T.R.

USKUDAR UNIVERSITY

INSTITUTE OF SCIENCE

DEPARTMENT OF MOLECULAR BIOLOGY

MOLECULAR BIOLOGY PROGRAM

MASTER THESIS

ENHANCING THE EFFICACY OF EPICATECHIN GALLATE THROUGH SINGLE-WALLED CARBON NANOTUBE

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DECLARATION

I declare that this study is my thesis study, that I have committed no unethical behavior at any stage from planning to writing, that I have obtained all the information in the thesis within academic and ethical rules, and that I resource all the information and comments that are not obtained through the thesis study.

Date:

FOREWORD

First and foremost, I would like to express my deepest gratitude to my esteemed advisor, Dr. Handan Emişoğlu Külahlı, for her invaluable guidance, unwavering support, and insightful feedback throughout the course of this research. Her expertise and dedication have been instrumental in shaping the direction and quality of this thesis.

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I would also like to extend my heartfelt thanks to my husband, whose love, patience, and constant support have sustained me during the most challenging moments of this journey. To my children, who have been a source of joy and motivation, thank you for your understanding and for giving me the strength to persevere.

My deepest appreciation goes to my family—my mother, father, and sisters—who have always believed in me and encouraged me to pursue my dreams. Your love and support have been my foundation your presence in my life has been a blessing, and I am truly thankful for each one of you.

I am also grateful to my friends and all the beloved people around me, whose encouragement and understanding have made this journey easier.

This thesis is as much a result of your support as it is of my efforts, and I dedicate this work to all of you with profound gratitude.

Thank you.

ABSTRACT

Single-walled carbon nanotubes (SWNTs) hold great promise for various applications due to their exceptional electronic, mechanical, and structural properties. One particularly important application is their use in drug delivery systems (DDS), where SWNTs can control the rate and location of drug release, improving efficacy and minimizing side effects. This study explores the molecular interactions between epicatechin gallate (ECG) molecules and SWNTs through molecular dynamics (MD) simulations. Two systems were analyzed: pristine SWNTs and SWNTs modified with nanoholes. Five ECG molecules were randomly placed on the surfaces of both systems to examine their behavior. The interactions between ECG molecules and SWNT surfaces were primarily driven by non-covalent π-π stacking between ECG's aromatic rings and the nanotube surface. The distance measurement results obtained from the aromatic groups (A, B, D) of ECG and the SWNT surface showed that groups A and B were as necessary being closer to each other, which indicated a stronger binding state, while group D displayed tendency to more mobility and weaker interactions. The addition of a nanohole significantly altered the interaction dynamics, creating a more heterogeneous interaction environment. Some ECG molecules exhibited stable binding near the nanohole, while others displayed increased mobility in the pristine regions of the SWNT. These results suggest that structural modifications, such as the introduction of nanoholes, could be used to optimize molecular interactions in SWNT systems. This has potential applications in drug delivery, sensing, and catalysis by improving binding and controlling molecular diffusion, ultimately advancing SWNT-based technologies.

Key words: Single-walled carbon nanotube (SWNT), Epicatechin gallate (ECG), Molecular dynamics simulations, Nanohole, Drug delivery systems

ÖZET

Tek duvarlı karbon nanotüpler (SWNT'ler), üstün elektronik, mekanik ve yapısal özellikleri nedeniyle çeşitli uygulamalar için büyük bir potansiyel taşımaktadır. Özellikle; SWNT'lerin ilaç salınımının hızını ve yerini kontrol edebildiği, etkinliği artırdığı ve yan etkileri en aza indirdiği ilaç taşıma sistemlerinde (DDS) kullanılması önemli bir uygulama,alanıdır. Bu çalışma; epikateşin gallat (ECG) molekülleri ile SWNT'ler arasındaki moleküler etkileşimleri moleküler dinamik (MD) simülasyonları yoluyla incelemektedir. Kusursuz SWNT'ler ve nanodeliklerle modifiye edilmiş olmak üzere iki sistem analiz edilmiştir: Beş ECG molekülü, davranışlarını incelemek amacıyla rastgele her iki sistemin yüzeylerine yerleştirilmiştir. ECG molekülleri ile SWNT yüzeyleri arasındaki etkileşimler, esas olarak ECG'nin aromatik halkaları ile nanotüp yüzeyi arasındaki kovalent olmayan π-π etkileşimi ile yönlendirilmiştir. ECG'nin aromatik grupları (A, B, D) ile SWNT yüzeyi arasındaki mesafe ölçüm sonuçları, A ve B gruplarının birbirine daha yakın olduğunu ve bu durumun daha güçlü bir bağlanma durumunu gösterdiğini, D grubunun ise daha hareketli olduğunu ve daha zayıf etkileşimler sergilediğini göstermiştir. Nanodelik eklenmesi, etkileşim dinamiklerini önemli ölçüde değiştirerek daha heterojen bir etkileşim ortamı oluşturmuştur. Bazı ECG molekülleri nanodelik etrafında kararlı bağlanma gösterirken, diğerleri SWNT'nin kusursuz bölgelerinde artan hareketlilik sergilemiştir. Bu sonuçlar, nanodeliklerin eklenmesi gibi yapısal modifikasyonların, SWNT sistemlerindeki moleküler etkileşimleri optimize etmek için kullanılabileceğini göstermektedir. Bu, bağlanmayı iyileştirerek ve moleküler difüzyonu kontrol ederek ilaç taşıma, algılama ve kataliz gibi alanlarda potansiyel uygulamalara sahip olup, nihayetinde SWNT tabanlı teknolojilerin ilerlemesine katkıda bulunabilir.

Anahtar kelimeler: Tek duvarlı karbon nanotüp (SWNT'), Epikateşin gallat (ECG), Moleküler dinamik simülasyonlar, Nanodelik, İlaç taşıma sistemleri

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ABBREVIATIONS

C - Catechin

CDs - Carbon Dots

CG - Catechin Gallate

CHARMM-GUI - Chemistry at Harvard Macromolecular Mechanics Graphical User Interface

CMECs - Cerebral Micro vessel Endothelial Cells

CNTs - Carbon Nanotubes

COM - Centers of Mass

CoMoCAT® - Cobalt Molybdenum Catalyst

CT - Computerized Tomography

CVD - Chemical Vapor Deposition

DNA - Deoxyribonucleic Acid

EC - Epicatechin

ECG - Epicatechin Gallate

EGC - Epigallocatechin

EPR - Enhanced Permeability and Retention

GSH - Glutathione

LAMMPS - Large-scale Atomic/Molecular Massively Parallel Simulator

MD - Molecular Dynamics

MRI - Magnetic Resonance Imaging

MSD - Mean Squared Displacement

MWCNT - Multi-Walled Carbon Nanotube

MWNT - Multi-Walled Nanotube

NBO - Natural Bond Orbital

NIR - Near-Infrared

NP - Nanoparticles

NVE - Constant Number of Particles, Volume, and Energy

NVT - Constant Number, Volume, and Temperature

OH - Hydroxyl Group

PDA - Polydopamine

ROS - Reactive Oxygen Species

RNS - Reactive Nitrogen Species

SWNT - Single-Walled Nanotube

XO - Xanthine Oxidase

1. INTRODUCTION

Nanomaterials have become integral to modern drug delivery systems, offering unique advantages in terms of drug solubility, stability, and targeted delivery. The ability of these materials to operate at the nanoscale allows for precise control over drug release, improving both the therapeutic efficacy and safety of treatments. Nanotechnology-based systems have been ultimately successful in overcoming the limitations of conventional drug delivery methods, such as poor bioavailability and nonspecific distribution, by delivering therapeutic agents directly to specific tissues or cells. As a result, they have shown great potential in the treatment of chronic diseases, including cancer, cardiovascular disorders, and infections (Patra et. al. 2018). While there are a myriad of nanomaterials suited for therapeutic delivery, carbon nanotubes (CNTs) are emerging as particularly interesting tools for drug delivery due to their considerable structural and associated physicochemical properties. In particular, carbon nanotubes (CNTs) are emerging as attractive therapeutic agents due to their unique physicochemical properties, including a high aspect ratio, substantial surface area, and significant ability to penetrate biological membranes, making them an efficient delivery agent for targeted amine delivery systems. One major benefit of CNTs for drug delivery is their ability to be functionalized with a broad spectrum of amines for drug delivery, peptides, or nucleic acids yielding highly selective delivery agents for disease treatment and targeted therapeutic mechanisms. Functionalized CNTs can be engineered to bypass biological barriers, offering the possibility of more effective intracellular delivery of drugs while minimizing systemic toxicity and improving bioavailability. Recent studies have shown the promise of CNTs in cancer therapy, where they have been used to deliver chemotherapeutic agents directly to tumor cells, thereby reducing the side effects associated with conventional chemotherapy. Additionally, CNT-based delivery systems have demonstrated potential in overcoming multidrug resistance, a major challenge in cancer treatment. These capabilities position CNTs as valuable tools for developing more targeted and efficient drug delivery systems (Bianco et. Al. 2005; Ji et. al. 2010).

In this study, using molecular dynamics simulations, we investigate the interaction dynamics of epicatechin gallate (ECG) molecules (a bioactive compound in green tea) with single-

walled carbon nanotubes (SWNTs), which are important for drug delivery, sensing, energy conversion and storage, and structural reinforcement. By calculating the van der Waals and electrostatic energy dynamics as well as the molecular displacement, our study provides an understanding of the potential of ECGs to interact with SWNTs for different morphological configurations, as well as of the impact of nanoholes on the structural changes and binding strength, and thus the molecular stability in the aqueous phase under physiological conditions.

2. GENERAL INFORMATIONS

2.1. Introduction to epicatechin Gallate

Tea extracts are rich in natural compounds, including flavanols, caffeine, and terpenes, with catechins a subgroup of flavanols- being the most prominent and biologically active components. The major catechins include epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC), and epigallocatechin gallate (EGCG), while minor catechins include catechin (C), catechin gallate (CG), gallocatechin (GC), and Gallo catechin gallate (GCG), which are epimers of the major forms (Shikha et al., 2024). Catechins are well-known for their health benefits, including antioxidant, anti-inflammatory, and anticancer properties (Aggarwal et al., 2022). Various studies have demonstrated significant therapeutic potential for green tea catechins (Muial et al., 2020) (Figure 1).

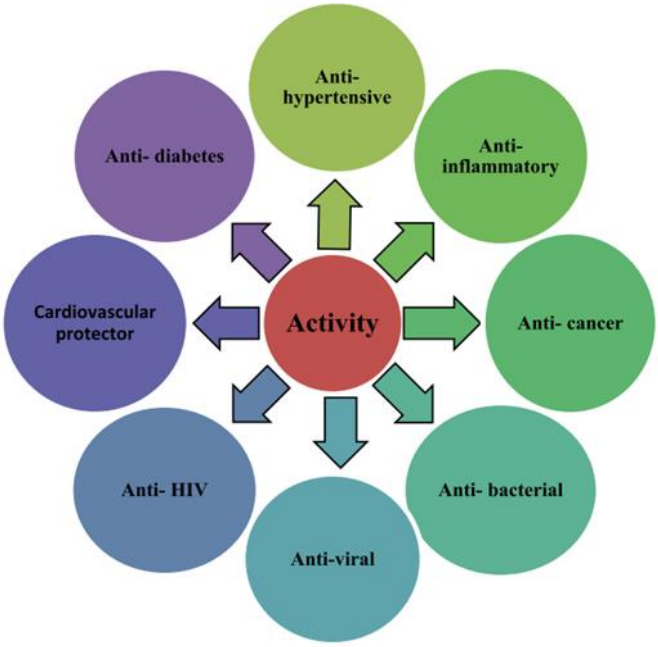

Figure 1: Anticancer mechanisms of catechin derivatives (Shikha et al., 2024).

Epicatechin gallate (ECG), found in plants such as cocoa, apples, and particularly green tea, has shown considerable promise due to its antioxidant, anti-inflammatory, and anticancer properties (Figure 2) (Mokra et al., 2022).

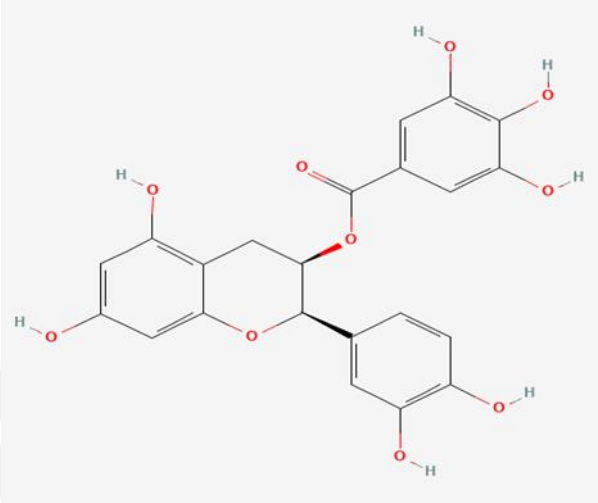

Figure 2: Epicatechin gallate structure (Schuldesz et al., 2024).

Like other catechins, ECG exhibits antioxidant activity by scavenging free radicals, which helps reduce oxidative stress and inflammation, improving cardiovascular health and lowering the risk of chronic diseases (Babu & Liu, 2008). However, challenges in clinical applications arise from the low absorption, poor stability, and short plasma half-life of certain catechins, which can limit their therapeutic potential (Chen et al., 2022). These limitations are largely attributed to the chemical structure of catechins, particularly the numerous hydroxyl groups attached to their aromatic rings, which contribute to both their bioactivity and poor stability. To overcome these limitations, recent interdisciplinary research has focused on enhancing the stability, bioavailability, and therapeutic effects of catechins through nanocarrier-based delivery systems (Hamano et al., 2020). Nanoparticles, such as those encapsulated with polysaccharides like chitosan, have emerged as a promising solution. For instance, epigallocatechin gallate (EGCG) loaded into folate-modified nanoparticles has shown enhanced anticancer activity in breast cancer cells (MCF-7) by regulating key proteins involved in cell survival and apoptosis (Cheng et al., 2020). Nanoparticles penetrate tumor tissues through the enhanced permeability and retention (EPR) effect, accumulating in the

tumor's leaky vasculature. Factors such as size, shape, and surface properties of the nanoparticles determine their interaction with the tumor microenvironment, facilitating their uptake by cancer cells through endocytosis and improving the targeted delivery of therapeutic agents. In cancer treatment, catechin-loaded nanoparticles exhibit superior pharmacokinetic profiles, including longer plasma half-life and greater drug retention in tumor tissues, enhancing their therapeutic efficacy. In the application of catechin-loaded nanoparticles for cancer treatment, upon entering systemic circulation, the nanoparticles migrate from the bloodstream into tumor tissues (Figure 3). This effect arises from the abnormal distribution of endothelial cells in tumor vasculature, which results in the formation of large pores, typically ranging from 100 to 800 nm, facilitating the extravasation of nanoparticles into the tumor microenvironment (Jiang et al., 2021).

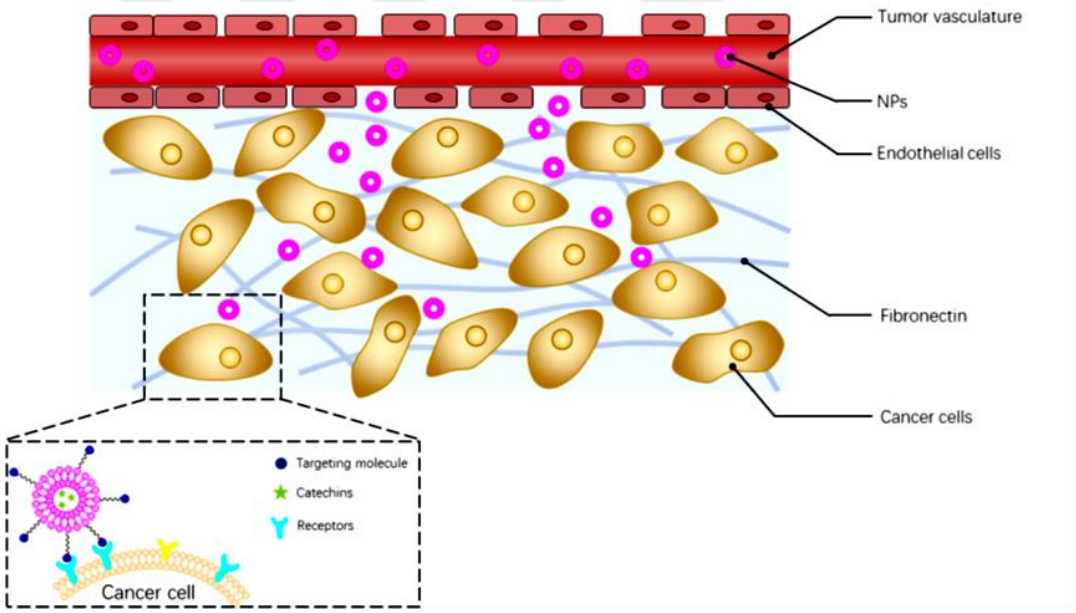

Figure 3: Nanoparticle Delivery of Catechins to Tumor Sites (Jiang et al., 2021).

In a study, it was demonstrated that nanoparticles loaded with epigallocatechin-3-gallate exhibited enhanced targeting efficiency towards folate receptor-positive breast cancer cells in both in-vitro and in-vivo models. EGCG-loaded nanoparticles displayed superior pharmacokinetic profiles, including a longer plasma half-life and increased drug retention in tumors, resulting in greater tumor inhibition. These findings underscore the therapeutic potential of folate-decorated EGCG nanoparticles in breast cancer treatment, particularly by

addressing the limitations of free EGCG, such as poor bioavailability and rapid degradation (Kazi et al., 2020). These advances underscore the potential of nanoparticle-based catechin delivery systems in cancer therapy, particularly in overcoming the pharmacokinetic challenges associated with free catechins.

2.2. Carbon-based Nanomaterials

Carbon-based nanomaterials encompass a wide array of substances, including fullerenes, carbon nanotubes (CNTs), graphene and its derivatives, graphene oxide, nano diamonds, and carbon-based quantum dots. Each of these materials is characterized by distinctive structural dimensions and exceptional physical and chemical properties, making them highly applicable in a variety of fields, including environmental remediation, energy storage, and biomedical applications. The unique sp2 and sp3 hybridization of carbon atoms allows for the creation of diverse structures, such as spherical fullerenes, cylindrical carbon nanotubes, and 2D graphene sheets, all of which exhibit excellent mechanical strength, electrical conductivity, and thermal stability. This versatility renders carbon-based nanomaterials invaluable in applications ranging from pollution control and energy conversion to advanced biomedical therapies, such as drug delivery systems and diagnostic tools (Patel et al., 2019; Ayanda et al., 2024).

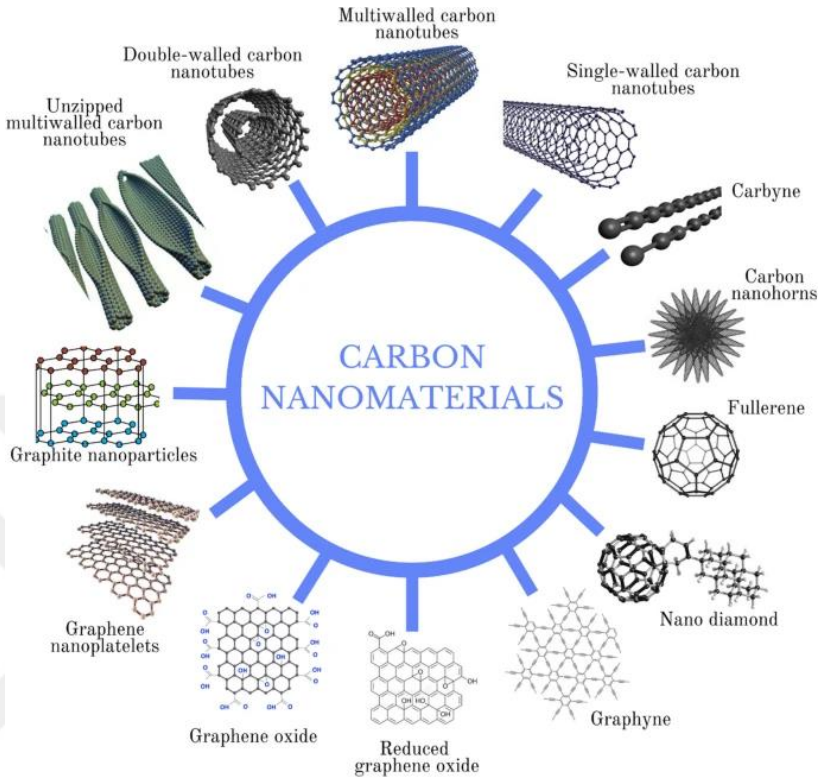

Figure 4: Structures of various carbon-based nanomaterials (Ayanda et al.,2024).

In particular, their application in biomedicine has garnered attention due to their ability to be functionalized with various biomolecules, enabling targeted therapeutic applications such as drug delivery, bioimaging, and diagnostics. Fullerenes, for example, have shown promise in photodynamic therapy, while graphene-based materials, due to their high surface area and ease of chemical modification, offer excellent platforms for drug delivery and gene therapy. Nanodiamonds, known for their exceptional hardness and chemical stability, are emerging as valuable tools for drug delivery and imaging, while carbon quantum dots, with their unique optical properties, are becoming crucial in bioimaging and sensor technologies (Ayanda et al., 2024).

The potential for functionalizing these nanomaterials to interact with biological systems has opened up new avenues in personalized medicine, especially in creating more

efficient, targeted drug delivery systems that minimize side effects while maximizing therapeutic efficacy. Their biocompatibility and tunable properties position carbon-based nanomaterials as a key component in the next generation of medical technologies (Patra et. al. 2018).

2.3. Carbon nanotubes

Carbon atoms arranged in a hexagonal lattice in two dimensions, called graphene, make up a single layer of single-walled carbon nanotubes (SWCNTs), which are cylindrical nanostructures. These SWCNTs can exhibit different structural configurations, such as zigzag and armchairs, contributing to their unique electronic properties (Zeng et al., 2022; Akai- et al., 2022) (Figure 5). The high aspect ratio and large surface area of carbon nanotubes make them promising candidates for functionalization, enabling the attachment of various molecules, such as drugs or biomolecules, onto their surface. (Predtechenskiy et al.2022). Carbon nanotubes are materials with incredible potential and remarkable properties. Single-walled carbon nanotubes have been the subject of intense research and development activity worldwide, as well as significant expenditure in production techniques, characterization, and application development. Given the extraordinary qualities these materials have and the variety of unique species, each with its own special characteristics, the reasons for this are pretty obvious (Gifford et al., 2020). The diameters of SWNTs range from 0.7–2.0 nm (Banerjee et al., 2022). When utilized in composites, for example, only the outer wall typically makes a substantial contribution to the electrical mechanical properties of Multi-Walled Carbon Nanotubes (MWNTs), allowing for much lower loading of SWNTs compared to MWNTs. Single-walled carbon nanotubes are the more remarkable of the two forms of carbon nanotubes (Balarak et al., 2021). The SWNTs, are a mixture of tubes with varying chiralities, some of which are semiconducting and some of which are electrically conducting. Isolating different tube types such as metallic from semiconducting and, in certain cases, tubes with distinct individual chiralities is preferable for a variety of applications (Banerjee et al., 2022).

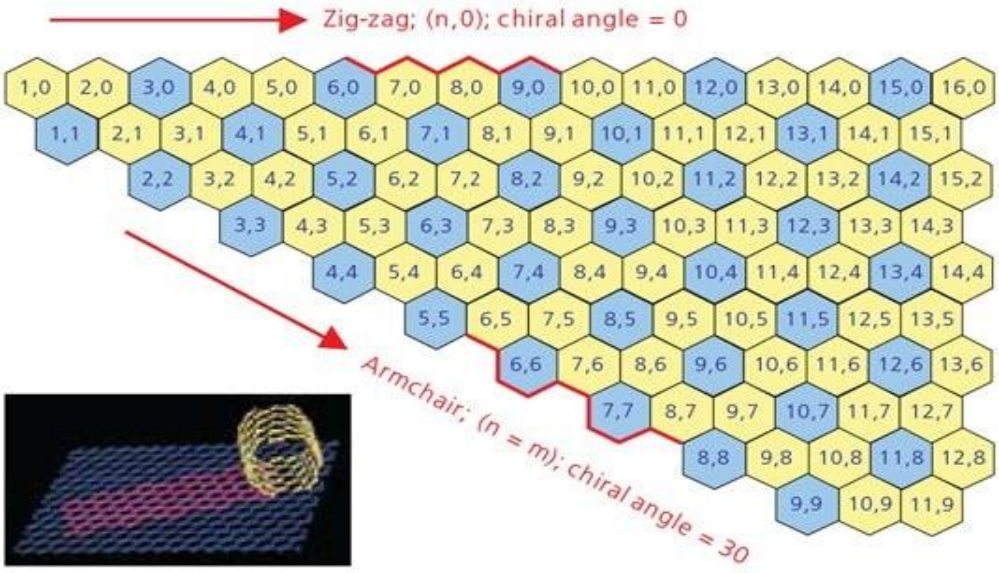

Figure 5: Schematic representation of carbon nanotubes illustrating zigzag and armchair configurations (Zeng et al., 2022).

Compared to steel, a single SWNT is far stronger. Tensile strengths of SWNTs at 1/16th the weight is calculated to be around 100 times stronger than those of steel. The greatest measured value, which may be the result of structural flaws, is about half of the theoretical strength that is predicted (Samy et al., 2020). The current carrying capacity of individual SWNTs is 109 amp/cm2, which is greater than that of copper or gold (Kashtiban et al., 2021). Additionally, compared to silicon, semiconducting species have higher electron mobility (Panasenko et al., 2022). Every chirality in SWNT exhibits a unique optical absorption and fluorescence spectrum, giving rise to a distinctive optical absorption and fluorescence response (Banerjee et al., 2022).

In drug delivery applications, CNTs have shown potential in enhancing drug stability, controlling release, and targeting specific cells or tissues. (Yaghoubi & Ramazani, 2020). Their unique properties, such as high drug loading capacity, cellular uptake, and the ability to penetrate cell membranes, make them attractive as drug delivery vehicles. Functionalized CNTs have been explored for delivering a wide range of therapeutic agents, including both hydrophilic and hydrophobic molecules, and have shown promise in overcoming multidrug resistance. Moreover, CNTs can be functionalized to improve their hydrophilicity, enabling their use in diverse drug delivery systems, including oral

administration and targeted delivery to specific sites (Zare et al.2021). In the evolving field of nanomedicine, CNTs also exhibit versatility in cancer treatment, combining drug delivery with advanced imaging techniques such as photoacoustic imaging and magnetic resonance imaging (MRI). This dual utility in therapy and diagnostics underscores their potential as powerful tools in cancer theragnostic (Figure 6) (Tang et al., 2021).

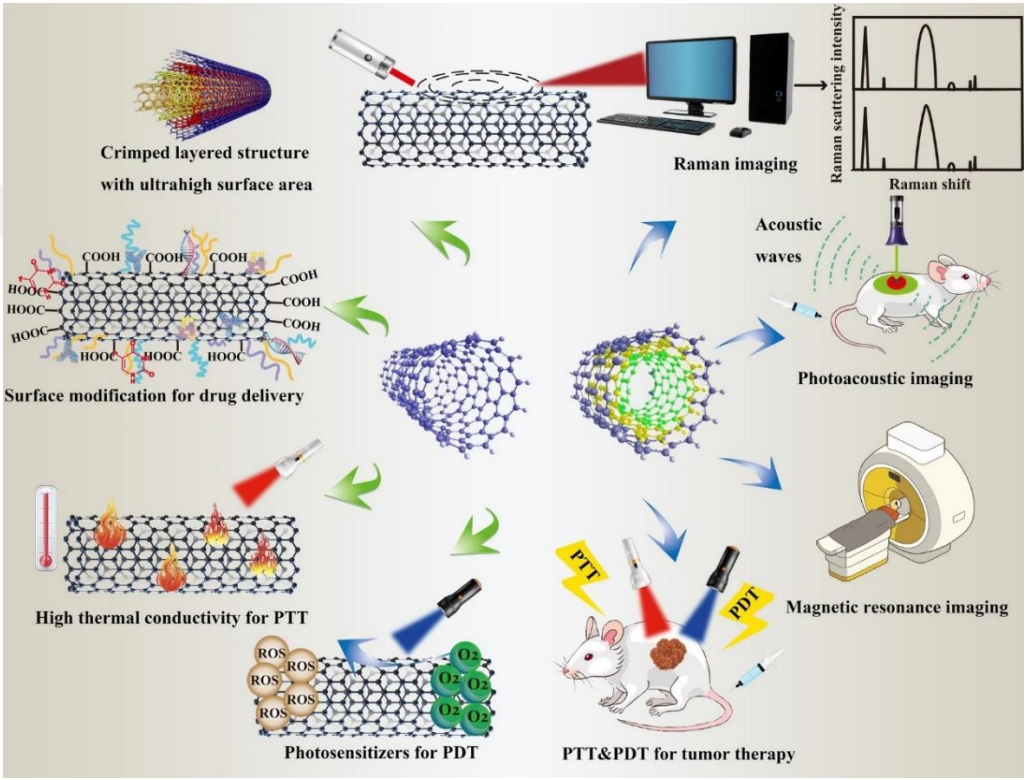

Figure 6: A schematic representation of the various applications of CNTs in cancer therapy and diagnostics (Tang et al., 2021).

Defects like vacancies or abnormalities in the carbon lattice can affect the characteristics of SWCNTs. Chemical functionalization is another method that can be used to add functional groups (such as hydroxyl or carboxyl) to the surface of SWCNTs, changing their chemical reactivity and interactions with other materials. (Villalva et al., 2021). Non-covalent attachment of molecules to SWCNTs, also known as physical adsorption, relies on weak forces such as van der Waals forces, π-π stacking interactions, hydrogen bonding, and electrostatic interactions (Hofferber et al., 2020). Due to the large surface area of SWCNTs, which results from their graphene-like structure, they interact with nearby molecules through van der Waals forces. Molecules with non-polar or weakly polar groups can adsorb onto

SWCNT surfaces through van der Waals interactions, which are proportional to the surface area of the nanotubes and the polarizability of the molecules (McKernan et al., 2021).

2.4.Types of Defects in CNTs

There are various types of defects in carbon nanotubes (CNTs), including point defects, extended defects, and topological defects. Point defects involve atoms being in abnormal positions within the nanotube lattice, causing disruptions in localized areas (Figure 7). Localized defects, such as vacancies, and extended defects like grain boundaries can occur due to deviations in the regular arrangement of carbon atoms along the tube axis. These defects can have a significant impact on the mechanical and electronic properties of CNTs. Moreover, topological defects such as Stone-Wales defects and pentagon-heptagon pairs can create curvature and strain in the nanotube structure, affecting their behavior and reactivity (Pugno et al., 2009).

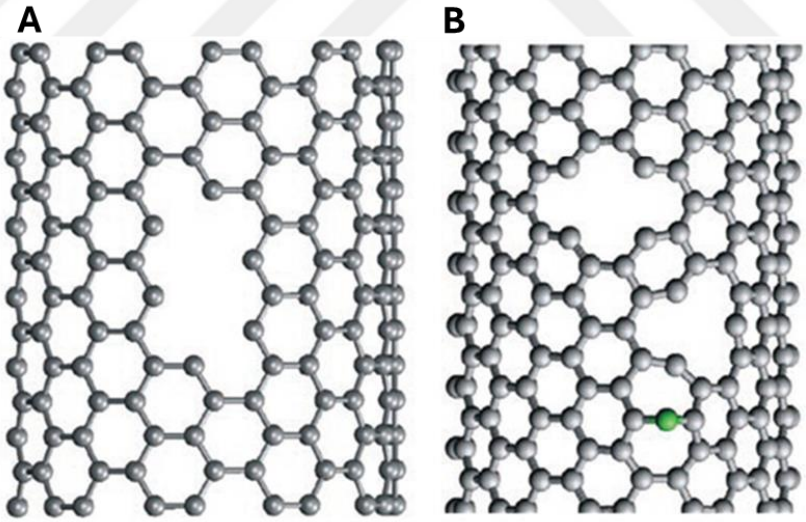

Figure 7: Illustrations of defects within a carbon nanotube structure: a) Stone-Wales defect b) Vacancy defect (Pugno et al., 2009).

Understanding defect classifications is crucial for tailoring the properties of CNTs for specific applications, such as nanoelectronics, composite materials, and biomedical devices (Singh et al., 2016; Mishra et al., 2024). Different types of defects can have diverse

effects on the tensile strengths and behavior of CNT-based networks, making their classification and study essential for the development of advanced materials and technologies. Defects in carbon nanotubes (CNTs) play a significant role in drug delivery systems. The presence of defects can impact the loading and release of drugs within CNTs, as well as the interaction between CNTs and biological environments. Modified CNTs have been investigated for their role in drug delivery due to their capability to effectively penetrate cells, making them suitable carriers for small-molecule therapeutics (Singh et al., 2016). Both hydrophilic and hydrophobic molecules can be bound to CNTs, and polymers can be grafted to their surface, enhancing their potential as efficient drug carriers. Additionally, the physical and chemical properties of CNTs, including their high surface area and potentially greater adsorption abilities, make them a novel nanomaterial for drug delivery, addressing limitations such as poor solubility and rapid deactivation of therapeutic agents (De Andrade et al., 2024).

2.5.Molecular Dynamics Simulations

Molecular dynamics (MD) simulations are powerful computational techniques that model the behavior and interactions of atoms and molecules over time by solving Newton's equations of motion. Based on classical mechanics, the forces between particles are calculated using interaction potentials, and their positions and velocities are updated numerically. MD simulations are widely employed to explore diverse phenomena, including biomolecular dynamics, material properties, and chemical reactions. The flexibility of MD allows for the sampling of thermodynamic variables like temperature and pressure across different ensembles, offering valuable insights into the system’s thermodynamic behavior (Binder et al., 2003; Zhou et al., 2023). Before running an MD simulation, the system's initial conditions, such as atomic positions, velocities, and environmental factors, must be defined, along with force fields representing atomic interactions. The simulation then calculates forces and accelerations at each time step, updates positions and velocities using numerical algorithms, and evaluates energy and forces under varying thermodynamic conditions. Once equilibrium is reached, structural and dynamic properties of the system can be assessed. The development of MD simulations has enhanced force fields and methods like constant pressure and isothermal molecular dynamics, enabling their application in non-equilibrium

systems and extending their utility in studying macroscopic properties (Mouvet et al., 2022; Mandal et al., 2022; and Mao et al., 2023).

Molecular dynamics (MD) simulations are computational techniques used to directly solve Newton's equations of motion for a system of interacting particles, formalizing the application of classical mechanics to molecular systems. The motion of each atom is governed by Newton's second law, where the force acting on the atom is determined by its mass, position, and the forces exerted by surrounding atoms (Kumar et al., 2022). The accuracy of MD simulations largely depends on the integration algorithm employed to solve these equations of motion. The general form of Newton's second law for particle i is given as:

$$mi\ \frac{d^2 ri}{dt^2} = \sum Fi \qquad (1.1)$$

Where Fi represents the sum of all forces acting on particle i due to interactions with other particles in the system. The forces are derived from predefined force field functions, which dictate how atoms interact. To optimize computational efficiency, cutoff distances are applied only atoms within this distance are considered when calculating interatomic forces, as interactions decay with distance. Since the equations of motion cannot be solved analytically due to the complexity of the force fields, numerical integration methods are employed to update atomic positions and velocities. Several integration algorithms are available, each evaluated based on criteria like energy conservation, computational efficiency, stability over long time steps, and accurate approximation of particle trajectories.

The most commonly used numerical integration methods in MD simulations include the Verlet, Leap-Frog, Beeman's, and Accelerated Verlet algorithms. Among these, the Verlet algorithm is widely favored due to its balance between accuracy and computational simplicity (Qi et al., 2021; Mao et al., 2023; and Turalija, 2023). The position of an atom at time t+Δt can be approximated using the following equations based on the Taylor expansion of the atomic coordinates: (Velocities (v_i), Acceleration (a_i).

$$r(t + \Delta t) = r(t)\Delta t + \frac{1}{2}a(t)\Delta t^2 \qquad (1.2)$$

$$v(t+\Delta t) = v(t) + \frac{1}{2}[a(t) + a(t+\Delta t)]\Delta t \quad (1.3)$$

The choice of integration method and accurate definition of force fields are crucial for obtaining reliable and meaningful simulation results in molecular dynamics. Considerations for numerical stability limit the selection of integration methods to those that do not introduce unrealistic effects. The most widely used integration method is the velocity-Verlet method, which is time-reversible and preserves volume, with second-order accuracy in time steps. These properties are essential for a reliable simulation method. The time-reversal property is necessary for stable integration of the motion equations over extended periods, and volume preservation ensures accurate reproduction of equilibrium volume fluctuations. Second-order accuracy is desirable, but the associated errors are rarely problematic in practice, even at very high temperatures (Weidong et al., 2023; and Mao et al., 2023). In classical molecular dynamics, the equation of motion is a second-order differential equation with respect to time. To progress from a specific initial state, a unique initial condition must be specified. This involves determining not only the positions of each particle at the initial time but also their velocities. With the positions and velocities of all particles at a given time, it is possible to uniquely determine the configuration of the system at the next moment. This process can be repeated indefinitely, theoretically allowing for the complete determination of the system's dynamic trajectory. In practical situations, it is the statistical ensemble of trajectories that accurately describes the time evolution of the thermodynamic properties of the system, rather than a single trajectory. However, the ability to uniquely solve the equations of motion is what makes molecular dynamics such a powerful tool (Brooks et al., 2021; and Shariati et al., 2021).

One advantage of molecular dynamics (MD) simulation over other statistical mechanics simulation methods is that it can easily realize not only the microcanonical ensemble (NVE: constant number of particles, volume, and energy) but also canonical (NVT: constant number, volume, and temperature) and isothermal-isobaric (NPT: constant number, pressure, and temperature) ensembles. To achieve this, the equations of motion for external parameters, such as the temperature T_0, the thermostat mass Q, and the degrees of freedom of the thermostat, are incorporated into the system and solved alongside the particle dynamics.

Several thermostats are commonly implemented in conventional MD codes, such as the Berendsen and Nose-Hoover chains (extended-ensemble methods). MD users must understand the statistical mechanical meaning behind the employed thermostat (Hu et al., 2022; Ke et al., 2022). In molecular dynamics (MD) simulations, the Nose-Hoover thermostat is one of the most popular thermostats used to regulate system temperature. This thermostat extends simple velocity rescaling to satisfy the ergodic hypothesis, allowing both the integration of equations of motion and the sampling of the canonical ensemble. There are guidelines for selecting the control parameters to ensure stable and accurate results (Hu et al., 2022; Hicks et al., 2021). The Nose-Hoover thermostat is an example of a deterministic thermostat, manipulating the equations of motion such that the microcanonical trajectory is modified to realize the desired canonical ensemble. It achieves this by introducing an additional term to the equations of motion, dependent on two variables: the position and momentum of a fictitious particle associated with the thermostat. This particle, with mass Q, modifies the usual particle dynamics, exerting an extra force on all particles to ensure correct isothermal evolution (Vaezi et al., 2023; and Yasbolaghi & Khoei, 2022).

3. METHODOLOGY

3.1. Creation of ECG and SWNT Models

The simulation was designed to explore the behavior of ECG molecules on the external surface of a single-walled carbon nanotube (SWNT) under both realistic and nanohole-bearing conditions. Five ECG molecules were placed randomly on the external surface of both the pristine and nanohole-bearing SWNTs to investigate their interactions. A nanohole was generated on the surface of the SWNT by removing carbon atoms from the middle section. The ECG molecules were placed on the surface with their various aromatic groups (A, B, and D) to study their interactions with the SWNT surfaces. The TIP4P/2005 model of water was used to fill the simulation box (40×40×40Å3), providing an environment that mimics realistic conditions. The SWNT model was created to simulate a typical nanotube with a chirality of (6,6).

Molecular Structure of ECG

(-)-Epigallocatechin-3-Gallate (ECG) is a complex molecule with distinct structural components (Figure 8):

- *A-ring:* A benzene ring with hydroxyl groups at positions 5 and 7.
- *B-ring:* A benzene ring with hydroxyl groups at positions 3', 4', and 5'.
- *C-ring:* A pyran ring connecting the A-ring and B-ring.
- *D group:* A gallate group (benzoate with three hydroxyl groups at positions 3, 4, and 5).

These structural elements contribute to ECG's chemical properties and its interactions with other molecules.

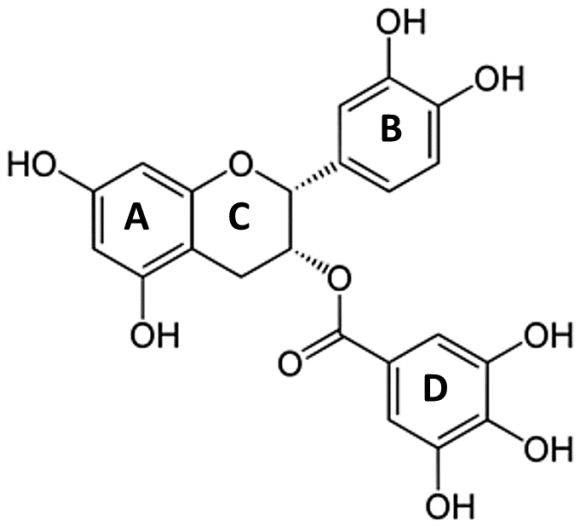

Figure 8: Molecular Structure of Epigallocatechin-3-gallate (EGCG) (Bernatoniene and Kopustinskiene 2018).

3.2. Molecular Dynamics Simulations

The molecular dynamics (MD) simulations were performed using the Large-scale Atomic/Molecular Massively Parallel Simulator (LAMMPS). LAMMPS is a versatile MD simulation software capable of handling large-scale systems with high computational efficiency. The simulations were executed on high-performance computing clusters to manage the computational demands.

3.3. Stability Analysis

Comprehensive stability analyses were performed on a system comprising a pristine single-walled carbon nanotube (SWNT) loaded with epicatechin gallate (ECG) molecules. The temperature was rigorously monitored throughout a 5000-picosecond molecular dynamics simulation. Both van der Waals and electrostatic energies were calculated to observe the interaction dynamics between the SWNT and ECG molecules. The kinetic and potential energies were continuously recorded to evaluate the system's dynamic stability.

3.4. Visualization and Structural Analysis

The trajectory files generated from the LAMMPS simulations were visualized and analyzed using Ovito, an open-source visualization tool for atomistic simulations. Ovito was used to inspect the structural changes, visualize atomic movements, and identify any significant conformational alterations during the simulations.

3.5. Distance Calculations

To further understand the interactions between ECG and the SWNT surface, the distances between the centers of mass of the aromatic groups (A, B, and D) of ECG and the SWNT and the nanohole-bearing SWNT surface were calculated. This was achieved using custom Python scripts that processed the simulation trajectory data to extract the coordinates of the relevant atoms and compute the distances over time. These distance calculations were essential to identify the preferential binding sites and interaction strengths of different aromatic groups with the SWNT surface.

3.6. Calculation of Mean Squared Displacement (MSD)

The mean squared displacement (MSD) of the ECG molecules was calculated to investigate their diffusive behavior on the nanohole-bearing SWNT surface. The MSD calculations were performed using custom Python scripts, which processed the trajectory data and computed the displacement of atoms over time.

4. RESULTS

4.1. Stability Analysis

4.1.1. Temperature Analysis

Temperature stability was assessed by measuring the fluctuations over a 5000-picosecond period during the molecular dynamics simulation of a pristine single-walled carbon nanotube (SWNT) loaded with epicatechin gallate (ECG) molecules (Figure 9).

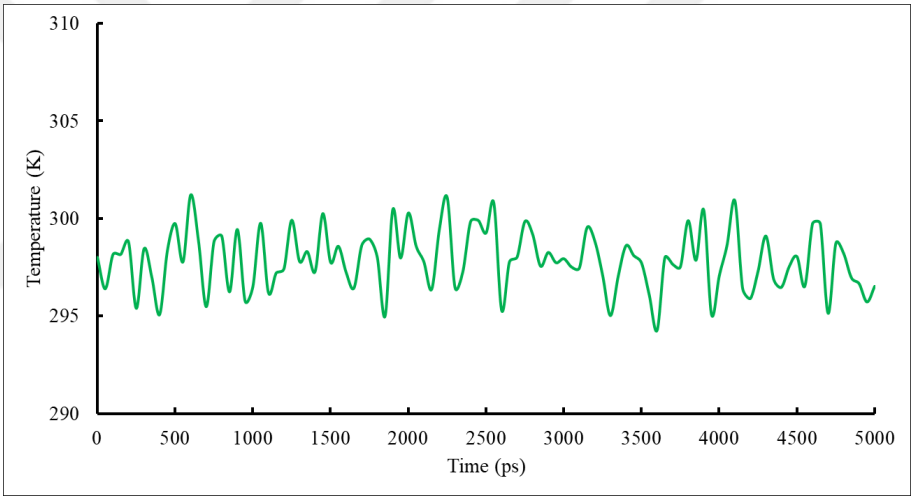

Figure 9: Temperature fluctuations over time.

The observed temperature range is confined between 295 K and 305 K, demonstrating a narrow oscillation band of approximately ±5 K around the target temperature. This constrained variability indicates effective temperature control throughout the simulation, suggesting a well-equilibrated system. The maintenance of a consistent thermal environment is crucial for ensuring that observed energy variations within the system are primarily attributable to molecular interactions rather than artifacts of temperature fluctuations. This stability in temperature control enhances the reliability of the simulation results, allowing for more accurate analysis of the molecular behavior and interactions between the ECG molecules and the single-walled carbon nanotubes (SWNTs).

4.1.2. Van der Waals Energy Dynamics

The molecular dynamics simulation tracked the evolution of van der Waals energy for pristine SWNT loaded with ECG molecules, as depicted in Figure 10.

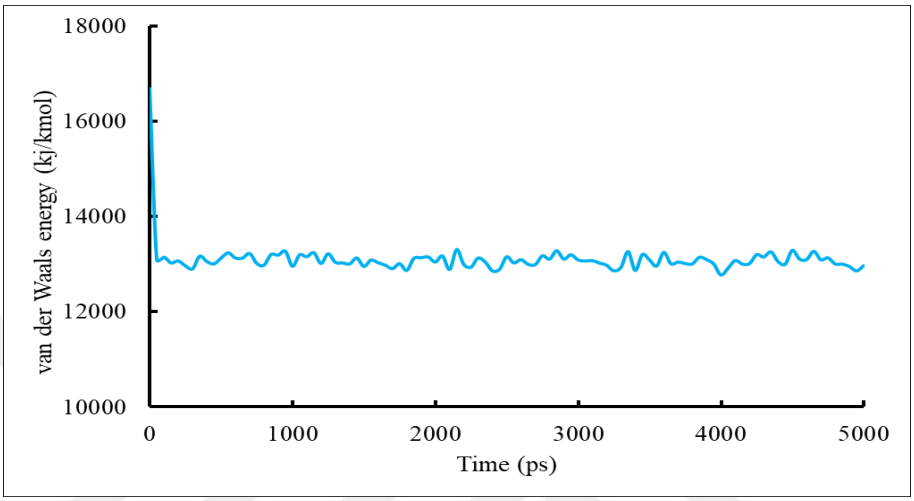

Figure 10: Evolution of van der Waals energy over the course of the simulation.

The plot reveals a significant initial decrease in van der Waals energy, indicative of the system progressing towards a more energetically favorable configuration. This rapid decline is characteristic of the equilibration phase, during which the ECG molecules and SWNT adjust their relative positions to minimize repulsive interactions and maximize attractive forces. Following this initial equilibration, the van der Waals energy stabilizes around -13,000 kcal/mol. The negative value signifies net attractive interactions between the SWNT and ECG molecules. Minor fluctuations around this equilibrium value are observed, which are typical in molecular dynamics simulations and reflect the dynamic nature of the system at the molecular level. The attainment of this stable energy state suggests that the ECG molecules and SWNT have reached a thermodynamically favorable arrangement. This equilibrium configuration likely represents an optimized balance of interactions between the ECG molecules, the SWNT surface, and the surrounding solvent molecules, contributing to the overall stability of the system.

4.1.3. Electrostatic Energy Analysis

The molecular dynamics simulation meticulously captured the evolution of electrostatic energy for pristine SWNT loaded with ECG molecules, as illustrated in Figure 11.

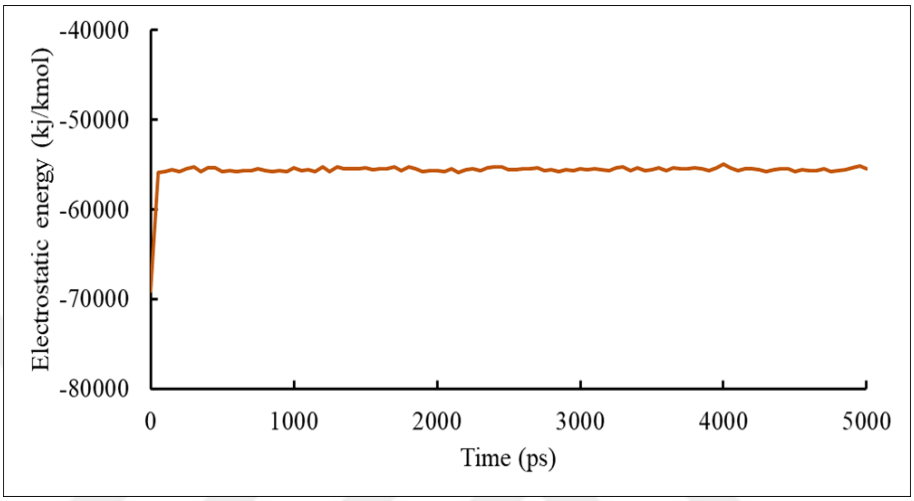

Figure 11: Evolution of electrostatic energy throughout the molecular dynamics simulation.

In contrast to the van der Waals energy profile, the electrostatic energy exhibits a notable initial increase as the system adapts from its starting configuration. This initial rise likely reflects the reorganization of charged and polar groups within the ECG molecules, as well as the reorientation of water molecules in response to the presence of the SWNT. Following this initial adjustment period, the electrostatic energy stabilizes and oscillates around a mean value of approximately -56,000 kcal/mol. The negative value indicates that attractive electrostatic interactions dominate within the system. The observed fluctuations around this mean are characteristic of thermal motion and continuous rearrangements at the molecular level. The stabilization of electrostatic energy signifies the establishment of a balanced network of electrostatic interactions among the ECG molecules, the SWNT surface, and the surrounding water molecules. This equilibrium state suggests that the system has reached a configuration where favorable electrostatic interactions, such as hydrogen bonding and charge-π interactions, are optimized. The interplay between these electrostatic forces and the previously discussed van der Waals interactions contributes significantly to the overall stability and behavior of the ECG-SWNT system in the aqueous environment.

4.1.4. Kinetic Energy Analysis

The total kinetic energy of the system (SWNT/ECG) over time during the molecular dynamics simulation is illustrated in Figure 12.

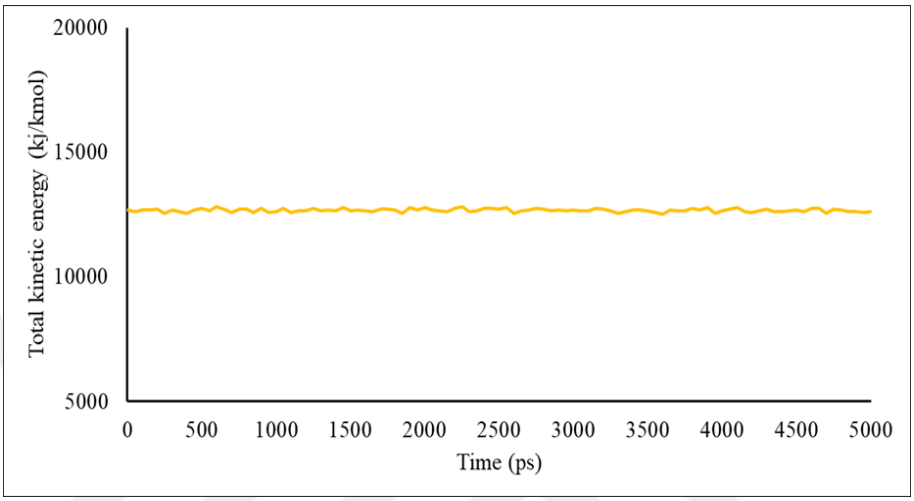

Figure 12: Total kinetic energy of the system (SWNT/ECG) over simulation time.

The graph reveals consistent oscillations in kinetic energy, which are indicative of a system maintaining a stable temperature and dynamic equilibrium. These observations are significant for several reasons;

Temperature Control: the steady variations in kinetic energy directly correlate with the system's temperature, as kinetic energy is a measure of the thermal motion of particles. The consistency of these fluctuations suggests effective temperature control throughout the simulation.

Equilibration verification: the absence of significant drifts or abrupt changes in the kinetic energy profile indicates that the system achieved proper equilibration early in the simulation and maintained this state throughout. This is crucial for ensuring that the observed molecular behaviors are representative of the system under study, rather than artifacts of a non-equilibrated state.

Ergodicity: the stable kinetic energy profile suggests that the system is sampling a consistent ensemble of microstates, which is essential for the ergodic hypothesis underlying molecular dynamics simulations.

4.1.5. Potential Kinetic Analysis

The total potential energy of the system (SWNT/ECG) over time is depicted Figure 13.

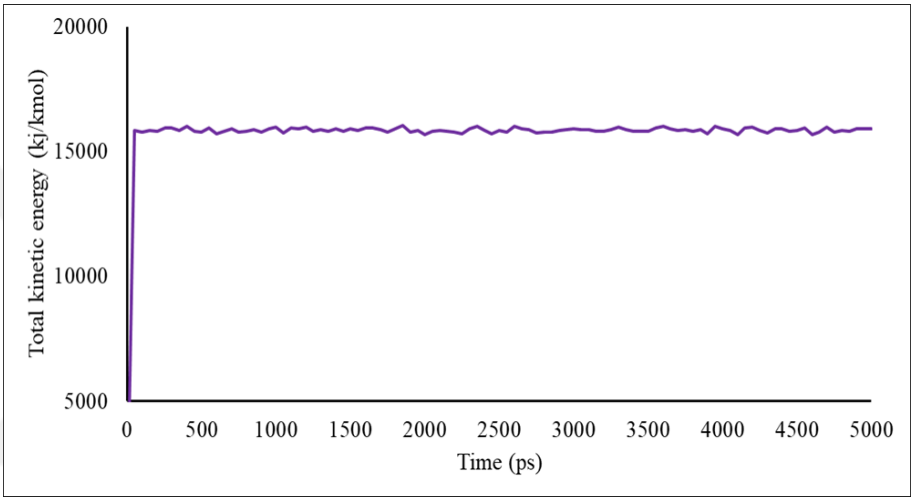

Figure 13: Total potential energy of the system (SWNT/ECG) over simulation time.

The potential energy profile provides insights into the interactions between system components and their configurational changes;

Initial Spike: an early spike in potential energy, likely corresponding to the initial relaxation phase of the simulation, is shown in Figure 13. During this period, the system rapidly adjusts from its starting configuration to a more energetically favorable state.

Stabilization: following the initial spike, the potential energy stabilizes and oscillates around a mean value of approximately 16,000 kcal/mol. This stabilization indicates that the system has reached a quasi-equilibrium state.

Fluctuations: the observed fluctuations around the mean potential energy value are characteristic of thermal motion and continuous rearrangements at the molecular level. These

fluctuations represent the system exploring different conformational states within its energy landscape.

System Stability: The stable potential energy profile, in conjunction with the steady kinetic energy, suggests that the system has achieved a balanced state. In this state, the interactions between ECG molecules, the SWNT surface, and surrounding water molecules have optimized to a thermodynamically favorable configuration.

Energy Conservation: The complementary behavior of kinetic and potential energy profiles is consistent with the principle of energy conservation in the simulation, further validating the reliability of the molecular dynamics results.

This combined analysis of kinetic and potential energy profiles provides strong evidence for the proper equilibration and stability of the simulated ECG-SWCNT system in an aqueous environment. These energy characteristics form a foundation for interpreting other observed phenomena and properties in the simulation with confidence.

4.2. Distance Analysis

The distances between the SWNT surface and aromatic groups (D, A, B) of ECG Molecule 1 over 5000 ps are analyzed (Figure 14). D group (blue line in figure) of ECG molecule, exhibits large fluctuations (4-12 Å), suggesting dynamic, weaker interactions with the SWCNT surface. A (orange) and B (green) groups of ECG molecule, exhibit More stable trajectories, maintaining closer distances (3-6 Å) to the SWCNT surface, indicating stronger, more consistent interactions. A and B groups likely serve as primary anchoring points for ECG Molecule 1 on the SWNT surface, while the D group shows more mobility. This analysis reveals the heterogeneous nature of ECG-SWNT interactions, suggesting a preferred orientation of ECG Molecule 1 on the nanotube surface.

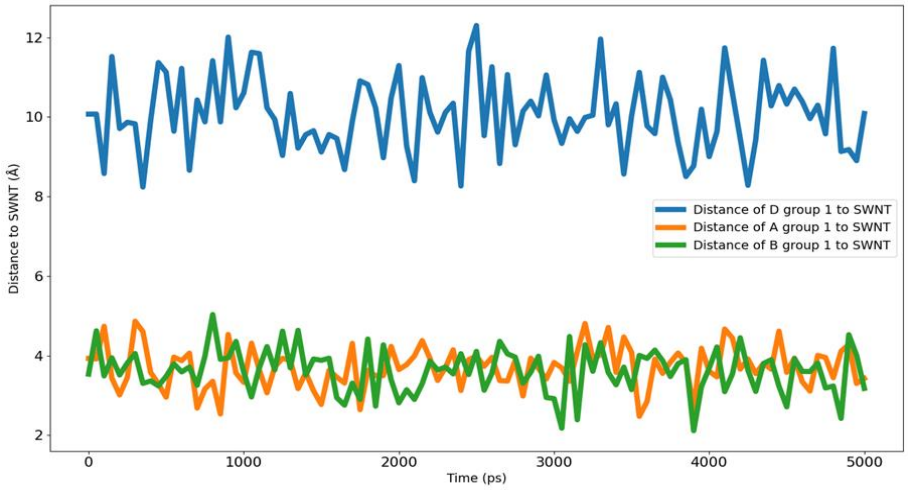

Figure 14: Distances between the SWNT surface and aromatic groups (D group (blue), A (orange) and B (green) groups) of ECG Molecule 1.

Figure 15 illustrates the distances between the SWNT surface and aromatic groups (D, A, B) of ECG Molecule 2 over time. D group (blue), displays highly variable behavior, with distances frequently exceeding 10 Å. This suggests more erratic interactions with the SWNT surface compared to ECG Molecule 1. A (orange) and B (green) groups: Maintain closer proximity to the SWNT surface (approximately 4-6 Å), indicating more stable and consistent interactions.

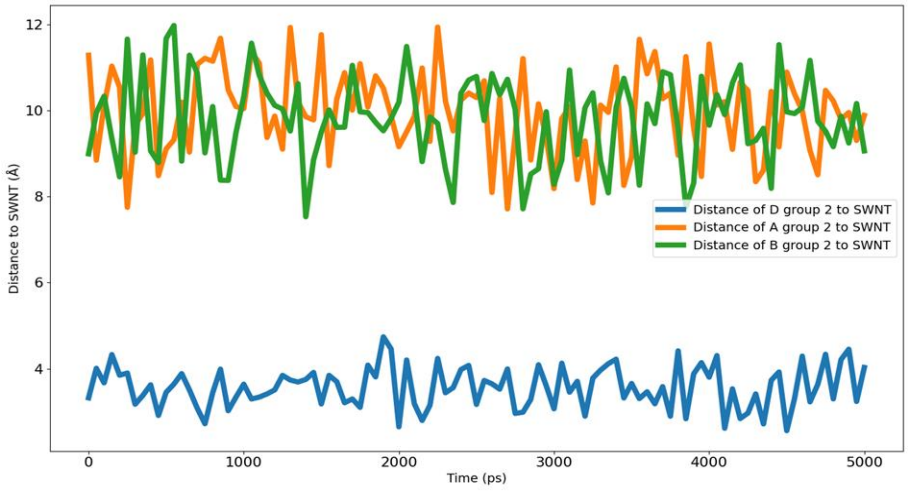

Figure 15: Distances between the SWNT surface and aromatic groups (D group (blue), A (orange) and B (green) groups) of ECG Molecule 2 over time.

The distances between the SWNT surface and aromatic groups (D, A, B) of ECG Molecule 3 over time depicted in Figure 16. D group (blue) exhibits variable behavior, with distances occasionally exceeding 12 Å, indicating inconsistent interactions with the SWNT surface. A (orange) and B (green) groups maintain closer proximity to the SWNT surface, with distances primarily clustering between 3-5 Å, suggesting more stable and consistent interactions.

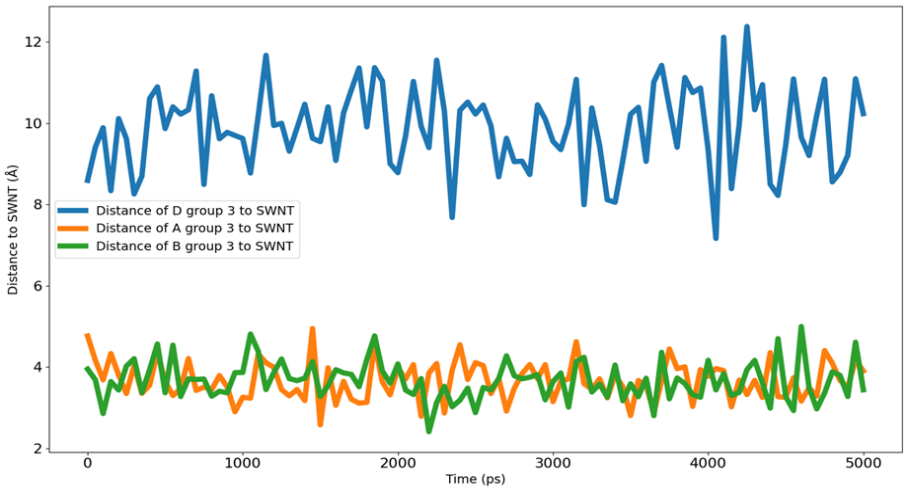

Figure 16: Distances between the SWNT surface and aromatic groups (D group (blue), A (orange) and B (green) groups) of ECG Molecule 3 over time.

The distances between the SWNT surface and aromatic groups (D, A, B) of ECG Molecule 4 over time is depicted in Figure 17. All groups (D, A, B) exhibit consistently close distances to the SWNT surface, ranging between 3.5 and 4.5 Å.

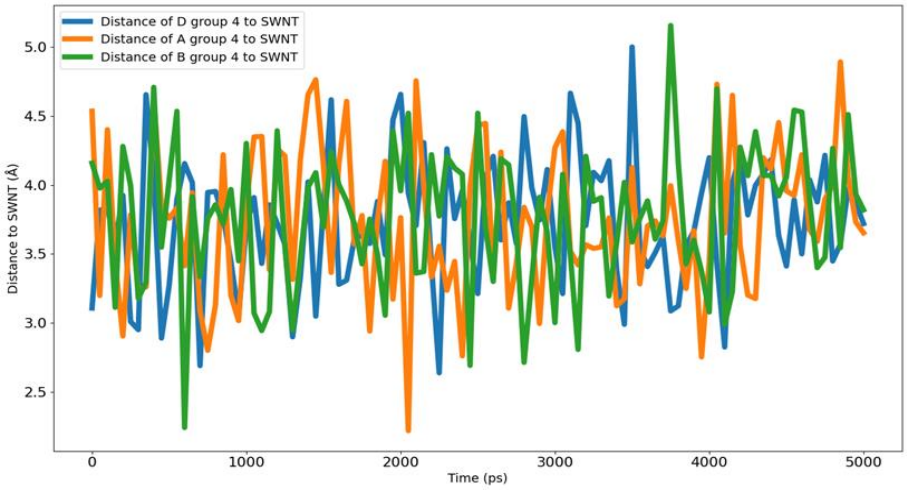

Figure 17: Distances between the SWNT surface and aromatic groups (D group (blue), A (orange) and B (green) groups) of ECG Molecule 4 over time.

This uniform proximity across all groups differs significantly from the behavior observed in previous molecules. The consistent short-range interactions suggest that ECG Molecule 4 may have adopted a stable orientation on the SWNT surface, with all aromatic groups contributing similarly to the adsorption process.

Figure 18 illustrates the distances between the SWNT surface and aromatic groups (D, A, B) of ECG Molecule 5 over time. All groups show significant distance fluctuations, with the D group exhibiting the most pronounced variability.

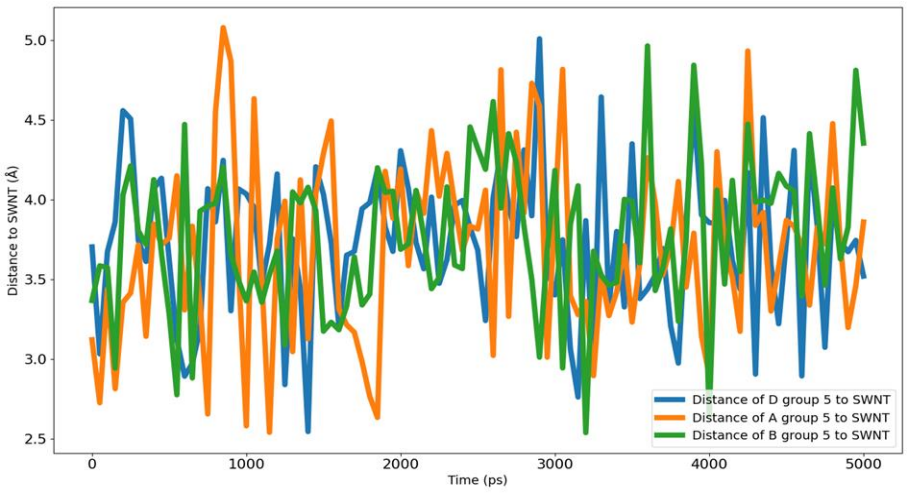

Figure 18: Distances between the SWNT surface and aromatic groups (D, A, B) of ECG Molecule 5 over time.

Unlike in Molecules 1-3, these groups display increased distance variability, suggesting fewer stable interactions with the SWNT surface. The high variability across all groups indicates that ECG Molecule 5 may have a less stable connection with the SWNT surface compared to other analyzed ECG molecules. While the D group still shows the weakest connection (similar to Molecules 1-3), the increased variability in A and B groups represents a departure from previously observed patterns.

The analysis of distances between ECG aromatic groups (A, B, and D) and the SWNT surface provides crucial insights into their interactions, primarily governed by non-covalent π-π stacking between aromatic rings. These interactions are particularly significant in systems involving carbon-based nanomaterials like SWNTs due to their extensive conjugated π-systems. Observations reveal that the D group maintains distances of 8-12 Å from the SWNT surface, indicating weaker interactions, while A and B groups remain closer (3-5 Å), suggesting stronger interactions. These distance variations reflect differential binding strengths of the aromatic groups to the SWNT surface, with A and B groups likely playing a primary role in ECG-SWNT interactions. The observed interaction patterns may influence the orientation and stability of ECG molecules on the SWNT surface, potentially affecting the overall behavior and properties of the ECG-SWNT system. This differential binding

could have significant implications for the system's applications in various fields, highlighting the importance of understanding these molecular-level interactions in designing and optimizing ECG-SWNT-based materials and technologies.

4.3. The Mean Square Displacement (MSD) of ECG molecules ECG molecules ECG with SWNT

The Mean Square Displacement (MSD) of ECG molecules over a 5000 ps simulation for pristine SWNT loaded with ECG molecules was analyzed. The linear increase in MSD values with time indicates the diffusive behavior of the molecules in the system. The slope of each line represents the diffusion coefficient, with steeper slopes indicating faster diffusion (Figure 19).

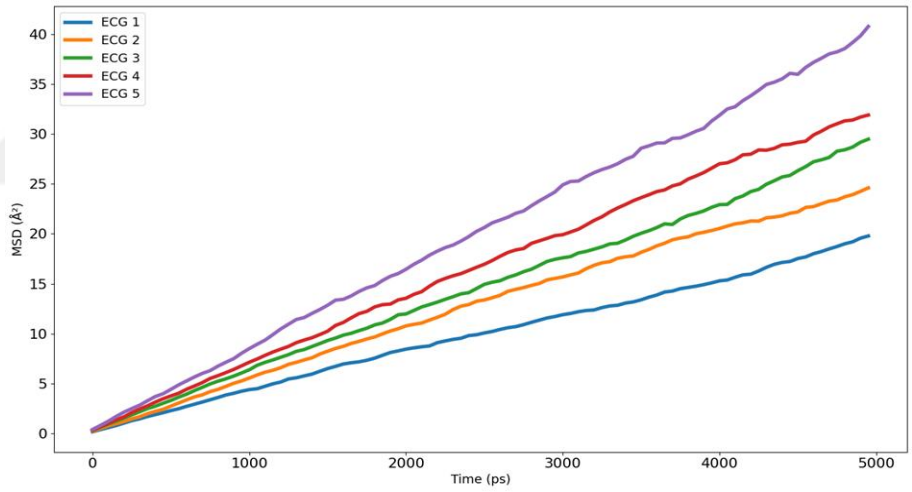

Figure 19: Mean Square Displacement (MSD) of ECG molecules over a 5000ps simulation.

This mobility gradient suggests varying degrees of interaction between the ECG molecules and the SWNT surface. ECG 5, with the lowest MSD, likely exhibits the strongest interaction with the SWNT, resulting in reduced mobility. Conversely, ECG 1, showing the highest MSD, appears to have the weakest association with the SWNT surface, allowing for greater freedom of movement. These observations provide valuable insights into the relative binding strengths and dynamics of different ECG molecules within the SWNT system, which may have implications for their behavior and functionality in potential applications.

4.4. Analysis of Proximity Trends Between Nanohole-Bearing SWNT Surface and Aromatic Groups

The dynamic behavior of ECG molecules interacting with a nanohole-bearing Single-Walled Carbon Nanotube (SWNT) over a 5000 ps simulation was analyzed. Figure 20 shows the average distance evolution of the D, A, and B groups of three ECG molecule to the SWNT surface. Interestingly, the D group exhibits significantly larger fluctuations in distance, ranging approximately from 6 to 11 Å, while the A and B groups maintain a more consistent proximity to the SWNT surface, fluctuating between roughly 2.5 to 4.5 Å. This suggests that the D groups of three ECG molecules have greater mobility and potentially weaker interactions with the SWNT surface compared to the A and B groups, which appear to be more tightly associated with the nanotube.

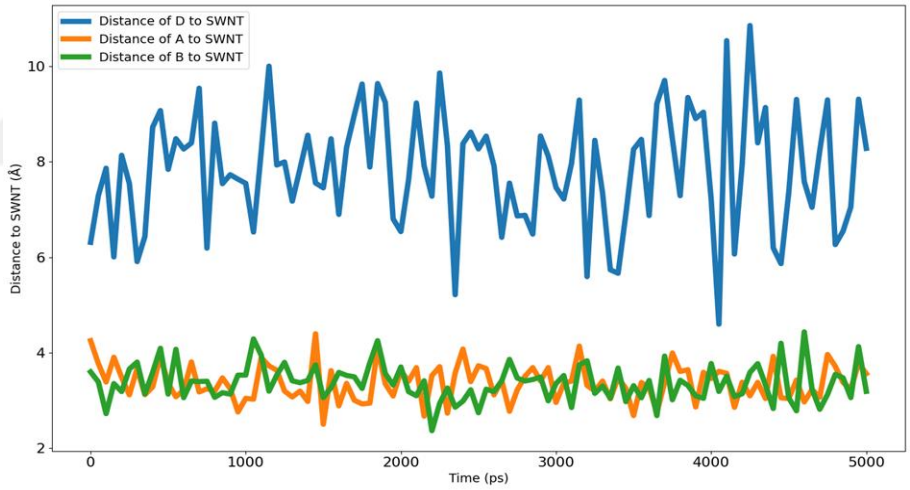

Figure 20: Average distances between the nanohole-bearing SWNT surface and aromatic groups (D, A, B) of three ECG over time.

Figure 21 depicts similar distance measurements for another two ECG molecules, but with strikingly different behavior. In this case, all three groups (D, A, and B) show comparable distance fluctuations, generally ranging between 2.5 to 4.5 Å from the SWNT surface. The similar behavior of all three groups in ECG suggests a more uniform interaction with the SWNT surface, possibly indicating that this molecule is oriented differently or interacting with a distinct region of the nanotube, such as near the nanohole, which could influence its overall binding mode.

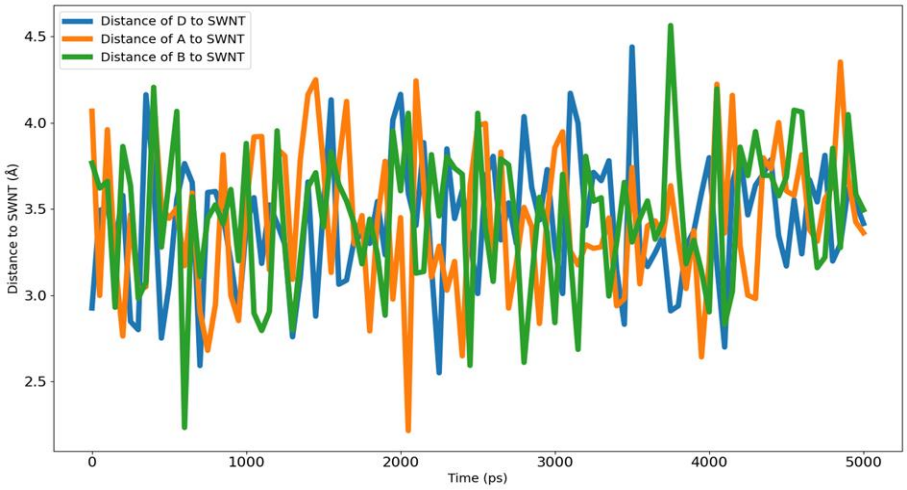

Figure 21: Average distances between the nanohole-bearing SWNT surface and aromatic groups (D, A, B) of two ECG over time.

4.5. The Mean Square Displacement (MSD) of ECG molecules ECG with Nanohole-Bearing SWNT

The Mean Square Displacement (MSD) of five ECG molecules over a 5000 ps simulation, interacting with a Single-Walled Carbon Nanotube (SWNT) that has a single nanohole on its surface is illustrated in Figure 22. This unique configuration provides insights into how a localized structural modification can influence molecular behavior across the entire nanotube.

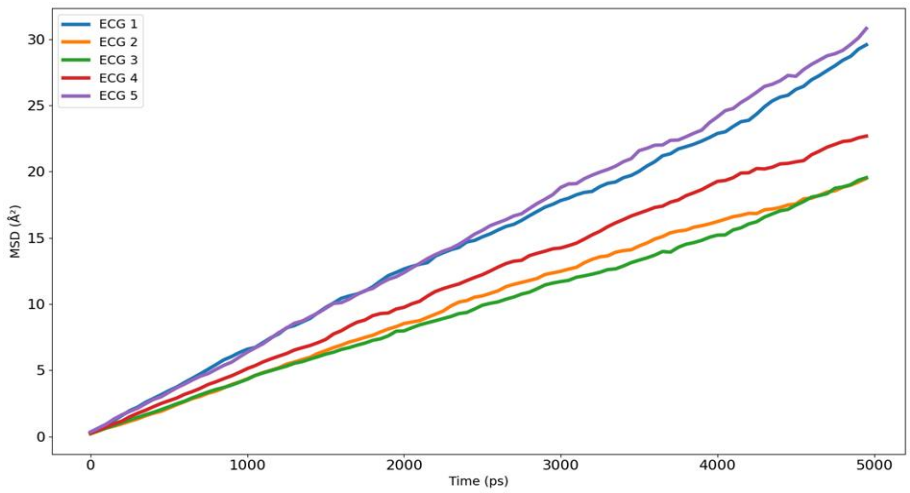

Figure 22: Mean Square Displacement (MSD) of five ECG molecules over a 5000 ps simulation load on nanohole-bearing SWNT.

The diverse MSD trajectories observed for ECG 1 through ECG 5 suggest that the single nanohole creates a heterogeneous interaction landscape along the SWNT. ECG 5 and ECG 4, showing the highest MSD values, are likely interacting primarily with the pristine areas of the SWNT surface, allowing for greater mobility. In contrast, ECG 3, with the lowest MSD, might be more directly influenced by the nanohole, possibly through partial insertion or stronger localized interactions near the hole. ECG 1 and ECG 2 exhibit intermediate mobility, which could indicate periodic interactions with the nanohole region as they diffuse along the SWNT surface. This variability in molecular mobility, despite there being only one nanohole, highlights the long-range effects that a single structural modification can have on molecular behavior in nanotube systems. It suggests that the nanohole not only affects local interactions but also influences the overall surface dynamics of the SWNT, creating distinct mobility zones that ECG molecules experience as they move along the nanotube.

5. DISCUSSION

The molecular dynamics simulation study comparing ECG molecule interactions with pristine and nanohole-bearing Single-Walled Carbon Nanotubes (SWNTs) reveals significant changes in molecular behavior upon the introduction of a nanohole. The analysis of distances between the aromatic groups (A, B, and D) of ECG molecules and the SWNT surfaces provides crucial insights into their interactions, primarily governed by non-covalent π-π stacking between aromatic rings. For the pristine SWNT, a general pattern emerges where the D group maintains distances of 8-12 Å from the surface, indicating weaker interactions, while A and B groups remain closer (3-5 Å), suggesting stronger interactions. This differential binding reflects varying interaction strengths of the aromatic groups with the SWNT surface, with A and B groups likely playing a primary role in ECG-SWNT interactions. However, the introduction of a nanohole in the SWNT structure significantly alters this interaction landscape. In the case of the nanohole-bearing SWNT, two distinct behaviors are observed among the five ECG molecules. Three ECG molecules maintain a similar pattern to that seen with the pristine SWNT, with the D group showing larger distance fluctuations (6-11 Å) and A and B groups staying closer to the surface (2.5-4.5 Å). However, the other two ECG molecules exhibit markedly different behavior, with all three groups (D, A, and B) showing comparable and consistently lower distances from the SWNT surface, generally ranging between 2.5 to 4.5 Å. This suggests that these two molecules have found a more stable and uniform interaction with the modified SWNT surface, possibly near or within the nanohole region.

The Mean Square Displacement (MSD) analysis further corroborates these observations. For the pristine SWNT, the ECG molecules show a range of mobilities, with ECG 5 exhibiting the lowest MSD (strongest interaction) and ECG 1 the highest (weakest association). In contrast, the nanohole-bearing SWNT shows a different pattern. The two ECG molecules that displayed uniform distance profiles also show significantly lower MSD values compared to their behavior on the pristine SWNT. This reduction in MSD indicates decreased mobility

and suggests that these molecules are more tightly bound or confined in their interactions with the nanohole-bearing SWNT.

These observations highlight the significant impact that a single structural modification, such as a nanohole, can have on molecular interactions in nanotube systems. The nanohole appears to create a localized region of enhanced binding, possibly due to changes in the electronic structure or the creation of additional binding sites at the nanohole edges. This heterogeneity in molecular behavior between pristine and nanohole-bearing SWNTs underscores the potential for tailoring SWNT surfaces to achieve desired molecular interactions. Such findings have important implications for applications like drug delivery, where controlled release and targeted binding are crucial, or in the development of sensors or catalysts where specific molecular orientations and interactions are desired.

6. CONCLUSION

This study has demonstrated the significant impact of structural alterations, specifically the introduction of nanoholes, on the molecular interactions between epicatechin gallate (ECG) molecules and single-walled carbon nanotubes (SWNTs). Through molecular dynamics simulations, we observed distinct differences in the binding behavior of ECG molecules on pristine versus nanohole-bearing SWNTs. The attractive interactions between aromatic groups, especially group A and B, with the nanotube were considerably strengthened and stabilized over time, mainly due to non-covalent π-π stacking. On the other hand, the D group showed weaker interactions, indicating a more dynamic behavior on both pristine and nanohole-modified surfaces. The addition of a nanohole introduced localized changes in the interaction dynamics, with some ECG molecules showing enhanced stability and reduced mobility near the nanohole region. This behavior suggests that nanoholes can act as additional binding sites, altering the electronic structure of the nanotube surface and creating heterogeneous interaction landscapes. This finding represents a concrete example and a first step toward the development of more universally precise characterization and tuning of SWNTs surface properties and SWNTs for various applications such as the drug delivery, sensing, catalysis, and transistors devices.

In drug delivery systems, the characteristics of these specific binding can certainly improve retention and release profile of therapeutic molecules under desired condition in well controlled manner. Similarly, in sensor and catalytic applications, the ability to control molecular orientation and interaction strength could enhance performance and efficiency. Overall, this research highlights the versatility of SWNTs and the importance of structural modifications in optimizing their functionality for a range of biomedical and technological applications.

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