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Chitosan–GrapheneOxide Nanocomposites for Biomedical Engineering: Recent Advances in Bone, Wound, and Neural Regeneration

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Abstract - *Chitosan (CS) and graphene oxide (GO) form multifunctional nanocomposites that unite CS's biocompatibility, hemostatic capacity, and antimicrobial activity with GO's high surface area, mechanical reinforcement, and tunable interfacial chemistry. This narrative review synthesizes recent advances in CS–GO systems for bone, wound, and neural regeneration, emphasizing structure–property–function relationships, fabrication strategies, and biological performance. In bone tissue engineering, CS–GO scaffolds and injectable hydrogels enhance osteogenic differentiation, mineralization, and mechanical integrity, supported by emerging in vivo evidence from rodent critical-size defect models. For wound care, CS–GO films, nanofibers, and hydrogels provide antibacterial, hemostatic, and pro-angiogenic functions, including in diabetic and infected models, although clinical translation remains at an early stage. In neural regeneration, conductive and topographically aligned GO-containing constructs improve Schwann cell behavior and neurite outgrowth; however, direct CS–GO in vivo evidence is still limited compared to GO-only or CS-only systems. Cross-cutting challenges include inconsistent reporting of CS degree of deacetylation and molecular weight, heterogeneous GO physicochemical characterization, dose-dependent cytotoxicity concerns, and scarce long-term in vivo biodistribution and degradation data. We conclude that CS–GO nanocomposites represent a promising platform for regenerative medicine, but standardized reporting, rigorous biosafety evaluation, scalable manufacturing, and validation against clinically relevant endpoints are essential before widespread translational adoption.*

Key Words: chitosan, graphene oxide, nano composites, bone tissue engineering, neural regeneration, regenerative medicine

1. INTRODUCTION

The global burden of traumatic injury, chronic non-healing wounds, and degenerative musculoskeletal and neurological conditions continues to drive demand for advanced regenerative biomaterials capable of actively directing cell behavior, resisting infection, and integrating seamlessly with host tissue[1–4]. Among natural and synthetic polymers, chitosan (CS) a linear polysaccharide obtained by the partial deacetylation of chitin stands out for its structural biocompatibility, enzymatic biodegradability, cationic nature, intrinsic hemostatic capacity, and broad-spectrum antimicrobial activity [1]. These inherent biological attributes render CS an attractive candidate for tissue engineering scaffolds, topical wound dressings, and in situ gelating systems [5–7].

However, pristine chitosan matrices frequently suffer from mechanical fragility in hydrated states, uncontrolled swelling, and rapid enzymatic degradation, which can compromise structural support during tissue repair. To overcome these limitations, graphene oxide (GO) a two-dimensional carbon nanomaterial rich in oxygenated functional groups (epoxides, hydroxyls, carboxyls) has emerged as an exceptional nano-reinforcement and functional additive [1–3]. GO possesses extraordinary mechanical strength, high specific surface area, and versatile surface chemistry that facilitates biomolecule adsorption, cellular engagement, and interfacial crosslinking [3, 4].

Integrating CS and GO generates highly synergistic nanocomposite architectures [1]. Hydrophilic CS matrices facilitate the uniform dispersion of GO nanosheets via electrostatic and hydrogen-bonding interactions, mitigating GO's propensity to aggregate and reducing potential dose-dependent cytotoxicity [1][8–9]. Conversely, GO reinforces CS networks, enhancing tensile and compressive moduli, tailoring swelling and degradation kinetics, and imparting electroactive and bioactive characteristics [2–4–10]. This review critically examines CS-GO nanocomposites encompassing hydrogels, electrospun nanofibrous mats, porous scaffolds, dense membranes, and injectable platforms—focusing on three major biomedical engineering domains:bone tissue engineering, wound healing, and peripheral neural regeneration.

2. Materials Science Foundations of Chitosan–Graphene Oxide Nanocomposites

2.1 Chitosan: Molecular Characteristics and Biomedical Relevance

Chitosan is composed of randomly distributed β-(1→4)-linked D-glucosamine and N-acetyl-D-glucosamine units[1]

[11–12]. Its chemical functionality and biological behavior are dictated by its degree of deacetylation (DD) and molecular weight (MW) [11][13]. High DD (>80%) provides a higher density of primary amino groups (-NH_2), which become protonated (-NH_3^+) under acidic conditions, conferring solubility and strong electrostatic affinity for anionic biomolecules, cell membranes, and negatively charged GO nanosheets [1,12]. High MW enhances mechanical stability and film-forming ability but increases solution viscosity, whereas low MW improves aqueous solubility and cellular uptake [11,13].

2.2 Graphene Oxide: Structure, Physicochemical Properties, and Biological Considerations

GO features an sp^2 carbon network interspersed with sp^3 domains bearing hydroxyl (-OH) and epoxide (-O-) groups on basal planes, alongside carboxyl (-COOH) groups at sheet edges [1, 3, [14]. Lateral dimension, layer number, C/O ratio, and synthesis-derived impurity content (e.g., residual heavy metals) dictate GO's mechanical performance, dispersibility, cellular toxicity, and cellular endocytosis pathways [3, 8, 14]. At controlled, low concentrations (≤1 wt%), GO enhances cellular adhesion and proliferation through protein adsorption, but high concentrations can induce reactive oxygen species (ROS) generation and cell membrane shear stress [8, 9, 14].

2.3 Interfacial Interactions and Nanocomposite Design

The synthesis of robust CS-GO nanocomposites relies on strong interfacial non-covalent interactions, predominantly hydrogen bonding between hydroxyl/amino groups of CS and oxygenated moieties of GO, alongside electrostatic attraction between cationic -NH_3^+ and anionic carboxylates [1]. Covalent crosslinking via genipin, glutaraldehyde, or oxidized polysaccharides further stabilizes the network [2, 6, 10]. Common fabrication techniques include: (i) solvent casting and freeze-drying for 3D macroporous scaffolds; (ii) electrospinning for extracellular matrix (ECM)-mimicking nanofibers; (iii) 3D bioprinting for custom geometries; and (iv) in situ gelation for injectable, minimally invasive hydrogels [1, 5].

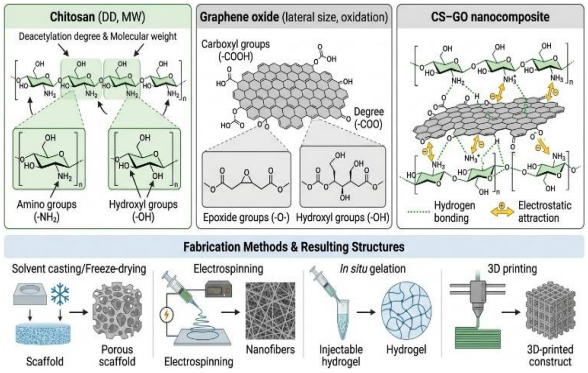

Figure 1. CS-GO chemical interactions and fabrication. (A) Hydrogen bonding and electrostatic coupling between CS and GO. (B) Synthesis routes: freeze-drying, electrospinning, and 3D printing.

3. Bone Regeneration and Bone Tissue Engineering

Bone tissue engineering requires scaffolds that provide structural integrity matching host trabecular or cortical bone, highly interconnected porosity (100-300 μm) for vascular ingrowth, osteoconductivity, and osteoinductivity [2-4, 15]. CS-GO nanocomposites fulfill these criteria by serving as biomimetic templates that stimulate osteogenic differentiation and biomineralization [2, 5].

Incorporation of GO (typically 0.5-2 wt%) into CS scaffolds markedly elevates compressive strength and Young's modulus, counteracting the structural collapse often observed in pure CS hydrogels [2, 5]. Furthermore, GO acts as a nucleation site for hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) deposition by concentrating calcium ions through its oxygenated functional groups [3, 4]. In vitro studies confirm up-regulated expression of key osteogenic markers, including alkaline phosphatase (ALP), Runt-related transcription factor 2 (Runx2), and osteocalcin (OCN) in mesenchymal stem cells (MSCs) and osteoblasts cultured on CS-GO platforms [2, 5].

In vivo preclinical evaluation in rodent critical-size calvarial and femoral defect models demonstrates that injectable CS-GO hydrogels (e.g., glycol CS / oxidized hyaluronic acid + GO) accelerate bone healing, promoting osteogenesis and robust neo-vascularization without systemic toxicity [6]. Hybrid systems incorporating biomimetic minerals (CS-GO-HA) further bridge mechanical durability and osteoinduction [4, [9].

4. Wound Regeneration and Advanced Wound Dressings

Chronic, non-healing wounds particularly diabetic ulcers are characterized by prolonged inflammation, excessive oxidative stress, high bacterial burden, and impaired angiogenesis [7,10,16, 17]. CS-GO dressings address these

complex pathological microenvironments through synergistic antimicrobial, anti-inflammatory, and exudate-managing mechanisms [7, 8].

Chitosan's intrinsic antibacterial activity, driven by membrane lysis via protonated amines, is supplemented by GO's physical sharp-edge membrane truncation, ROS-mediated oxidative stress, and photothermal disruption under near-infrared (NIR) laser irradiation [1, 7, 8]. CS-GO nanofibrous mats and hydrogels exhibit potent bactericidal efficiency against Gram-positive (e.g., Staphylococcus aureus) and Gram-negative (e.g., Escherichia coli) pathogens, including multidrug-resistant strains [7, 10]. Additionally, CS-GO platforms serve as versatile drug delivery vectors for antibiotics, growth factors (e.g., VEGF, bFGF), and natural bioactive compounds (e.g., curcumin, quercetin) [15, 16]. In diabetic full-thickness wound models, CS-GO hydrogels accelerate re-epithelialization, enhance granulation tissue maturation, promote angiogenesis, and reduce pro-inflammatory cytokines (TNF-α, IL-6) [10, 17].

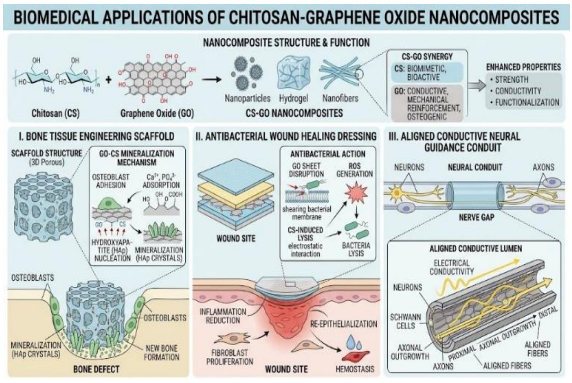

Figure 2. Biomedical applications of CS-GO nanocomposites. Targeted mechanisms in bone regeneration (mineralization), wound healing (antibacterial/angiogenesis), and neural conduits (aligned bioelectricity).

5. Neural Regeneration and Bioelectronic Interfaces

Peripheral nerve injury repair demands bio-instructive conduits that combine topographical alignment, mechanical flexibility, and electrical conductivity to guide axonal elongation and support Schwann cell (SC) proliferation 18–21]. While pristine CS offers good biocompatibility and tubular guidance, its lack of electrical conductivity limits active bioelectric signal propagation [19,21].

Incorporation of GO into aligned CS electrospun nanofibers or extruded guidance conduits yields electroactive substrates (electrical conductivity ~10^{-2} S/cm) [18, 20]. Aligned CS-GO constructs provide both contact guidance and passive bioelectric coupling, significantly enhancing SC elongation, S100β and myelin basic protein (MBP) expression, and dorsal root ganglion (DRG) neurite outgrowth in vitro [18, 20].

6. Biocompatibility, Biosafety, and Translational Barriers

Despite compelling preclinical efficacy, the translational trajectory of CS-GO nanocomposites from bench to bedside faces several technical and regulatory obstacles [1, 8, 13, 14]:

Dose-Dependent Cytotoxicity: GO concentrations exceeding 1.0-2.0 wt% can induce membrane rupture, ROS overload, and apoptosis. CS coating shields cellular membranes, but precise safety thresholds must be defined [1, 8].

Long-term Biodegradation & Biodistribution: While CS degrades via lysozyme, the long-term metabolic fate, degradation kinetics, and clearance routes of non-biodegradable GO sheets in vivo remain poorly understood [8, 14].

Physicochemical Heterogeneity: Substantial inter-study variability in CS molecular weight/DD and GO lateral size, oxidation level (C/O ratio), and purity hinders reproducibility and standardized manufacturing under GMP conditions [1, 13].

Lack of Clinical Trials: Current evidence remains strictly preclinical; no standardized human clinical trials have yet been completed for CS-GO regenerative devices [1].

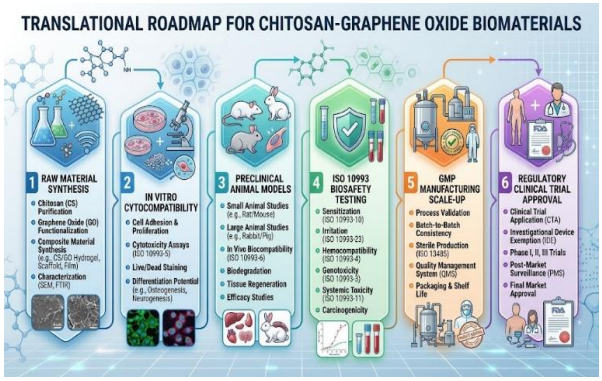

Figure 3. Translational pipeline for CS-GO biomaterials. Sequential stages from material synthesis and ISO 10993 testing to preclinical models, GMP scale-up, and regulatory approval.

7. CURRENT KNOWLEDGE GAPS AND FUTURE PRIORITIES

To overcome translational barriers, future research must prioritize: (i) standardized reporting of CS DD/MW and GO lateral dimensions/purity; (ii) ISO 10993-compliant

biocompatibility and hemocompatibility testing; (iii) long-term fate and clearance studies in large animal models; (iv) integration of electrical stimulation paradigms in neural constructs; and (v) head-to-head benchmarking against established clinical standards (e.g., autografts, commercial collagen dressings) [1, 9, 15, 22].

8. CONCLUSIONS

Chitosan-graphene oxide (CS-GO) nanocomposites represent a versatile, multifunctional material platform for regenerative medicine. By unifying the intrinsic bioactivity, hemostatic capability, and antimicrobial properties of chitosan with the mechanical strength, high surface area, and electroactive capabilities of graphene oxide, CS-GO systems demonstrate outstanding performance in bone, wound, and neural tissue repair. Continued focus on standardized synthesis, scalable GMP fabrication, long-term biosafety, and rigorous clinical validation will be key to unlocking their full translational potential.

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