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Chitosan and Carbon Nanotubes in Biomedicine: A Comprehensive Review of Applications in Biosensors, Cancer Treatment and Bone Regeneration

J. R. González-Martínez[1], R. Gámez-Corrales[2], F. Barffuson-Dominguez[2], G.T. Paredes-Quijada[3]

[1]J.R. González-Martínez, Departamento de Investigación en Física, Universidad de Sonora, Apdo. Postal 1626, 83000 Hermosillo, Sonora, México.
[2]R. Gámez-Corrales, Professor, Departamento de Física, Universidad de Sonora, Apdo. Postal 1626, 83000, Hermosillo, Sonora, México.
[2]F. Barffuson-Dominguez, Departamento de Física, Universidad de Sonora, Apdo. Postal 1626, 83000, Hermosillo, Sonora, México.
[3]G.T Paredes-Quijada, Departamento de Ciencias Químico-Biológicas, Universidad de Sonora, Hermosillo, Sonora, México.

Abstract - *Nanocomposites of chitosan (CHs) and carbon nanotubes (CNTs) have emerged as a multifunctional platform with promising applications in biomedicine and technology. Their unique combination integrates the biocompatibility, biodegradability, and biological activity of CHs with the electrical conductivity, mechanical strength, and high specific surface area of CNTs. In biosensors, these nanocomposites improve the detection of biomarkers and pathogens by optimizing electron transfer and stabilizing bioactive components. In oncological therapies, their functionalization with specific ligands allows the active targeting of drugs to cancer cells, facilitating a controlled release in tumor microenvironments and reducing adverse effects on healthy tissues. Additionally, in tissue engineering, they act as structural supports that favor cell adhesion, bone mineralization, and regeneration of damaged tissues. Recent studies highlight their versatility to adapt to challenges in diagnostics, disease treatment, and the development of bioactive materials, consolidating their relevance in applications that demand precision, efficacy, and sustainability. These synergistic properties position CH-CNT nanocomposites as innovative tools in the convergence of nanotechnology and life sciences.*

Key Words: Chitosan, Carbon nanotubes, Cancer, Biosensors, Bone Regeneration

1. INTRODUCTION

The advent of nanocomposites has precipitated a paradigm shift across diverse scientific and technological domains, owing to their augmented properties, which emanate from the amalgamation of materials at the nanometer scale. Within this paradigm, the integration of chitosan and carbon nanotube nanocomposites has emerged as a particularly salient combination, capitalizing on the inherent strengths of these two materials to address a broad range of applications in key domains such as biosensors[1], cartilage and bone regeneration[2–3], and cancer diagnosis and treatment[4–5].

Chitosan, a natural biopolymer derived from chitin, possesses noteworthy characteristics, including biocompatibility[6], biodegradability[7], and antimicrobial properties[8], rendering it a material of considerable interest for various healthcare and environmental engineering applications [9]. In contrast, carbon nanotubes (CNTs) are materials that exhibit exceptional electrical conductivity, high mechanical strength, and a large surface area, rendering them ideal for enhancing the properties of other compounds in various technological applications.

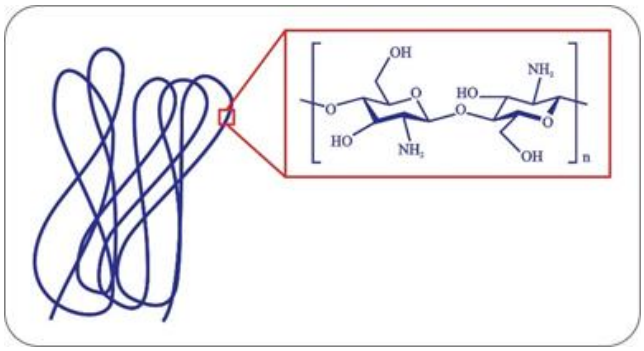

Fig 1. Chitosan

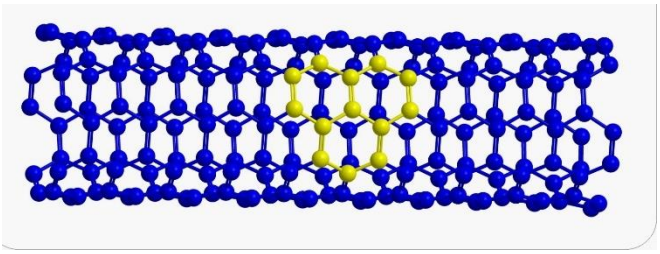

Fig-2. Carbon nanotubes

In the field of medicine, nanocomposites have found application in the fabrication of drug delivery systems [10], biomedical devices [11], and functionalized tissues [12–13], a testament to their biocompatibility and capacity to interact with human cells and tissues[13] .

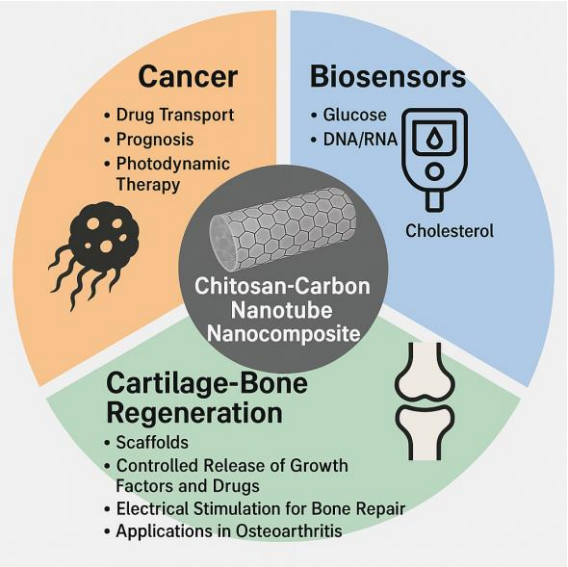

Fig-3. Nanocomposite-Based Strategies for Medical Applications: Oncological Therapies, Biosensing, and Bone Tissue Engineering

1. Chitosan Nanocomposite and Carbon Nanotubes in Biosensors: Advances and Perspectives.

This article reviews the most recent and relevant applications of chitosan and carbon nanotube nanocomposites in these areas, highlighting research advances and the opportunities these materials offer for the development of innovative and sustainable solutions across multiple disciplines.

The combination of chitosan CHs and CNTs has emerged as a promising nanocomposite system for biosensor development, notable for its synergy between biocompatibility and electrochemical functionality. In the context of biosensors for clinical biomarkers[14], designed a nanohybrid of CH, Fe_3O_4 nanoparticles, and carboxyl-functionalized MWCNTs (c-MWCNTs) was designed, which demonstrated a significant improvement in the sensitivity and stability of the L-lactate biosensor. The covalent immobilization of the lactate oxidase enzyme was facilitated by the presence of the CHs, while the CNTs optimized electron transfer, achieving a detection limit of 0.15 µM and an extended lifetime of 100 days. In the context of electrochemical applications, the potential of glassy carbon electrodes modified with CHs and CNTs for nicotine detection was investigated [15]. The functionalization of the CNTs with carboxyl groups resulted in enhanced conductivity and an augmented active surface area, thereby reducing the oxidation potential of nicotine to 0.74 V in the presence of oxygen. CHIT, in turn, functioned as a stabilizing matrix for the P450-CYP2A6 enzyme, thereby enhancing the sensor's reproducibility.

In the context of pesticide detection, a biosensor has been developed that utilizes an immobilized esterase on CHs/CNTs, employing an enzyme-inhibition mechanism [16]. Their study revealed that functionalized carbon nanotubes (GNP-COOH) exhibited the most significant inhibition (9.94%) against methyl parathion, attributed to their substantial surface area and electron transfer capability. The incorporation of CHs has been shown to enhance enzyme adhesion and mitigate CNT aggregation, a prevalent challenge in carbonaceous nanocomposites. This finding highlights the dual role of chitosan in biosensors, underscoring its function as both a biocompatibility agent and structural support for CNTs[17]. The capacity of CHS to form stable films, in conjunction with its chemical reactivity (-NH2 and -OH) facilitates targeted functionalization. The incorporation of CNTs enhances conductivity and sensitivity, as demonstrated by the detection of microRNA-21 with limits in the nanomolar range.

A collective analysis of these studies underscores the fact that the CHs/CNTs nanocomposite combines ideal properties for biosensing: high sensitivity, enzymatic stability, and adaptability to diverse applications. Nevertheless, challenges persist in the standardization of CNT functionalization and industrial scalability. Nonetheless, recent innovations suggest the emergence of integrated solutions for personalized medicine and environmental monitoring.

The development of a glucose biosensor characterized by exceptional stability was achieved through the incorporation of a nanocomposite constructed on a foundation of CHs and MWCNTs [18]. They developed a cryo-gel composed of chitosan and albumin (Chi-BSA) that incorporated MWCNTs and ferrocene as a redox mediator. The cryo-gel's macroporous structure, which is obtained by freeze-thaw cycles, provides a high specific surface area that facilitates the efficient immobilization of the glucose oxidase (GOD) enzyme. The MWCNTs, situated as an intermediate layer between the gold electrode and the cryo-gel, enhance electron transfer, reducing the working potential to 0.175 V and minimizing interference from electroactive species such as ascorbic and uric acid. The synergistic effect of the biocompatible and reactive amino groups of the chitosan and the high conductivity and surface area of the MWCNTs endows the biosensor with remarkable sensitivity (7.77 µA mM-1 cm-2), a wide linear range (0.010-30 mM), and exceptional operational stability. This work underscores that the incorporation of chitosan with carbon nanotubes not only enhances the stability and selectivity of the biosensor but also provides a versatile model for other enzymatic applications. This

approach has emerged as a promising strategy for the design of high-performance electrochemical devices.

A novel electrochemical biosensor for the detection of glucose has been developed, which utilizes a nanocomposite array of MWCNTs, polyaniline (PANI), and carboxymethylated chitosan (CCs) for the immobilization of glucose oxidase (GOx) enzyme onto a glassy carbon electrode [19]. The synergistic effect among these components enhances both the electrical conductivity (due to MWCNTs and PANI) and the biocompatibility (via CCs), thereby facilitating enzyme stabilization and efficient electron transfer. The biosensor exhibits a wide linear range (10 nM to 10 µM), high sensitivity (1791 µA mM-1 cm-2), low detection limit (1.41 µM), and an apparent Michaelis-Menten constant (18 nM), suggesting a high affinity for glucose. The biosensor demonstrated exceptional stability and additionally exhibited selectivity against interferents such as uric and ascorbic acid, and precision in human serum samples. These characteristics underscore its potential for clinical applications in glucose monitoring, particularly in the control of diabetes, providing a rapid, sensitive, and cost-effective method.

An enzymatic biosensor for histamine based on a nanocomposite of CHs and MWCNTs. The MWCNTs, which had undergone functionalization and deposition on a screen-printed electrode, served as a support medium for Prussian blue (PB) electrodeposition, thereby enhancing surface charge and conductivity [20]. The MWCNTs-PB layer facilitated electron transfer and catalysis of hydrogen peroxide (H2O2), a by-product of the diamine oxidase (DAO) enzymatic reaction. In addition to the aforementioned structure, a macroporous CHs-gold nanoparticles (AuNPs) cryo-gel was incorporated. The incorporation of CHs, a biocompatible material with a high concentration of amino groups, resulted in the formation of a three-dimensional matrix that provided an ideal environment for the stable immobilization of DAO. The porosity of the cryo-gel was found to optimize the diffusion of the analyte and increase the active area. Furthermore, the AuNPs were found to improve the intrinsic conductivity of the CHs, thereby enhancing the electrochemical signal. The CS-MWCNTs nanocomposite exhibited remarkable performance, with a detection limit of 1.81 µmol L^{-1}, two linear ranges (2.50-125.0 and 125.0-400.0 µmol L-1), and exceptional selectivity towards interferents such as amino acids and other biogenic amines.

In a separate study, Soyalp et al. (2025) developed an electrochemical biosensor based on CHs nanocomposites and MWCNTs to analyze the interaction between mitomycin C (MC), an anticancer pharmaceutical, and calf thymus double-stranded DNA (ctdsDNA) [21]. The biosensor facilitated concurrent monitoring of the oxidation signals of MC and guanine from DNA by differential pulse voltammetry (DPV), revealing a decline in both signals upon interaction, suggesting a preferential covalent binding mechanism in GC pairs. This study emphasizes the synergistic relationship between a biocompatible matrix composed of CHs and multifunctional MWCNTs that function as conductivity enhancers. This establishes a stable, reproducible, and economically viable platform for elucidating drug-DNA interactions. The findings of this investigation offer a promising foundation for advancing pharmaceutical development and toxicological assessment.

Zhang et al. (2018) developed an electrochemical biosensor based on single-walled carbon nanotubes (SWCNTs) and CHs nanocomposites for the ultrasensitive detection of leptin in serum. In addressing the aqueous insolubility of SWCNTs, the approach entails functionalizing the nanotubes with CS and activated carboxyl groups using EDC/NHS, thereby achieving a homogeneous and stable dispersion [22]. The SWCNTs-CS nanocomposites enhanced the conductivity of the glassy carbon electrode (GCE), demonstrating a wide linear range (0–1000 ng mL-1) and an exceptional detection limit (5 pg mL-1) using electrochemical techniques (cyclic voltammetry, impedance, and differential pulse). In the context of clinical validation, the biosensor demonstrated recoveries with superior precision (RSD <3%) in comparison to ELISA, exhibiting reduced interference in real samples. According to Zhang et al. (2018), this approach demonstrates the potential of SWCNTs-CS nanocomposites for precise diagnostic applications, offering advantages in sensitivity, stability, and cost for biomarkers such as leptin, which is key to obesity and inflammatory processes.

2. Chitosan/Carbon Nanotube Nanocomposites in Oncology: Smart Systems for Targeted Drug Delivery and Combined Therapies

CNT nanocomposites have emerged as a promising platform for targeted drug delivery in cancer treatment [23-24]. These nanocomposites are distinguished by their biocompatibility, controlled-release capacity, and sensitivity to stimuli such as pH. Recent studies, including that of [25], have demonstrated that tryptophan-coated carbon nanotubes (TRP@CNT) function as effective nanocarriers for drugs such as topotecan, releasing them in a controlled manner under acidic conditions, which are characteristic of the tumor microenvironment. Furthermore, the combination of CHs with CNTs enhances the solubility and stability of the nanocarriers, leveraging the biodegradable properties of chitosan and the high loading capacity of CNTs. This allows for controlled drug release in response to pH changes, mitigating side effects, and enhancing therapeutic efficacy [26].

A targeted nano-therapy was designed to target breast (MCF7) and liver (HepG2) cancer cells. This therapeutic modality employs modified MWCNTs that are loaded with

cisplatin (Cis) and anthocyanins (Ant). The MWCNTs are coated with folic acid-conjugated CHs. The biocompatibility and biodegradability of the CHs facilitated the uniform coating necessary for the controlled release of the drug. The MWCNTs provided a robust platform with a high loading capacity and cell penetration. This nano-formulation exhibited remarkable efficacy in terms of its cytotoxic, pro-apoptotic, antioxidant, anti-inflammatory, anti-angiogenic, and anti-metastatic properties, with the combination treatment (Cis + Ant) demonstrating particularly notable outcomes. The results of the study demonstrated up-regulation of pro-apoptotic genes (Bax), antioxidant genes (Nrf2, HO-1), and metastasis suppressor genes (TIMP1), along with the inhibition of VEGF, TNFα, and MMP9. These results position this strategy as a promising alternative for targeted therapies against resistant cancers [27].

The development of CMCS-FA-MWCNT-BA nanocomposites, which are based on carboxymethyl chitosan (CMCS) and MWCNTs, signifies a significant advancement in the field of targeted therapy for oral squamous cell carcinoma (OSCC) [28]. CMCS, when functionalized with folic acid (FA), has been shown to enhance biocompatibility and enable active targeting of tumor cells that overexpress folate receptors. In addition, MWCNTs have been demonstrated to facilitate high baicalin (BA) loading and controlled release in acidic microenvironments (pH 5.5) [28]. In vitro studies have demonstrated that these nanocomposites increase cell apoptosis (↑40% vs. free BA), inhibit migration (↓70%) and invasion of CAL27 cells, and reduce tumor colony formation [28]. In vivo, the nanocomposites demonstrated selective accumulation in tumors, tumor volume reduction (60% decrease), and liver metastasis, in addition to modulating epithelial-mesenchymal transition (downregulated vimentin, increased E-cadherin) [1]. The functionalization process with CMCS has been shown to mitigate the cytotoxic effects in healthy cells, with a reported viability greater than 90%. Additionally, it has been demonstrated to enhance colloidal stability, as evidenced by a decrease in zeta potential from -44 mV [28]. These results underscore the synergy between chitosan (a biocompatible modifier) and MWCNTs (a multifunctional vehicle), positioning the system as a promising platform for precise and low-toxicity oncology therapies [28].

3. CHs/CNT Composite Materials for Bone Regeneration

A novel scaffold was developed, composed of polyurethane (PU) functionalized with CHs and functionalized multi-walled carbon nanotubes (fMWCNTs), in addition to metal oxide nanoparticles such as superparamagnetic iron oxide (SPIONs) and strontium dioxide (SrO_2). CHs have been demonstrated to enhance cell adhesion, cell proliferation, and osteoinductive activity of the scaffold due to their biocompatibility, hydrophilic nature, and structural similarity to components of the extracellular matrix. In contrast, fMWCNTs demonstrated heightened mechanical strength, electrical conductivity, and an augmented specific surface area, thereby fostering cell differentiation and interaction with other nanoparticles. The results demonstrated an elevated expression of osteogenic markers, including ALP, RUNX2, and COL-I, as well as remarkable hydroxyapatite formation. In addition, the scaffold exhibited effective inhibition of bacterial growth against Staphylococcus aureus and Escherichia coli, supporting its potential in bone tissue engineering and regenerative medicine applications [30].

A study was conducted to develop thermosensitive injectable hydrogels composed of CHs and collagen (Coll). These nanomaterial-based hydrogels were nano-engineered with single-walled carbon nanotubes (SWCNTs) that were functionalized with carboxyl groups (COOH-SWCNTs). The primary objective of this study was to explore the potential of these hydrogels for minimally invasive applications in bone regeneration. CHs provided biocompatibility, antimicrobial properties, and a porous structure, while COOH-SWCNTs significantly improved the mechanical strength, thermal stability, and crystallinity of the hydrogel. The hydrogels demonstrated an increase in Young's modulus of over 60%, reaching values in the MPa range, which is suitable for load-bearing bone defects. Furthermore, the study demonstrated a promotion of cell adhesion, osteoblast proliferation, and hydroxyapatite deposition. The synergistic integration of these components resulted in the formation of a three-dimensional network that was stable at physiological temperature and exhibited optimal porosity, rapid gelling, and adequate biodegradability for bone tissue engineering applications [31].

Double network (DN) hydrogels, composed of CHs, sodium alginate (SA), and polyvinyl alcohol (PVA), fortified with MWCNTs and graphene nanoplatelets (GNPs), signify a paradigm shift in the field of bone tissue engineering [32]. CHs are notable for their biocompatibility and antibacterial activity, which have been demonstrated in several studies. In MG63 osteoblasts, for example, CHs have been shown to increase viability by 170% over seven days. Similarly, CHs have been observed to reduce infections by 93.38% in S. aureus cases. MWCNTs, functionalized with carboxyl groups, exhibited increased mechanical strength (Young's modulus: 47.5 ±5 kPa) and electrical conductivity (5.7 ×10-3 S/m), thereby facilitating hydroxyapatite mineralization (Ca/P ratio ≈2.29). The CHs-MWCNTs synergy-optimized porosity (pore size increased by 17.0 ±35.3 μm with GNPs) and controlled degradation (46.5% in 40 days), which are essential for bone regeneration, were also observed. These scaffolds, with 680% swelling, have demonstrated their versatility for clinical applications by combining mechanical properties, bioactivity, and antimicrobial functionality [32].

Scaffolds based on CHs, hyaluronic acid (HA), and hydroxyapatite (HAp), reinforced with f-MWCNTs, demonstrate significant advances in bone regeneration [33]. CHs are distinguished by their biocompatibility and antimicrobial activity, which promote cell adhesion and proliferation. In addition, f-MWCNTs enhance mechanical strength (Young's modulus: ~9.43 MPa) and structural stability through synergistic interactions with the polymer matrix [33]. The incorporation of f-MWCNTs, which exhibited optimized porosity (16.1%) and controlled degradation (20.4% within seven days), was found to be instrumental in facilitating tissue integration. CHs/HA/HAp/HAp/f-MWCNT scaffolds demonstrated high efficiency in hydroxyapatite mineralization (Ca/P ratio ≈2.29) and stimulation of osteogenic stem cell differentiation, outperforming composites with graphite or graphene oxide [33]. Preliminary biocompatibility studies have confirmed the viability of cells, with a viability rate greater than 85%. Furthermore, these studies have demonstrated a low level of toxicity, attributed to the acid functionalization of MWCNTs. However, challenges such as the homogeneous dispersion of nanomaterials persist, necessitating the optimization of synthesis methods [33]. These findings position CHs/f-MWCNT nanocomposites as promising candidates for clinical applications, combining mechanical properties, bioactivity, and antimicrobial functionality.

CONCLUSIONS

The nanocomposite of CHs and CNTs has demonstrated its potential as a versatile material in the field of biomedicine, with applications ranging from biosensors to tissue regeneration and cancer treatment. The incorporation of chitosan's distinctive properties, including its biocompatibility, biodegradability, and antimicrobial capacity, with the exceptional characteristics of CNTs, such as their high electrical conductivity, mechanical strength, and large surface area, has resulted in a composite material with considerable potential to address critical challenges in human health.

In the domain of biosensors, the nanocomposite has exhibited notable enhancements in sensitivity, stability, and selectivity, thereby facilitating the precise detection of clinical biomarkers, pesticides, and other analytes of significance. The combination of CHs´ capacity to immobilize enzymes and its inherent chemical reactivity, in conjunction with the enhanced conductivity of CNTs, has contributed to the development of high-performance electrochemical devices. These advancements are of particular relevance for applications in medical diagnostics, environmental monitoring, and food safety, where rapid and accurate detection is imperative.

In the domain of tissue regeneration, particularly in the contexts of cartilage and bone regeneration, nanocomposites have demonstrated their efficacy as a material for tissue engineering. The combination of CHs´ biocompatibility and CNTs' capacity to augment the material's mechanical and electrical properties renders it a promising candidate for the fabrication of scaffolds that facilitate cell adhesion, proliferation, and differentiation. This phenomenon is especially evident in the domain of regenerative medicine, where the objective is to restore the functionality of damaged or lost tissues.

Conversely, in the domain of cancer diagnosis and treatment, nanocomposites have emerged as an effective platform for controlled drug release. The combination of CHs´ pH-responsive properties, which are well-matched to the acidic tumor microenvironment, and the high loading capacity of CNTs, facilitate targeted delivery of anticancer drugs, thereby reducing systemic toxicity and enhancing therapeutic efficacy. Recent studies have demonstrated the potential of these nanocomposites to enhance drug uptake in cancer cells, inducing apoptosis and reducing metastasis. This suggests that they could serve as a valuable tool for developing more targeted and less toxic cancer therapies.

In summary, the chitosan-carbon nanotube nanocomposite signifies a substantial advancement in biomedicine, providing innovative and sustainable solutions for a broad spectrum of applications. Despite the challenges, including the standardization of CNT functionalization and industrial scalability, recent research advances indicate that this composite material possesses considerable potential to transform diagnosis, treatment, and tissue regeneration in the future.

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