delivery systems.

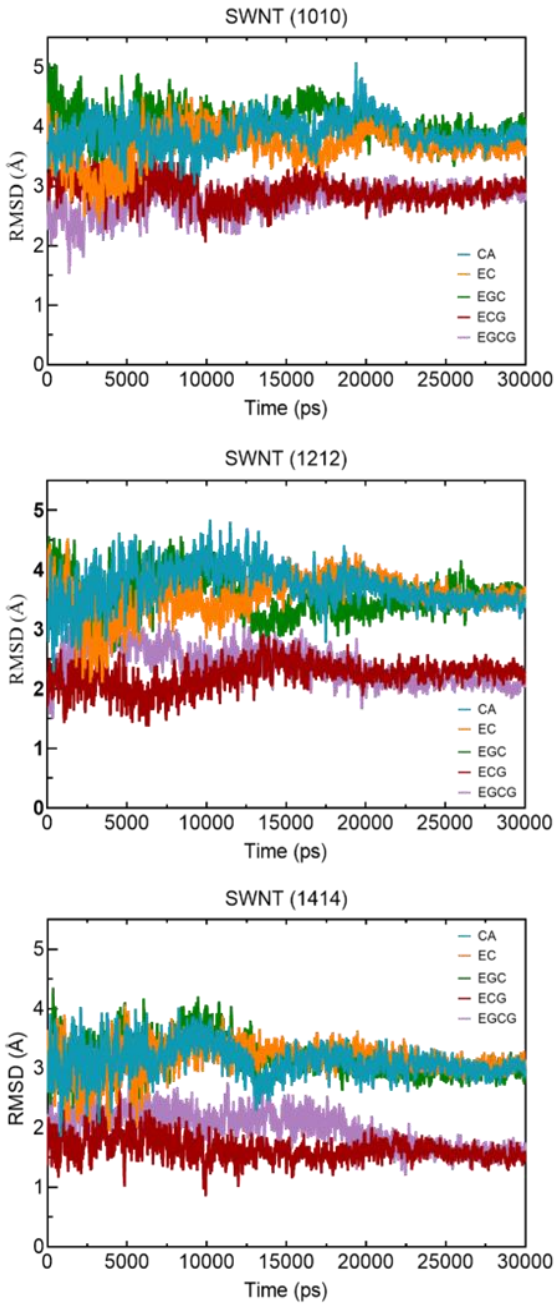

Figure 3: RMSD profiles for catechin derivative loaded SWNTs with different chiralities. a) SWNT (10,10) b) SWNT (12,12) c) SWNT (14,14).

3.2. Distance Evolution between catechin derivatives and SWNT

To evaluate the π- π interaction strength between catechin derivatives and single-walled carbon nanotubes (SWNTs), distances from Ring B of catechin derivatives (CA, EC, EGC, ECG, EGCG) to the external surfaces of SWNTs with diameters (10,10), (12,12), and (14,14) were measured, as depicted in Figure 4. Specific details regarding the median distances and interquartile ranges (IQRs), which reflect the stability and variability of these interactions, are provided in Table 1.

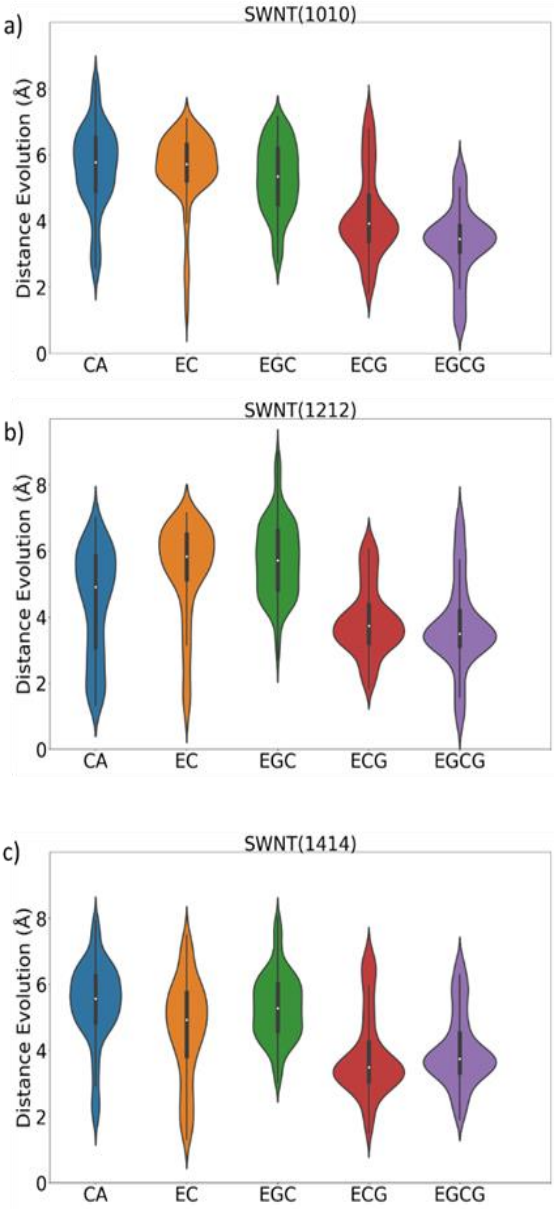

Figure 4: Distance measurement of ring B of catechin derivatives for A) Low (5 molecules) B) Medium (10 molecules) C) High (15 molecules) with SWNT

This analysis revealed significant variations in interaction patterns, which were markedly influenced by the diameter of the SWNTs. Specifically, for SWNT (10,10), median distances varied from 3.45 for EGCG to 5.77 for CA, with interquartile ranges (IQRs) indicating differing levels of interaction stability, ranging from 0.77 in EGCG to 1.58 in CA. This pattern of variability was similarly observed in other SWNT diameters; notably, SWNT (12,12) demonstrated increased variability, as evidenced by a larger IQR for CA (2.75). In contrast, ECG and EGCG showed consistently closer and more stable interactions across all SWNT types, characterized by lower median values and narrower IQRs.

Table 1: Median Distances and Interquartile Ranges (IQR) of Catechin Derivatives to SWNT Surfaces

Catechin Derivative	SWNT (10,10)		SWNT (12,12)		SWNT (14,14)	
	Median (Å)	IQR (Å)	Median (Å)	IQR (Å)	Median (Å)	IQR (Å)
CA	5.77	1.58	4.91	2.75	5.57	1.39
EC	5.71	1.07	5.82	1.34	4.92	1.90
EGC	5.35	1.66	5.71	1.78	5.28	1.41
ECG	3.93	1.37	3.72	1.13	3.49	1.16
EGCG	3.45	0.77	3.49	1.04	3.75	1.18

3.3. Diameter Evolution of Single-Walled Carbon Nanotubes (SWNTs)

The Figure 5 displays the results of a molecular dynamics (MD) simulation, which tracks the diameter evolution of single-walled carbon nanotubes (SWNTs) with three different chirality indices: (10,10), (12,12), and (14,14) over a 30 ns period. Diameter measurement is done through the calculation of coordinates of carbon atoms at the two ends and center of SWNTs. These carbon atoms are located on a circle and therefore at different timestep diameter of these circles was calculated and averaged for their circles in each SWNT. These simulations were conducted for SWNTs and SWNTs loaded with CA and epigallocatechin gallate (EGCG). The focus is on how the diameters of these SWNTs change when interacting with these specific catechins. Contrary to initial expectations that loading might increase the diameter due to internal stress or accumulation, the data shows a decrease in diameter for all SWNT chiralities upon loading with CA and EGCG. The decrease in diameter might be attributed to several factors including the molecular arrangement of the catechins on the SWNTs or the specific interaction dynamics like π-π interactions, which could lead to a tighter packing within the nanotube structure. The extent of decrease escalating with increasing SWNT diameter suggests that larger SWNTs may be more flexible or susceptible to internal re-arrangement when loaded watt catechins. This flexibility could allow for a more pronounced inward contraction of the tube structure.

3.4. Diffusion Coefficient (D)

The Figure 6 displays the diffusion coefficients for different catechin derivatives loaded onto single-walled carbon nanotubes (SWNTs). For each catechin derivative, diffusion coefficients increase as the diameter of the SWNTs increases. This trend suggests that larger diameter nanotubes provide efficient attachment for the catechins, potentially leading to increased interaction between the nanotube walls and the catechins [17]. The increased surface contact in longer diameters might enhance the van der Waals forces and other non-covalent interactions, restricting the

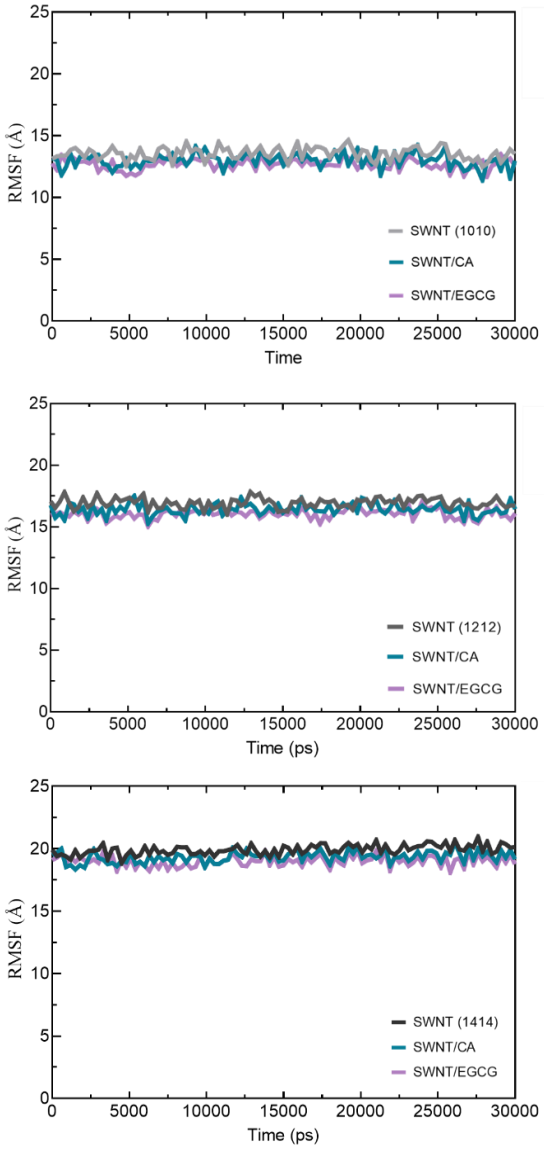

Figure 5. Diameter evolution of single-walled carbon nanotubes loaded with CA and EGCG. a) SWNT (10,10)

loaded with CA and EGCG b) SWNT (12,12) loaded with CA and EGCG c) SWNT (14,14) loaded with CA and EGCG

mobility of the catechins. Among the catechins, ECG and EGCG generally exhibit the lowest diffusion coefficients across all SWNT types. This might be attributed to its molecular structure, which allows better orientation or strong π-π interactions on the external surface of the nanotubes. Conversely, CA-like derivatives show the highest diffusion coefficients, which might be due to its simpler structure resulting in potentially fewer interactions with the nanotube surface that can facilitate movement. SWNT (14,14) consistently shows the highest diffusion coefficients for all catechins, supporting the notion that larger nanotubes facilitate more dynamic interactions. The increased diameter could lead to a lower curvature, affecting how catechins interact with the tube outer walls. As the diameter decreases with SWNT (12,12) and SWNT (10,10), a clear increment in diffusion coefficients is observed, which could be due to the increased curvature allowing less linear alignment of catechins along the axis of the nanotubes, thus increasing mobility.

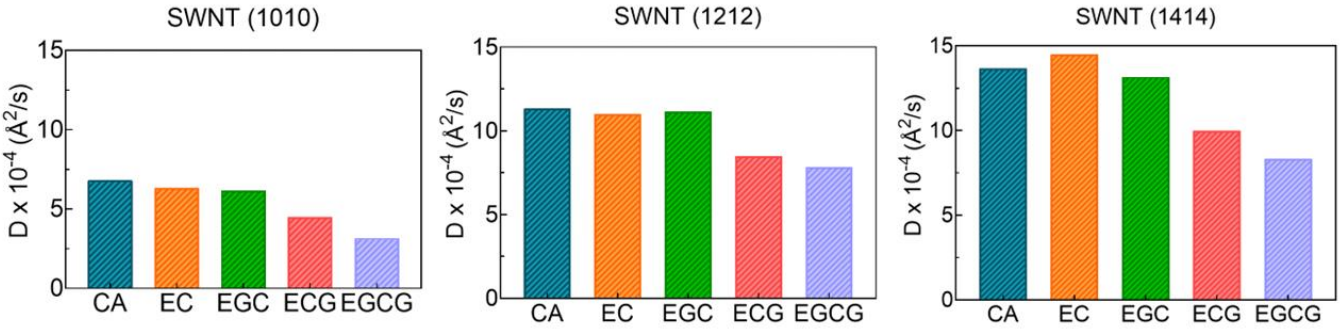

Figure 6. Diffusion Coefficient calculation for CA, EC, EGC, ECG, and EGCG derivatives at low, medium, and high concentrations

3.5. Electric Field Responsive Release

Electromagnetic fields play a significant role in enhancing drug delivery systems by enabling targeted, controlled, and efficient release of therapeutic agents. The integration of electromagnetic responsiveness into drug carriers, such as carbon nanotubes, offers promising avenues for improving treatment outcomes. The development of efficient drug delivery systems is a cornerstone of modern therapeutic strategies, and electromagnetic responsiveness has emerged as a pivotal tool in enhancing their precision and efficacy. In this study, carbon nanotubes (CNTs) were explored as electromagnetically responsive carriers for the targeted delivery of green tea catechins, leveraging their unique physicochemical properties and tunable response to external electromagnetic fields. By integrating CNTs with electromagnetic stimuli, we aimed to achieve controlled release mechanisms and enhanced bioavailability of catechins, which are known for their potent antioxidant and therapeutic benefits. This section presents the results of our investigation, highlighting the influence of electromagnetic fields on the release kinetics, interaction dynamics, and structural integrity of the CNT-catechin system. Furthermore, the findings underscore the potential of CNT-based systems in advancing the field of stimuli-responsive drug delivery, offering insights into their implications for precision medicine. [31-33]. Based on the van der Waals (vdW) interaction energy graphs provided for different catechin derivatives (CA, EC, ECG, EGC, and EGCG) interacting with single-walled carbon nanotubes (SWNTs) of varying chiralities, we can analyze the potential for release of these compounds under an applied electric field.

Figure 7 consistently show stronger interactions (more negative vdW energies) for larger diameter SWNTs, with the (14,14) SWNT exhibiting the strongest binding across all catechin types. This suggests that release from larger diameter SWNTs may require stronger electric fields. However, the fluctuations in interaction energies, particularly pronounced for larger SWNTs, indicate dynamic interactions that could facilitate release under appropriate conditions. The gradual increase in interaction energy over time for most systems implies that prolonged exposure to an electric field might be necessary to overcome initial strong adsorption. Notably, EGCG shows the strongest overall interactions, suggesting it may be the most challenging to release, while CA and EC exhibit weaker binding and may be more readily influenced by an applied electric field. The varying interaction strengths across catechin types and SWNT chiralities suggest that tailored electric field strengths could potentially allow for selective release of specific catechins from different SWNT carriers.

4. Conclusion

This study demonstrates the potential of single-walled carbon nanotubes (SWNTs) as effective nanocarriers for green tea catechin derivatives. Our molecular dynamics simulations revealed that the loading efficiency and stability of catechins on SWNTs are significantly influenced by both SWNT chirality and catechin structure. Larger diameter SWNTs consistently showed stronger adsorption, with epigallocatechin gallate

(EGCG) exhibiting the most robust interactions. The time-dependent nature of these interactions and the observed dynamic adsorption-desorption processes provide valuable insights for optimizing loading and release protocols. The application of an electric field emerged as a promising approach for triggered release, offering possibilities for developing stimuli-responsive drug delivery systems. These findings lay the groundwork for the rational design of SWNT-based delivery systems for catechin derivatives, potentially enhancing their bioavailability and therapeutic efficacy.

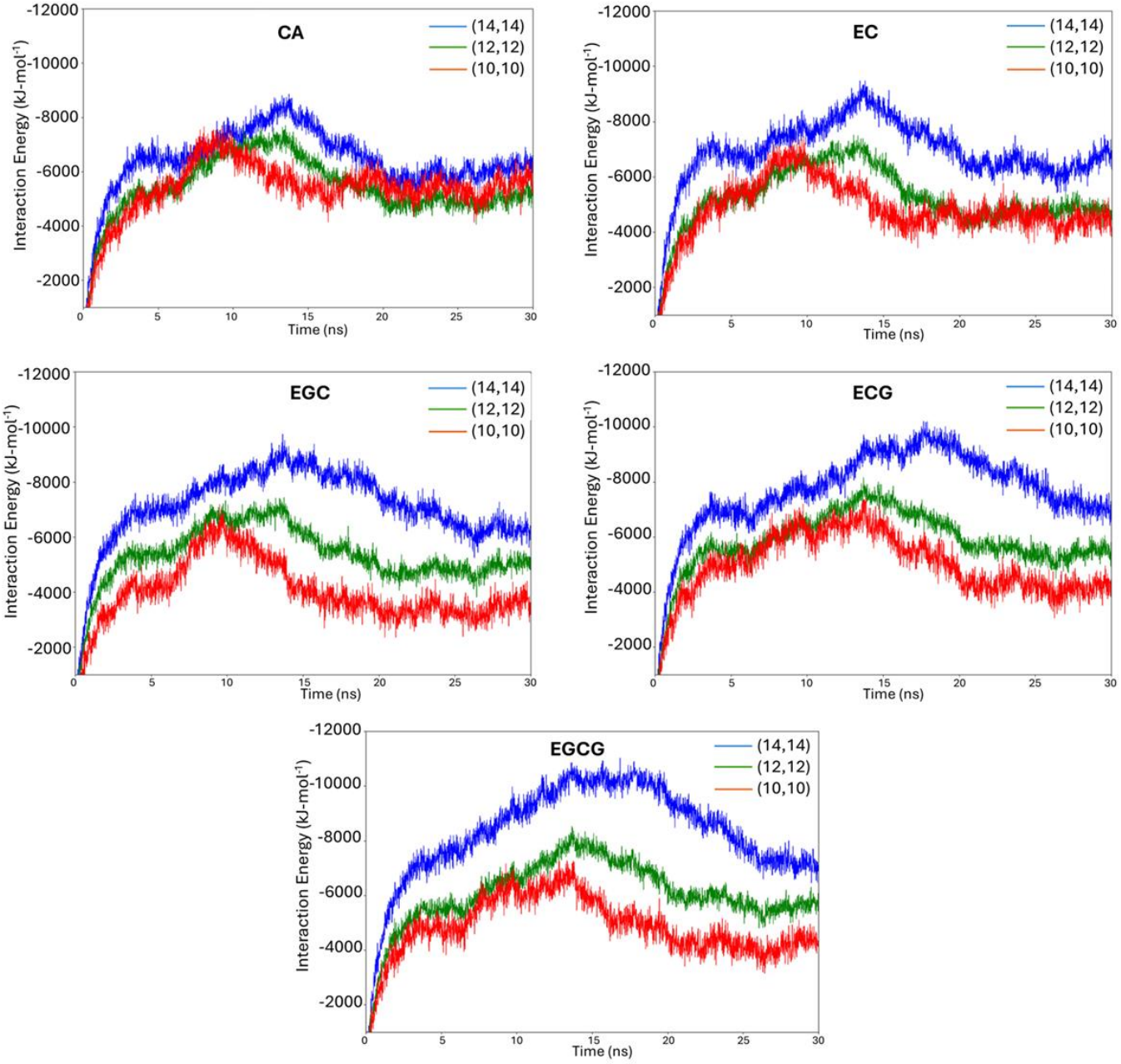

Figure 7. Van der Wales interaction energy for CA, EC, EGC, ECG, and EGCG derivatives with different SWNTs

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