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Marine Polysaccharides in Medicine

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Additional information is available at the end of the chapter

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Abstract

About 70% of the Earth's surface is covered with seawater and 90% biosphere wraps maximum biodiversity that offers resourceful novel bio-molecules. Marine species are enriched with organic compounds viz. terpenoids, polyethers/ketides, lipo-glycoproteins, peptides and polysaccharides that act as cell surface receptors and involve in cell development/differentiation, besides being antimicrobial agents. Algae, sponge and fish have various defense mechanisms developed via specific/potent natural molecules to survive under hostile, extreme conditions such as various degrees of salinity, pressure, temperature, darkness, besides microbial and viral attacks. Marine seaweeds and algae enriched with polysaccharides such as glycosaminoglycans, agar, alginate and chitin/chitosan owing to their diversified significance have received growing attention among researchers. Currently, marine-derived biomolecules cater 20% market drug load while other natural products bear 30% share. Chitins exhibit various biological and physicochemical properties that can be exploited in biotechnology and medicine/drug, cosmetic, food and textile industries. This chapter focuses on chitin/chitosan production, its physicochemical characterization and biological activities and relationship between its chemical structure and bio-activity, including chemical modification reactions such as acylation, substitution, sulfonation and other cross-linking strategies applied to skeletal modification with the recently updated literature.

Keywords: chitin, chitosan, marine polysaccharide, drug, modification, pharmaceuticals

1. Introduction

Nature is an ancient pharmacy known to human. Life originated over four billion years ago in oceans, besides sea aid ecosystems, and provides source of food for organism and man. Carbohydrates are abundant, essential natural polysaccharides consisting of carbon, hydrogen and oxygen atoms (H:O as 2:1 and empirical formula $C_m[H_2O]_n$, where m is different from n

and usually varies from 200 to 2500), having vast health benefits. Polysaccharides contain linear to high heterogeneity linkages of more than 10 monosaccharide/glycosides with slight repeating unit modifications (discrete from their monosaccharide) while oligosaccharides contain 3–10 monosaccharides. Amid carbohydrates, various polysaccharides are found in all marine organisms, which are accountable for an innate bio-active defense mechanism. Plant starch found as both amylose and amylopectin, which resemble cellulose (plant cell wall module), exhibit storage functions while chitin and glycogen in animals (same as starch/cellulose except NH-substitution) afford structural component enhancement in arthropod exoskeleton and fungus cell wall. Chitins, fucoidan, carrageenan and alginate are few polysaccharides that control cell proliferation and modulate metabolism in marine organisms besides own pharmaceuticals utility including antioxidative, antibacterial, antiviral, immunostimulatory, anticoagulant and anticancer activities poses novel ventures for harnessing potential of oceanic products.

Oceans occupy three-fourths of planet, which covers half of the global biodiversity envelope in certain marine species as the imperative resources for deriving novel bio-chemicals. Marine bacteria, macro/micro algae, sponges and fishes induce defensive actions via such bio-molecules that enable organisms to survive in hostile environment such as different degrees of salinity, pressure, temperature and no/deem light [1], as well as microbial/viral attack. Naturally occurring bio-chemicals viz., terpenoids, polyethers, polyketides, lipo-glycoproteins, and polysaccharides display various functions in nature such as defense against predators, aiding in cell development/differentiation, acting as cell surface receptors and providing innate immunity. Carbohydrates exacted from terrestrial marine organisms/sediments act as prospective feedstocks for medicine, fertilization, food storage, antioxidant, laxative, smooth/nonirritating hydrated bulk in the digestive tract, tablet ingredient and drug carrier agents, as shown in **Figure 1**.

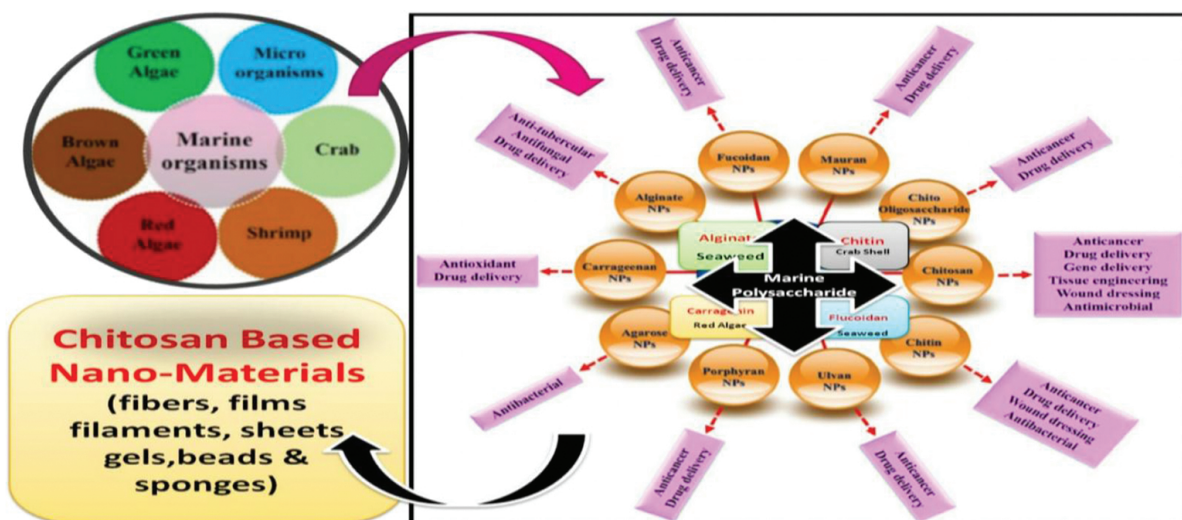


Figure 1. Resources of marine polysaccharides with their wide range of applications [2].

2. Marine biotechnology

Marine biotechnology focuses the following goals:

1. Discovery of bioactive molecules from marine organisms to reveal their functions and actions.
2. Study the environmental parameters, nutritional requirements and genetic factors that control the production of primary and secondary metabolites from marine species.
3. Understand the genetics, biochemistry, physiology and ecology of marine organism/mariculture.
4. Develop diagnostic tools to improve human health.
5. Explore bioremediation for waste processing/disposal, coastal clean-up and oil spilling.

3. Medical potential of marine products

About 20,000 metabolites yielded from marine bacteria, sponge, coral and starfish cater significant untapped promises and act as chemical library database in pharmaceuticals due to their intrinsic features. MARPOL-73/78 an international organization is engaged in enzymatic up-gradation/modification of marine polysaccharides being substitute to oil-based polymers in utilizing renewable resource. MARPOL via enzyme technology-modified chitin, alginate, fucoidan, and laminaran from marine with enhanced inherent quality to cater sustainable industrial/pharmacy needs in the below targets (**Figure 2**):

- To derive innovative bioactive chemicals from marine species.
- To increase value creation from biomass by refining/upgrading via enzymology.
- To generate cross-sectorial technology for enzyme evolution and biomaterial design.

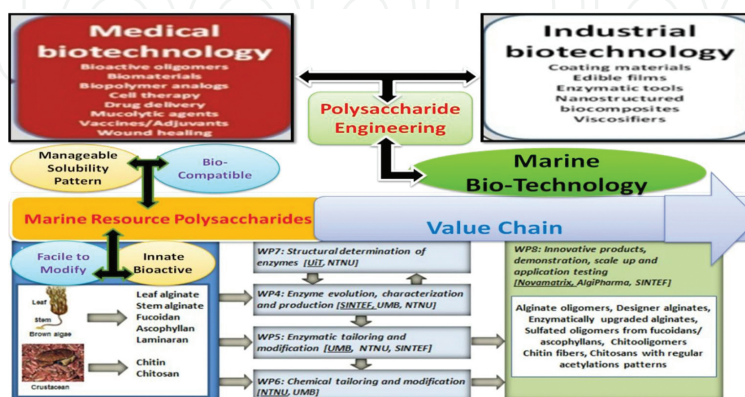


Figure 2. MARPOL via enzyme technology modified marine polysaccharide for wide application.

4. Pharmacological uses of marine polysaccharides

Advance molecular biology has innovated methods for marine organisms to isolate assorted polyunsaturated fattyacids, polysaccharides, minerals, vitamins, enzymes, and peptides. These marine polysaccharides own health benefits besides feedstock for pharmaceuticals, nutrition, and pharmaceuticals besides cosmetic industries (**Figure 3**) under the strategic activity of Horizon 2020: *Targeted specific activities focus on biodiversity exploration to understand how organism can withstand extremes of temperature-pressure and grows without light can be utilized to develop new industrial enzymes/pharmaceuticals*. Drug obtained from marine polysaccharide caters diverse pharmaceutical challenges by inventing various complex/novel chemicals to be used in cancer, AIDS-HIV treatments besides explicit broad spectrum activity for virus, bacteria, and fungus. Alginate and chitin polysaccharides have an extensive history of use in medicine, particularly, in pharmacy and basic sciences. Majority of carbohydrates in the nature occur as polysaccharides that consist not only glycosidic-link sugars, but also polysaccharides that are covalently linked to amino acids, peptides, proteins, and lipids. Glycan contains d-glucose, d-fructose, d-galactose, l-galactose, d-mannose, l-arabinose, d-xylose along with d-glucosamine, d-galactosamine, N-acetylneuraminic acid, N-acetylmuramic acid, and glucuronic acids. Branch structures are different polysaccharide from protein and nucleic acid polymers. Marine origin tunicin polysaccharide is a cellulose equivalent of invertebrate sea animal utilized for storage and/or structural functions. Exo-polysaccharide found in extracellular of a microbial cell component contains high sulfated and uronic contents to bestow negative charge besides acidity in seawater pH 7.5–8.4, which is used as adhesives, textiles, pharmaceuticals and anticancer agents and food additives [1–3].

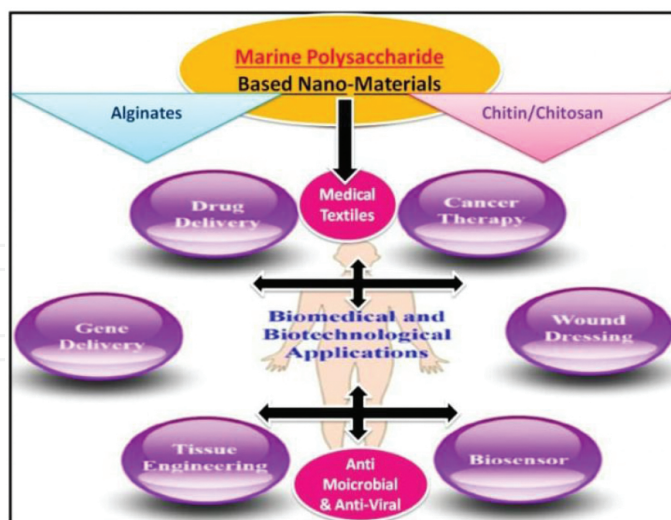


Figure 3. Marine polysaccharide materials for health benefits.

Agar and agarose have less sulfate content, but high uronic contents and corresponding beads are developed that exhibited better optical clarity with improved gel strength exploited in sustainable release of phenobarbital sodium hypnotic drug. Agars are effective for spatial

infections such as poliovirus, herpes simplex, dengue viruses and also meats gelling, laxatives and flexible molds in dentistry and criminology. Chitin hydrogel provides cell signaling *in vivo* physiology [2, 3] and hydroxylation enhances its biodegradability; while sulfonation generates heparin-like increased blood compatibility [4] besides amine quaternization imparts high solubility, muco-adhesiveness (via hydrogen bonding) responsible for elevated drug residence-time, inflammation reduction and antimicrobial activity). Nanochitosan-based drug delivery systems easily cross blood-brain barrier results in cell/tissue gap penetration to targeted spleen, spinal cord, liver, lungs, and lymphs.

5. Cosmetic applications

Polysaccharides formulated with vitamins, minerals, botanical extracts, and antioxidants can promote healthy skin, hair, and nails at a cellular level which are used as creams, lotions, ointments, liquids, and pills, as shown in **Figures 2 and 3**. The cosmetic industry and advance biotechnology are mainly focused on marine polysaccharides as compared to synthetic chemicals due to perceived inherent prominent effects such as reduce free radical provoked aging, inflammation, and skin degradation. Chitin shows resemblance with living tissues that aid to maintain cutaneous homeostasis, neutralize radical activity, and induces transcutaneous penetration of active drugs. Chitosan nanofibrils induce low TGF- β production results in skin protections by increasing the granular density of epithelial layers and fully compatible with skin cells besides complexing with vitamins, carotenoids, and collagens to facilitate transcutaneous penetration [5]. Chitosan without having amino/hydroxy groups. E.g., E-CE6 type aid cationic pH-sensitive molds into various shapes such as bead, hydrogel, nanofiber and nanoparticle owning fascination for other biomolecules. Chitosan hydrogel's excellent water absorption property is exploited in making of some moisturizers; it also provides wound healing and exhibits antioxidant and antimicrobial activities against various bacteria, yeast and fungi and metalloproteinase.

6. Nutrition-pharmaceutics applications

Marine-derived products used as food/ingredients are developed in nutrition-pharmaceutics to prevent/treat diseases pertaining anticancer, antiinflammatory, antioxidant, and antimicrobial activities, as shown **Figures 2–4**. *Ulva fasciata* derive sulfated galactans and fucans possess good anticoagulant, gel stabilizers, preservative, and flavoring agents that reduce LDL-cholesterol, plasma, and triacylglycerols [6]. Align emulsions are used as bio-flocculants in food formulation to obtain certain texture, mouth feel thickening effect, and stabilize suspended dispersed phases. Carrageenans-polyamide hydrocolloid with starch, locust bean gum, and carboxymethyl cellulose are used for milk protein stabilization [7]. Chitins are used in antidiabetic, hypocholesterolemic, adipogenesis inhibitor, food additives, and dietary supplements in nutrition-pharmaceutics which decrease body weight, serum lipids without digestions in GI tract (precipitates fat and reduces absorption via inhibiting pancreatic lipase

actions). Cationic chitosan-fatty/bile acid combinations delay cholesterol and steroidal emulsifications via hydrophobic interaction, thus lessening intestinal absorptions.

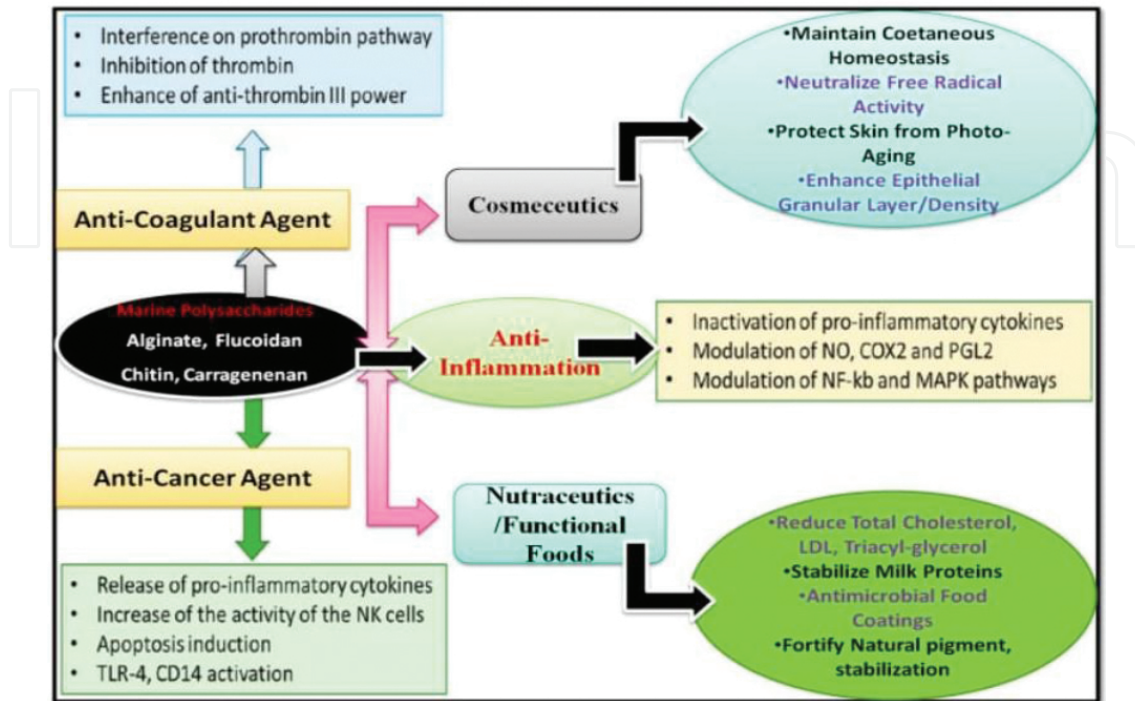


Figure 4. Pharmacology of assorted marine polysaccharides.

7. Chemical structure of chitin/chitosan

7.1. Preparations of chitin/chitosan

About 10 gigatons/year of chitins are produced in biosphere which are soft and leathery, encrusted with CaCO_3 as the harden mass to obtain translucent, pliable, resilient as a tough exoskeleton of vertebrates, insects, and crustaceans. Chitin exhibited distinct characteristic against fungus pathogens resistance, autolytic, nutritional, and morphogenetic functions in plant, pathogenesis in virus and elicits lysozyme inductions, immunizations and parasitism in bacteria. Chitin is antidiabetic, hypocholesterolemic, adipogenesis inhibitors which decreases body weight/serum lipids without GI digestion prohibiting pancreatic lipase crucial for cholesterol emulsification to precipitate fat and fatty/bile acids [8].

7.2. Chitosan production

Chitin is feedstock for chitosan conversion via enzymatic as well chemical degradation (Figure 5) because of its cheap and commercial production, as shown in Figure 6.

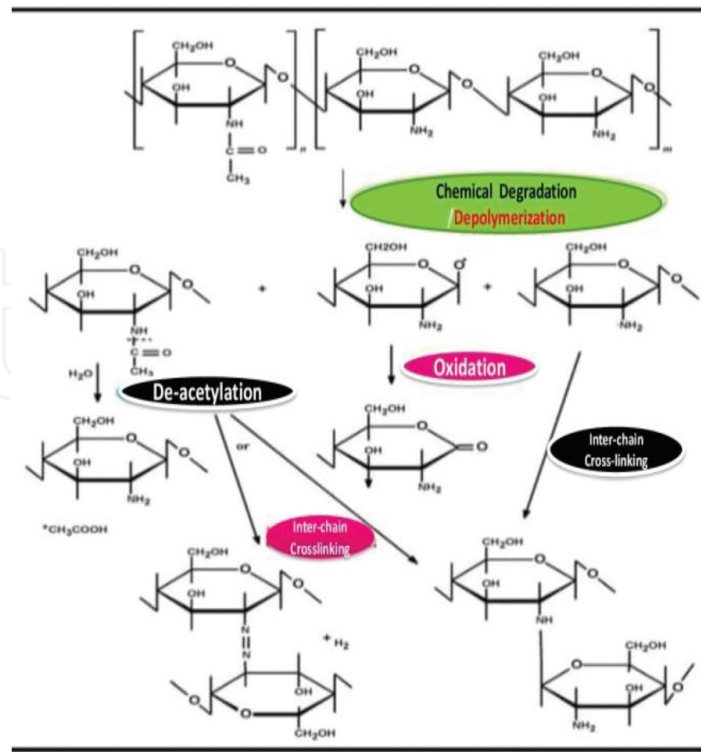


Figure 5. Chitosan chemical degradation.

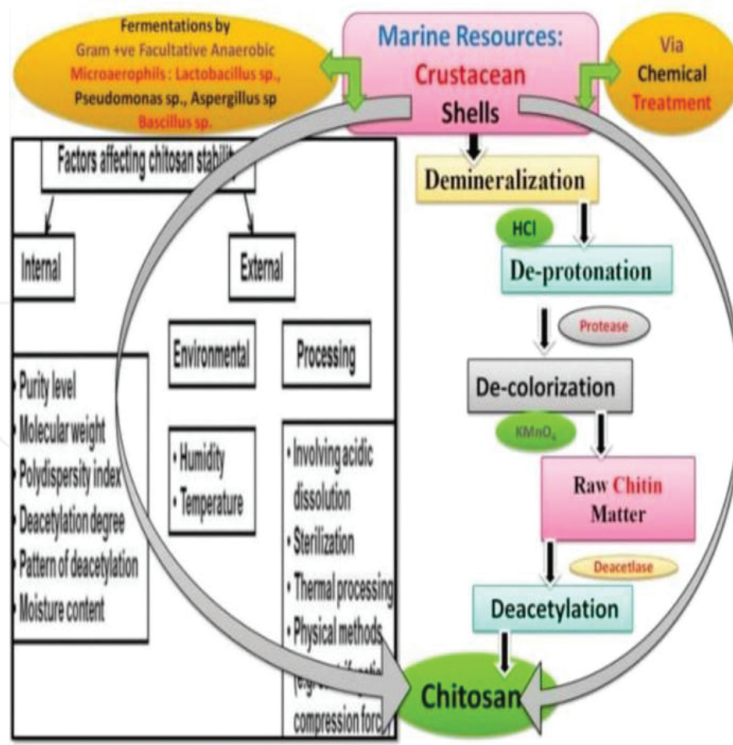


Figure 6. Production of chitosan and factors affecting stability.

8. Chitosan copolymerization: acetylation, sulfonation, and other cross-link substitutions

Chitosan differs from concordant chitin, cellulose in fraction and distributions of their comonomers in respective of polymeric length/sequences and found as an alternate, block, and random fashion as shown in **Figure 7**. N-acetyl-glucosamine and N-glucosamine constitutional monomers in chitin and chitosan displayed varied, respectively, solution properties and impart slightly hydrophobic terminal in chitin and ionic character at acidic pH in chitosan. Skeletally different than others amplified in acetyl sequencing that owes vivid outcome in chain conformation and aggregation besides hydrophobic substituents is vital for self-assembling and crumpling as found in liposphere micelles. The modification in chitin/chitosan's skeleton can be made by means of quaternization, glycosylation (via acetyl) and sulphonation (via sulphate groups) techniques that able grafting monomers at $-NH_2$ linkages to yield terpolymer rather intricate matrix as shown in **Figure 8**. Chitosan compositions varied with the degree of acylation as determined by many methods such as titration, circular dichroism, FTIR, UV, NMR, and N-acetyl group hydrolysis [9, 10]. Data from different techniques showed discrepancies in degree of acylation and solubility disparity as no technique points out appropriate clarification for solubility [11]. Differential scanning calorimetry study decomposition of amino/acetyls to provide sovereign composition and molecular weights 0–1 N-acylation degree cheaper than NMR but more accurate than FTIR. NMR easily recognizes O-acetyl groups that aid to obtain degree of acylation by integration/normalization of either anomeric proton or other ring protons.

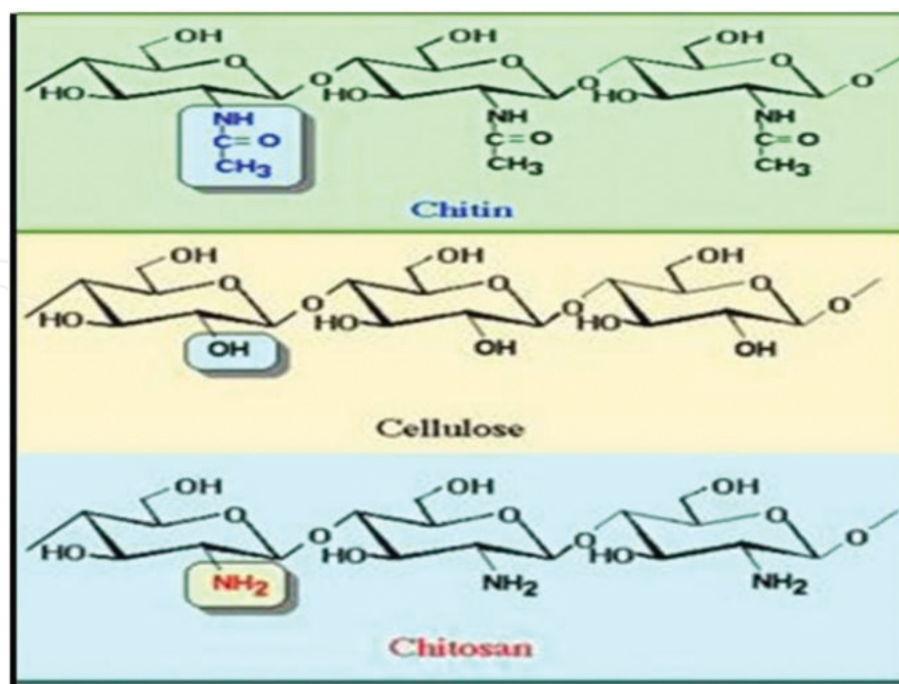


Figure 7. Comparison of chitin, cellulose, and chitosan.

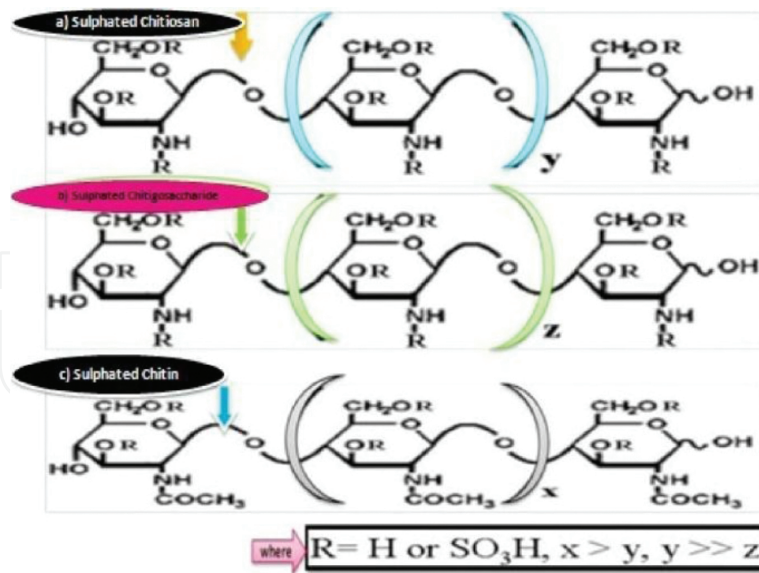


Figure 8. Structures of sulfated chitin, chitosan, and chitigosaccharide.

9. Structure and chemical modifications of chitin/chitosan

9.1. Chemical modification principles

Chitosan chemical modifications improved mechanical properties, biocompatibility, solubility, biodegradability, and shape/size by the following approaches:

- Doping/blending/grafting chemical linkages with synthetic materials;
- Micro/nanosphere surface coating by biocompatible synthetic polymers;
- Cross-linking by means of assorted physical/chemical reagents;
- Hydrophobization via alkylation;
- Modulating guluronic/mannuronic ratio; and
- Varying deacetylation degree.

Dry weight crustacean shells contain protein 30–40%, $CaCO_3$ and $Ca_3(PO_4)_2$ about 30–50%, and 20–30% chitin [11]. Industrially, acid treatment use to dissolve $CaCO_3$ and $Ca_3(PO_4)_2$ followed by alkaline extraction to solubilize proteins in chitin processing from crustaceans. Deacetylation removes enough acetyls to yield chitosan with high degree chemical reactive amines that can affect physicochemical properties such as biodegradability and immunological activity [12]. Chitosan's deacetylation degree is determine by the ninhydrin test, potentiometric titration, near-IR, NMR, HBr-titrometry, FTIR, and 1st derivative UV [10] analysis. Chitosan is soluble in dilute acetic acid which has free $-NH_2$ for modifications so supersede chitin.

9.2. Varied chemical modifications

Assorted chitosan matrix modifications at $-\text{NH}_2$ in C-2, at $-\text{OH}$ in C-3/C-6 carbon are performed via etherification/etherification and amine quaternization [13]:

1. Carboxyalkylation at O-/N: Carboxyalkylation at O-/N of chitosan imparts the amphoteric polyelectrolyte nature needed in biomedical applications such as wound dressings, artificial bone and skin, bacteriostatic agents, and blood anticoagulants [14]. Carboxyl and amino chitosan functionality elicits special biophysical properties for controlled/sustained drug-delivery, e.g., water-soluble O-carboxy methylchitosan microspheres for control pazufloxacin mesilate: antibiotic drug release.
2. Sulfonation: Chitosan sulfonation at amino/hydroxyl groups generates pharmaceutical heterogeneity (analogues to heparin: a natural blood anticoagulant) to pertain desired anticoagulant, antisclerotic, antitumor, and antiviral activities. Free NH_2/OH sulfonation mostly disrupts chitosan crystallinity by depleting inherent hydrogen bonding and amphiphilicity and imparted micelles can act as a drug carrier.
3. Acylation: Chitosan acylation by aliphatic carboxyl, hexanoyl, dodecanoyl acids, and tetradecanoyl chlorides/cyclic esters, e.g., 4-chlorobutyl and decanoyl acylation at free NH_2/OH showed higher fungicidal activities via induced hydro-phobicity to prevent particle aggregations by lowering drug irritation in stomach [14]. Such hydrophobic interaction via N-acylation encourages rapid self-expandability in tracheal cartilage, intervertebral discs, menisci, skin, liver, skeletal muscle, neural tissue, and urinary bladder cells. Such acylated chitosan are beneficial such as easy solubility, benign plasma proteins sorption, and drugs selectively with reduce free blood concentration [14].
4. Sugar-modified chitosan: Chitosan reductive N-alkylation by disaccharide or monosaccharide-aldehyde derivatives acts as a liver-specific drug carrier via specific binding at sialoglycoprotein receptors [15]. All these NH_2 -alkylated chitosan derivatives are soluble at neutral and basic pH conditions, whereas lactose, maltose, and cellobiose sugars imparted all pH range solubility. Galactosylated chitosan derivatives act as the synthetic extracellular matrix for hepatocyte attachment [14, 15].
5. Graft copolymerization of chitosan: Chitosans are tailored to yield composites so as to improve certain aspects such as inclusion complexation [14], mucoadhesivity retention [13, 14], adsorption [15], bacteriostaticity, biocompatibility, and biodegradability [12, 15]. Chitosan grafting with oligol-lactide increases hydrophilicity and control degradation rate as anticipated in wound dressing, drug carrier systems, as micelles hydrophobic core to entrap and control the release of hydrophobic drugs [12]. In last decades, grafting of chitosan with hydroxyethyl-methacrylate, methyl methacrylate, and vinyl monomers copolymers used for control cardiovascular drug release [14], tissue engineering [11, 15], and woundhealing [12].
6. Skeletal cross-linking: Cross-linking at chitosan yields hydrogel with adequate mechanical properties and high-drug-loading capability having potentials in controlled drug delivery systems [11, 15]. Cross-linking by glutaraldehyde, genipin, ethylene glycol,

diglycidyl ether, and diisocyanate at chitosan $-NH_2$ establishes speciality like nonionic/ionic drug interactions and pH-sensitivity aids swelling in gastric conditions anticipated in site-specific drug release [11]. Chitosan cross-link microspheres are nontoxic, biodegradable oral drug agents [12, 15] without potential deleterious impact. Tripolyphosphate-chitosan ionic gels encapsulate plasmid DNA/dsDNA *in vitro* transfection, cellular uptake, and *in vivo* gene expressions via intratracheal administration imparting high physical stability without DNA release (even after heparin incubation). Confocal studies revealed endocytotic cellular nanoparticle uptake with subsequent cytoplasm fast releases, mediated *in vivo* intratracheal strong β -galactosidase expression. Chitosan-tripolyphosphate nanogel is used in nonviral gene delivery liable to cause steric stabilization and targeting [9, 12]. Calcium sulfate-encapsulated alginate-N-succinylchitosan hydrogel pastes retained structural integrity and found to decrease resorption rate responsible for bone defect healing in bone regenerative techniques [11, 15]. Hydrogels are beneficial due to easy handling, suitable molding, and instant hardening (water release from hydrogel and transform $CaSO_4$ hemihydrate by partial cross-link with alginate to exert cementing via egg-box effect aid in bone regeneration).

10. Physicochemical properties of chitin/chitosan

10.1. Chitosan characterization

Chitosan quality like variable appearance, turbidity, molecular weight, and mechanical stability depends on chitin resource, isolation method [9, 16], and deacetylation degree as manifested in **Figure 6**. Degree of deacetylation >0.5 imparts in aqueous acids soluble to chitosan but not in alkaline/physiological pH as uneven acetyl distribution lowers solubility due to aggregation as determined by FTIR $^1H/^{13}C$ -NMR (liquid state, solid state) and potentiometric titration. Average molecular weight of chitosan is obtained from steric exclusion chromatography-viscometer, light scattering detector, matrix-assisted laser desorption, and MS spectrometry as mentioned in **Table 1**.

Physiochemical characteristics	Method of determination
Molecular weight	Viscometry; gel permeation chromatography; light scattering; HPLC; matrix-assisted laser desorption/ionization-mass spectrometer
Deacetylation degree	FTIR; UV; 1H -NMR and ^{13}C -NMR Spectroscopy; conductometry and potentiometry titration; TGA/DTA, differential scanning calorimetry
Crystallinity	X-ray diffraction

Table 1. Methods for physiochemical characteristics of chitosan derivatives.

Chitosan is the only cationic polysaccharide that is nontoxic and biodegradable in body, thus exploited by tissue engineering for wound dressings, drug delivery, and bone graft alternative

in orthopaedic beside scaffolds for cartilage, intervertebral disc, and bone tissue. The relevant physicochemical and biological properties of chitosan are presented in **Table 2**.

Physic-chemical parameters	Biological parameters
Cationic polyamine	Biocompatibility
On protonation adheres to negatively charged surface via bio/mucoadhesion and form hydrogel with polyanions	Second naturally abundant polymer after cellulose
Polar salt formations with organic and inorganic acids	Facile biodegradation to normal monomers/oligomers
It high molecular weight linear, flexible polyelectrolyte	Very safe and nontoxic
Viscosity can be altered (high, moderate to low) depending on degree of deacetylations	Own haemostatic, bacteriostatic, and fungistatic bio-activity
Chelate formations with transition/heavy metal ions	Its spermicidal
Benign to modify, both chemically and bio/enzymatically	Anticancerigen
Own free reactive amino/hydroxyl functionality	Anticholesteremic
High charge density (pH < 6.5)	Versatile, reasonable cost

Table 2. Physic-chemical and biological proprieties of chitosan [16].

10.2. Crystallographic studies of chitosan

X-ray diffraction and crystallography of chitin revealed two polymorphs, namely, hydrated/tendon and anhydrous/annealed conformers. Crystalline chitosan own ant parallel chains in two-fold helix, zigzag pattern with almost constant pitches of 10.34 Å for hydrate and 10.34 Å anhydrous forms (similar to cellulose). Chitosan conformations of two-fold extension with moderate flexibility due to salt formation/protonation of free $-NH_2$ with acids imparting tunable hypocholesterolemic and fungicidal activity and metal chelation besides chromatographic uses and gel production [9].

10.3. Critical physico-chemical properties of chitosan

Understanding of relation structure-properties in chitosan become a matter of great interest encountered by regulatory agencies in approving chitosan uses. The critical examination of literature results in correlation between properties of nanoconstructs with component structures as advantageous due to modulating. Thus, chitosan nanoparticles are exploited in modern pharmaceuticals/biomedicals by alteration of acylation, molecular weight/its distribution, nature, and fraction of substituents. In general, applications its need to examine molecular characteristics interplay with supramolecular interactions to provide size, shape, and surface-active nanomaterials [12].

11. Biological activities of chitin/chitosan

11.1. Chitosan properties and bio-activity from gel to nanobead in drug delivery

Chitin/chitosan own wide pharmaceutical utility due to excellent biocompatibility, biodegradability, nontoxicity, and adsorption properties which fuels global research interests, e.g., 1150 articles in 1981–1990, about 5700 reviews in 1991–2000, and 23,100 publications in 6 years [9, 15]. Among all natural polysaccharides, chitin/chitosan's outstanding benefited industrial and pharmaceuticals significance are depicted in **Figure 1**. Chitin/chitosan is the only high molecular weight cationic polyelectrolyte, while other polysaccharides are either neutral or anionic in nature. Moreover, chitosan owns some undesired features like large variable chemical composition differences in its resultant polymeric chain-size and assorted acetylation degree appropriately classified as “ugly,” frustrating research applicability. Nevertheless, chitosan skeletal optimization yields biomaterials with therapeutic and biological profiles useful in drug delivery formulations and as functional excipients. Chitosan interactions with some cosolutes/biostructures revealed subtle effects in classical solution thermodynamics and in biological utility like interactions with endotoxins.

11.2. Chitosan as antiinflammatory/immunomodulatory agents

Chitinous administration through vascular system enhances cytokines release by macrophage, and upregulates Th1-immunity and downregulates Th2-immune activity [12]. Chitosan cross-linked resin and chitosan poly- γ -glutamic acid nanoparticles are used as alternative vehicles for oral delivery of NSAID aceclofenac and diclofenac drugs, respectively, which inhibits prostaglandin E2 production to stifle ultimate local inflammatory responses.

11.3. Chitosan as anticoagulants

Sulfation at N-2 and O-3 link of chitin increases thrombin level and activates partial thromboplastin-thrombin time [12] and at C-2, C-3, and C-6 position showed anticoagulant activity at par with therapeutic heparin (mere heparin use infects animal proteins to own antiplatelet activity responsible for abnormal bleeding). Sulfated chitins anticoagulant action inhibits FXa-mediated antithrombin-III activity via N-sulfo/N-acetyls complexation with antithrombin-III, which prolongs thrombin-clotting time. Coagulation interfering factors in fibrin polymerization are assayed via antithrombin activity and prothrombin-atroxin time assessment (**Tables 1 and 2**).

11.4. Chitinous anticancer agents

Chitosan is trusted due to nontoxicity, biodegradability, efficient drug delivery, best cell-permeability, and antiproliferativity against adenocarcinoma HT-29 and caco-2, colon carcinoma HCT-116 in kinase protein of intestinal epithelial cells, which colorectally inhibits NF- κ B transcription and NF- κ B-mediated inflammations. Caffeic acid and doxorubicin individually doped chitosan composites revealed strong fluorescence intensity used to vehicle

anticancer drugs [17]. Curcumin-coated chitosan nanoparticles possess significant cytotoxicity and reduce human oral cancer cell line.

11.5. Chitosan vehicle drugs delivery systems

Distinctly doped glutamine, methionine, and tryptophan in chitosan matrix exerted protection to C-8166 cells against cytotoxicity of HIV-1RF strain and restrain HIV-induced syncytium formation with HIV-1 reverse transcriptase/protease enzymes by suppressing HIV-infected C8166 cells. Similarly, sulfated chitosaccharide-III found to suppress HIV-1 replications, syncytium formation, lytic action, p24 antigen production, and thwarted viral entry/cell fusion by intrusive HIV-1-gp-120 bound CD4-cell receptors (unsulfated chitosan lack such actions). Polyethylated-chitosan vehicle lamivudine curbs HIV-replication more powerfully than lamivudine/no chitosan carrier. Thioglycolic acid-conjugated chitosan carrying tenofovir disoproxil fumarate exhibited high mucoadhesion via intravaginal microspheres stabilization without vagina epithelial cells cytotoxicity and lactobacillus crispatus compared to native nanochitosan. Drug encapsulation and mucoadhesion are profound for chitosan-O-isopropyl-5'-O-d4T-monophosphate vehicle zidovudine since it reduces the diameter to stop HIV transmission. Nanochitosan carrying saquinavir drug imparted excellent antiHIV potential and high cell target efficiency to yield efficient HIV proliferation control [18, 19]. Poly-d,l-lactide-co-glycolide nanochitosan vehicle anti-HIV acyclic nucleoside and phosphonate aids cellular uptakes in target macrophage cells. Broad bioactivity pattern of chitosan vehicle drugs are summarize in **Table 3**.

Targets	Chitosan composites (antibiotic stock solution minimal inhibitory concentration in ppm)
Gram-negative bacteria	<i>Escherichia coli</i> (facultative anaerobic bacteria)
	chitosan-Zinc 0.003%; α/β -chitosan 9 ppm; chitosan-N,N-diethyl-N-methyl 16 ppm; chitosan-N,N-dihexyl-N-methyl 16 ppm; pure chitosan 0.02%
	<i>Escherichia coli</i> (ETEC-K88 type)
	chitosan 8 ppm; chitosan nano-particle 0.063 ppm; Copper-chitosan nanoparticle 0.03 ppm
	<i>Escherichia coli</i> (ATCC 25922)
	chitosan 8 ppm; chitosan nanoparticle 0.03 ppm; Copper dope chitosan nanoparticle 0.03 ppm
	<i>Escherichia coli</i> (O157 type)
	α -chitosan 9 ppm and β -chitosan 9 ppm
	<i>Pseudomonas aeruginosa</i>
	chitosan 0.012%; chitosan-Zinc complex 0.0063%; α -chitosan 9 ppm; β -chitosan 9 ppm; N,N-diethyl-N-methylated chitosan 32 ppm
	<i>Proteus mirabilis facultative anaerobic, bacterium</i>
	Pure chitosan 0.0251% and chitosan-Zinc complex 0.0063%

Targets	Chitosan composites (antibiotic stock solution minimal inhibitory concentration in ppm)
<i>Salmonella enterobacteriaceae</i>	chitosan 0.051% chitosan-Zinc solution 0.006%
<i>Salmonella choleraesuis</i> (ATCC 50020 type)	chitosan 16.0 ppm; chitosan nano-particles 0.063 ppm; Cu-chitosan nano-particle 0.03 ppm
<i>Salmonella typhimurium</i>	α -chitosan 5.0 ppm and β -chitosan 9 ppm
<i>Salmonella typhimurium</i> (ATCC 50013 type)	chitosan 16 ppm; chitosan nanoparticles 0.12 ppm; Copper-chitosan nanoparticles 0.063 ppm
<i>Enterobacter aerogenes</i> (nosocomial and pathogenic bacteria)	chitosan flakes 0.050% and chitosan-Zinc complex 0.0063%
Gram + vebacteria	<i>Listeria monocytogene</i> α -chitosan 9 ppm and β -chitosan 9 ppm
<i>Staphylococcus aureus</i> (gram-positive coccal bacteria)	chitosan 0.051%; chitosan-Zn complex 0.0063%; α -chitosan 9 ppm; α -chitosan 9 ppm & N-ethyl-N,N-dimethylchitosan 4 ppm
<i>Staphylococcus aureus</i> (ATCC 25923 type)	chitosan solution 8 ppm; chitosan nanoparticles 0.13 ppm; Cu-chitosan nanoparticles 0.063 ppm
Corynebacteriaceae (aerobic)	chitosan 0.0251%; chitosan-Zinc 0.031%
Staphylococcaceae epidermidis	chitosan 0.0251%; chitosan-Zinc complex 0.013%; α -chitosan 5 ppm and β -chitosan 5 ppm
Enterococcaceae faecalis (commensal bacterium)	chitosan 0.051%; chitosan-Zinc complex 0.013%; N,N-diethyl-N-methyl-chitosan 16 ppm
<i>Bacillaceae cereus</i>	α -chitosan 9 ppm and β -chitosan 9 ppm
Bacillaceae megaterium	α -chitosan 9 ppm and β -chitosan 9 ppm
Virus	IC ₅₀ : Half maximal inhibitory concentration for cyto-pathogenicity by HIV-1 strain Glutamine-, methionine-, and tryptophan-coated chitosan composite solution 48 ppm
IC ₅₀ :for cyto-pathogenicity by virus HIV-1 _{III} B strains	Tryptophan, Methionine and Glutamine WMQ-chitosan composite solution 48 ppm
IC ₅₀ of luciferase oxidative enzyme to produce bioluminescence for HIV1 _{RF}	Glutamine-, methionine-, and tryptophan-coated chitosan solution 68 ppm; Tryptophan-, methionine-, and glutamine-coated chitosan 164 ppm
IC ₅₀ of synergistic inhibition for V3 loop of gp41 and target cell CD4 by HIV-1 strains	Glutamine-, methionine-, and tryptophan-coated chitosan solution 39 ppm; Tryptophan-, methionine-, and glutamine-coated chitosan 52 ppm

Targets	Chitosan composites (antibiotic stock solution minimal inhibitory concentration in ppm)
IC ₅₀ of HIV-Induce syncytium by HIV-1 _{RF} strain	Aminoethyl/sulfated chitosan composite solution 2.2 ppm
EC ₅₀ for lysis of HIV-1-infected cells by HIV-1 strains	Carboxylated/sulfated chitosan composite solution 1.5 ppm
IC ₅₀ of p24 antigen synthesis by HIV-1 _{RF} strains	N-carboxymethylchitosan chitosan composite solution 4.5 ppm
IC ₅₀ of antigen p24 synthesis by HIV-1 _{Ba-L} strain	N,O-sulfated chitosan composite solution 7.8 ppm
Fungi	
<i>C. albicans</i> /Debaryomycetaceae	Chitosan-Zinc complex 0.11%; chitosan 5.0 ppm
<i>C. parapsilosis</i>	Chitosan-Zinc 0.051%; chitosan 40 ppm
<i>C. krusei</i>	Pure chitosan solution 5 ppm
<i>C. glabrata</i> /Torulopsisglabrata	Pure chitosan solution 20 ppm
<i>P. digitatum</i> (mesophilic)	Pure chitosan solution 65 ppm
<i>P. italicum</i>	Pure chitosan solution 58 ppm
<i>Fusarium moniliforme</i> (mould)	Pure chitosan solution 2.5 ppm
<i>Penicillium</i> , <i>Talaromyces</i>	Pure chitosan solution 2.5 ppm
<i>Aspergillus fumigates</i>	Pure chitosan solution 1 ppm
<i>R. stolonifer</i> (Bread Mold)	Pure chitosan solution 100 ppm
<i>C. neoformans</i> (yeast)	Pure chitosan solution 5 ppm
<i>Cryptococcus neoformanvargati</i>	Pure chitosan solution 2.5 ppm
<i>M. phaseolina</i>	Pure chitosan solution 12.5 mg/mL

Table 3. Broad bioactivity pattern of chitosan based drug delivery systems on varied targets.

Pharmaceutically, chitosan delivered tablets, microspheres, micelles, vaccines, nucleic acids, hydrogels, nanoparticles, and conjugates via implantable, injectable oral, nasal, and ocular routes. Chitosan facilitates transmucosal absorption vital in delivery of peptides and in protein vaccination [9, 12, 20] besides an excipient in oral tablet formulation. High molecularweight chitosan is more viscous to impart delayed ingredient release/drug duration activities which improve therapeutic efficiency by lessening side effects of oral tablets [12]. Chitosan-tripolyphosphate/alginate microspheres can control or protect proteins, drugs, and vaccines absorption in the digestive tract via paracellular route on epithelial layer release in oral and nasal administrations [9]. Hydrophilic chitosan imparts low surface activity that gets improved by glucosidic modifications, hydrophobic substitutions, and by providing hydrophilic shield at hydrophobic centers [12] to protect hydrophobic drugs with improved solubility and bioavailability [20]. Chitosan 3-D hydrogels are structured via diffusion, entrapment, and tethering with hydrophilic polymers to hold up thousands times more fluids than its dry

weights is best utilized in drug delivery. Thermosensitive chitosan solution when injected into the body at physiological conditions forms hydrogels which aids protection of drugs from degradation besides its prolonged-steady release [21]. Biocompatible chitosan drug carriers yield via ionotropic gelation, emulsion, cross-linking, solvent extraction, diffusion/droplet coalescence, reverse microemulsion, and self-assembly techniques. But ionotropic gelation is preferred due to mildness and less time involved in spontaneous aggregation. Chitosan-aided delivery systems protect drugs from chemical/enzymatic degradation in digestive system due to strong mucus binding that enhance drug adsorption in intestinal epithelial cells [20]. Chitosan-glycol nanogel uptakes endocytosis mediated by flotillin-1 with Cdc42 and macropinocytosis attended by actin cytoskeleton participation and internalization mechanisms by folate receptor are useful in drug delivery vectors for targeting different intracellular compartments [9]. Glipizide chitosan-xanthan beads exhibited control-drug release, mucoadhesion, pH-based swell kinetics, good bioadhesiveness, and comparable floating capacity in gastric fluids [22]. Insulin-chitosan-tris-buffer (pH 6.5) nano emulsions showed physical and chemical stability in a reverse micelle system and potent hypoglycemic activity in diabetic rat [20, 22]. Colon prolongs progesterone absorption for much first-pass metabolism with low oral bioavailability, but zinc-pectinate-chitosan vehicle increases drugs oral bioavailability with more residence time in plasma for colonic-specific delivery. Glutaraldehyde-Boswellia-resin doped chitosan composites (phosphate buffer pH 6.8) releases 70% drug load in 7 hours with augmented drug entrapment [9, 12, 20]. Chitosan-catechol carrier imparts higher retention for mussel adhesive proteins found in GI track via irreversible catechol-mucin cross-links aids in mucosal drug delivery [9]. Fish oil-based N-stearoyl O-butylglyceryl-chitosan microcapsules own desirable capacity and carrier encapsulation efficiency for sustained release of fish oil besides higher thermostability [9].

11.6. Chitosan as an antioxidant

Chito-oligosaccharide scavenges hydroxy, carbon-centered superoxide, alkyl, and 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radicals at free NH_2/OH site of pyranose skeleton and offers stability and *in vitro* antioxidants protection without damaging membrane lipids, protein, and DNA. Chitin-doped carboxyethyl possesses good water solubility above pH 6.5 and potent radical scavenging activity for 2, 2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid (ABTS) with $\text{EC}_{50} < 2 \text{ mg/mL}$ and good *in vivo* bioactivity (**Figure 3**). Methacrylic/sodium-acrylic etherified chitosans owing to their high surface area with micro-porosity and tensile strength can be molded into different shape, size/forms films, fibers, sponges, beads, powder, gel, and solutions for therapeutic antioxidant activity.

11.7. Chitosan in tissue engineering

Flexible mechanical and structural features of chitin is explored in tissue engineering to procure materials which impart improved bio-functions to be used to repair tissues like bone, cartilage, blood vessels, bladder, skin, and muscles. Tissue engineering induces varied dimensional/shape/size chitin forms like fiber, filament, film, sponge, and gel to provide instant mechanical support and compatibility to bio-fluids/tissues via cell, scaffold, and cell

scaffold interaction as shown in **Figure 9**. The 3-D chitosan scaffold act as an artificial extracellular matrix as reabsorbed by body with time till new tissue forms to aid to integrate new tissues [20]. Chitosan interacts with cellular glycosaminoglycans to enhance cell attachment and proliferation results for cell growth via mechanical enhancement which resembles replaceable hard/soft tissue like bones, cartilage, muscles, and blood vessels.

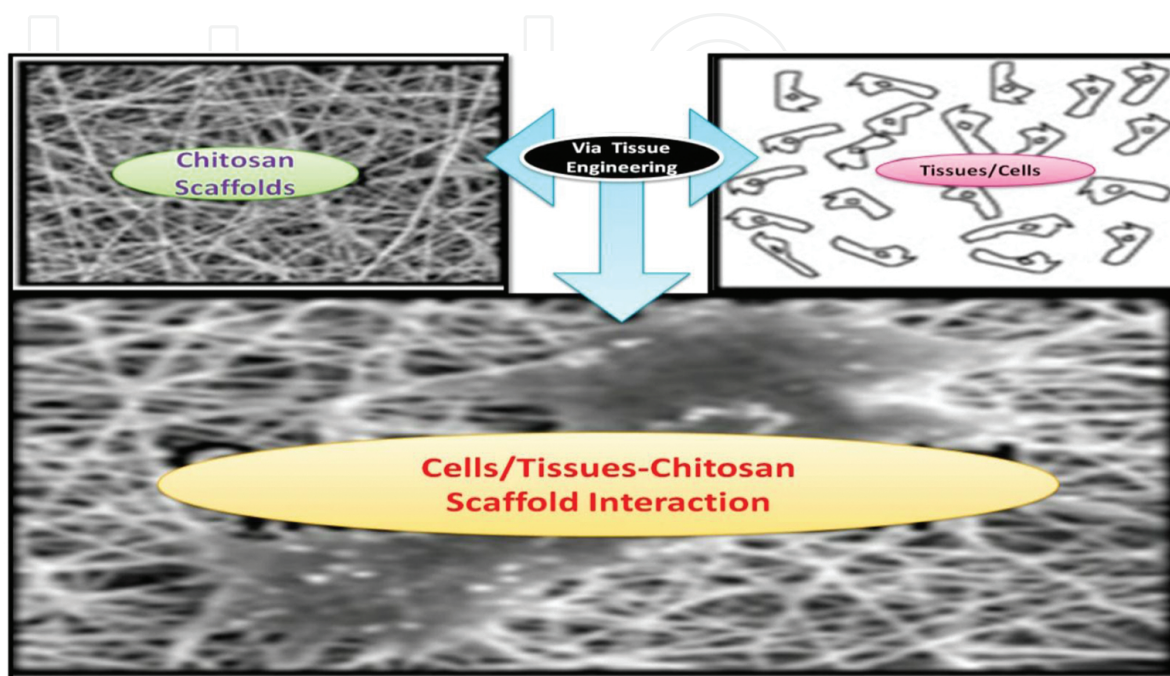


Figure 9. Schematic depiction of highly compatible cell-chitosan scaffold interactions [20].

Medical textiles or healthcare textiles is arapidly expanding technical textile market to prepare materials for medical and healthcare products like simple gauzes, bandages, tissue culturing scaffolds, and prostheses for permanent body implants [23]. Chitosan acquire basic requirements of textile material for medical applications like biocompatible, resistance to alkali, acids, and microorganisms, high-dimensional stability, elasticity, free from contaminates/impurities, absorption/repellence, and air permeability [24].

11.8. Chitosan in wound healing

Low immunogenicity characteristics of chitosan aids to provide 3-D tissue growth matrix with profound activities such as enhancing macrophage activity, stimulating cell proliferation to heal wound and facilitating polymorphonuclear leukocytes, macrophages besides fibroblasts induced granulation responsible for tissue repairs [25]. *N*-acetyl- β -*D*-chitosan degradation imparts peculiarity like fibroblast proliferation, collagen deposition, and hyaluronic acid stimulation at wound to accelerate healing without scar formation [26]. Nanochitosan adhesive mats own high porosity, tensile strength, surface area, and ideal H₂O vapour-O₂ transmission rate compatible with adipose-derived stem cells accountable for wound dressing (**Figure 10(A–D)**). Nanochitosan surgical dressing provides fast wound healing through adhesiveness with

strong sealing strength without sutures/staples and prohibits blood vessel bleeding and air leakage in lung surgery [26].

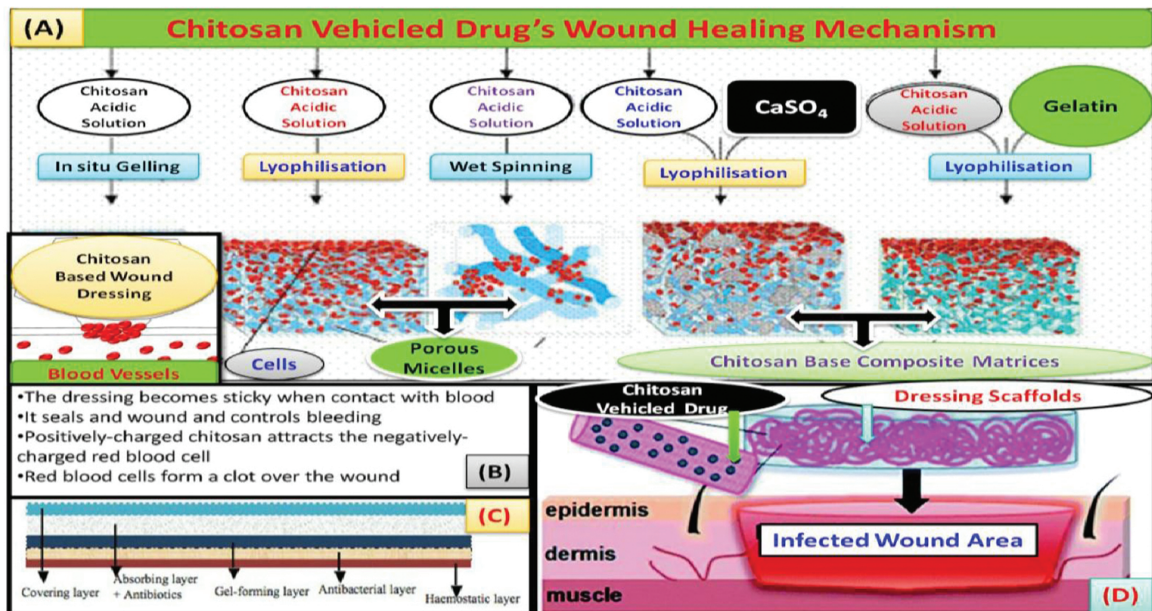


Figure 10. (A) Schematic pathway for chitosan vehicle drug's wound healings, (B) wound healing steps, (C) multilayered nanochitosan-fiber-based wound dressings, (D) chitosan compliance for fabrication: at pH < 6 amines get protonated to polycations and at pH > 6.5 amines get deprotonated to undergo interpolymer alliance yielding fiber/globule.

Clinically, chitosan-based nanofibers, composites, films, and sponges used for wound healing in plastic surgery [9, 25], skin grafting [9, 27], and endoscopic sinus surgery [26, 27]. HemCon® hemostatic latex-free bandages derived from chitosan-coatings acts as extreme adherent on blood contact to seal wound and controls bleeding (via affinity to red blood cells) and effectively reduces hemostasis span. ChiGel, Chitopack-C®, Trauma-Stat™, Tegasorb™ and Tegaderm™ Guarda-Care®, Chito-Flex®, and Chito-Gauze® are chitosan-based products used for dressings in surgical protective thickness, dermal, limb trauma, ulcers, injury, abrasions, and burns where chitosan swells with exudates to gel inaid healings. Celox™ granules/flakes are hemostatic gauze that controls emergency bleeding via swelling to gel-clot on contact with blood and induce hemostasis in penetrating limb trauma in contrast to conventional pressure bandages [9]. Topical chitosan-coated pads promote vascular hemostasis percutaneous catheters/tubes interventionally put on puncture site found to aggregate red blood cells and platelets, thus shortening the clot formation-5. Carboxypolyvinylalcohol-chitosan hydrogel film improved swelling ratio to maintain moisture over wound besides sustaining drug release and effective suppression of bacterial proliferations [27]. Curcuminbioglass-encapsulated chitosan found many uses like wound healing dressing, quenchingactivity of DPPH and superoxide, inhibit *Staphylococcus aureus* bacteria, and reduce tumor necrosis [9, 27]. Varied ionic cross-linkers aid in chitosan drug delivery as shown in **Table 4**.

Ionic cross-linker	Types of agents	
Metal cations	Fe(III)	
	Pt(II)	
	Mo(VI)	
Smaller anions/molecules	citric acid	
	Butanedioic acid	
	Glauber's salt	
	Ionic phosphate compound	tripolyphosphate (TPP) sodium beta glycerophosphate Sodium salt of cori ester/glucose 1-phosphate Sodium salt Robison ester/glucose-6-phosphate
Anionic polymers	Natural	Kappa/Iota-Carrageenin (linear sulfated polysaccharide)
		Collagens (partial hydrolysis protein)
		Hyaluronan (nonsulfated glycosaminoglycan)
		Acidic <i>gum</i> (high uronic acid % natural exudates)
		D-galacturonic acid/Heteropolysaccharide
	Gamma PGA (amino acid glutamic acid polymer)	
	Alginate/alginate from seaweed	
	Dextran sodium sulfate (DSS)	
	E 415 gum from <i>Xanthomonas campestris</i>	
	Synthetic	Acrylic acid polymer
	Methacrylate polymer	Eudragit
	PNIPA/NIPApolymer	Synperonic/Pluronic/Koliphor
Relationship of polyolphosphate with chitosan is unclear and not been elucidated.		

Table 4. Ionic cross-linkers used for chitosan-based drug delivery in biomedical devices [28].

11.9. Chitosan in water treatment

Chitosan acts as a natural adsorbent due to free amino and hydroxyl groups responsible for adsorptive interactions with water pollutants like dyes [29], metals [30–33], and organic compounds, etc. Functionality of chitosan is facile for modifications, viz., cross-linking and grafting so as to enhance its inherent absorption efficiency and specificity. Cross-linking of chitosan's functionality improved its sorption efficiency at low pH while grafting with sulfur/

nitrogen improves specificity and capacity for heavy metals [30–33]. Dye adsorption by unmodified chitosan is good; but its low stability prompted researchers to modify/graft at amino, carboxyl, sulfur, and alkyl groups. Chitosan can be cross-linked with epichlorohydrin, ethylene glycol diglycidyl ether, glutaraldehyde, and tripolyphosphate to improve its sorption efficiency besides mechanical and physical properties. Chitosan alteration is best for adsorption of dyes, phenols, polycyclic aromatic, pesticide, herbicides, and metal ions. Metal cations are chelated specifically at protonated amines in acidic conditions whereas anions by electrostatic interactions. Chitinous adsorptive interaction includes partition, diffusion, chelation, trapping, scavenging, cation exchange, hydrogen bonding, Van der Waals force, dipole–dipole, and electrostatic interactions [29–33]. Quaternary tetra-alkylammoniumchitosans own permanent +ve charge at -OH/NH₂ to boost antimicrobial activity (at wide pH) in orthopedic, wound dressing in surgery, anion exchange cartridge, dental implants, colorimetric analysis, and perchlorate removal of water [9, 20]. Fe-chelated-chitosan granules found to promote selective fluoride sorption over chloride from water in defluoridation technique. Protonated polyamidoamine-grafted chitosan-Zr (IV) beads selectively removed fluoride than other ions in spontaneous and endothermic way [34]. Magnetic hydroxypropyl-chitosan multiwalled-carbon nanotubes adsorbs lead (II) from water. Chitosan-glutaraldehydenanofibers exhibited double adsorption capacity (than chitosan) for Cr (VI) removal from water. Chitosan-polyphenol-oxidase quinine nanobeads rapidly eliminate bisphenols from water [33]. Chitosan-pyruvic acid composites are found to adsorb Cd (II) from wastewater. Chitosan-modified soil cyanobacterial breakdowns harmful algae blooms and microcystins via flocculation and inhibiting algal cells and sequester liberate toxins to promote biodegradation [9]. Chitosan-doped sodium tripolyphosphate nanorods mitigate toxic Cr⁺⁶ from water via multilayer adsorption and consequent oxidation to ambient Cr⁺³ ions [34]. These chitosan-based commercialized viable adsorbents own peculiar characters like high specific surface area, low internal diffusion resistance, biodegradability, quantum size effect, ecofriendliness, versatility, low cost, and high adsorption capability and selectivity.

11.10. Chitosan in regenerative medicines

N-methacryloyl chitosan possesses desirable features like hydro-solubility, UV-cross-linkability, and injectability facilitating cell-loaded microhydrogels and quick transdermal curing *in vivo* needed in localizing/sustaining protein delivery [20]. Chitosan- α -tricalcium phosphate exhibited histocompatibility for Beagle mesenchymal stem cells without effecting cellular growth and proliferation, further manifesting efficacy by enhancing osteogenesis and vascularization to repair bone defects in conjunction with mesenchymal stem cells [12, 20]. Silk reinforced chitosan promotes redifferentiation of caprine chondrocytes and retained more glycosaminoglycan to improve aggregate modulus construction, which resembles with native tissues. Bone morphogenic protein-chitosan scaffolds burst sustainable drug release and biocompatibility which is necessary for cartilage tissue [9, 20]. Chitosan hollow tubes regenerate repair sciatic and damage phrenic nerves via improved diaphragm movement besides slow phrenic nerve transfer by granulation in beagle-dogs [12]. Cell encapsulated chitosan gels/porous chitosan fibrous matrix with biocompatible materials like CaPO₄, gelatin modifying biomechanical stiffness, and cell-matrix interaction properties. These chitosan adaptations

optimize cell/tissue differentiation and tailor transplantation to different clinical cell delivery by improving adherent ability for seeding cells to allow encapsulations.

11.11. Chitosan in obesity treatment

Chitosan dietary supplement/nutraceutical lowers serum cholesterol besides controlling obesity imparted to no digestion in our gastrointestinal tract. Chitosan gets swelled up to feel satiety by physically filling the stomach [9, 20] and inhibition of pancreatic lipase enzyme chitosan reduces dietary fat absorption in intestines. Chitosan precipitates fat in intestines via anionic binding with carboxyls of fatty/bile acids and hinder neutral cholesterol/sterol emulsification through hydrophobic interaction, thus it remains reduced/unabsorbed in GI tract for obesity and hypercholesterolemia treatments [35].

11.12. Chitosan in cardiovascular treatment

Chitooligosaccharides entry in gastric gavages of mice in the treatment of apo-lipoprotein-E deficiency along with high-fat diet feeding showed peculiar changes like lowered triglycerides and cholesterol, undermined atherosclerosis, increased atherosclerotic plaque stability, unregulated hepatic expression of low density lipoprotein receptor, macrophage scavenger receptor BI, and ATP binding cassette transporter-A1. But in wild mice with low density lipoprotein receptors deficiency and high cholesterol absorption found no change in plasma lipid levels of LDL-R. Chitooligosaccharides aid in hypercholesterolemia, i.e., remove low-density lipoprotein (LDL) oxidized products: cholesterol which causes coronary atherosclerosis as toxic for endothelial cells. Chitosan increase binding of LDL to endothelium and smooth muscle by mediating inflammation such as TNF- α , IL-1, and macrophage colony-stimulating factors. Hypocholesterolemic effect lowers lipid and media-milled chitosan treatments found to decrease serum triacylglycerol, total, and LDL cholesterol which is highest than pure chitosan. The elevated serum cholesterol causing cardiovascular diseases, since 10% blood cholesterol reduction using chitosan consumptions reduces the risk of coronary heart disease by 30%.

11.13. Chitosan in aging treatments

Degenerative aging diseases like cardio-/cerebrovascular, diabetes, osteoporosis, and cancer are common in old people that are diet-affected [9]. Old people show deficiency of Zn, Fe, Se, Cu-metals, Vit-A, B, C, and E, which impacts immune responses or impair immunity. But chitosan-ascorbate can compensate such deficit and thrust neutrophils, NK/NKT/dendritic cell, monocyte/macrophage, and mediate initial pathogen interactions link to compromise signal transduction T cells pathway and gut microbiota homeostatic regulation to reduce low-grade inflammation in age-related diseases via triggering intestinal activity. Chitosan oligosaccharides used as functional food and aging disease therapy/treatment, pathophysiology via affecting oxidative stress, low-density lipoprotein oxidation, enhance tissue stiffness, govern protein conformational changes, and chronic inflammations [9, 20, 35].

11.14. Chitosan in mucosal immunity enhancer

Chitosan -C48/80 nanoparticle carried Bacillus anthracis protective antigen in mice have produced elevated serum titers of antibodies against protective antigen and a more balanced Th1/Th2 pattern than mere C48/80 solution and nanochitosan/alginate – C48/80 composite. C48/80 within chitosan found to promote a stronger mucosal immunity than other adjuvant groups indicating action in concert with a mast cell activator to affect nasal immunity [9, 20].

11.15. Chitosan in dry mouth syndrome therapy

Chitosan-thioglycolic-mercaptocotinamide conjugates are nontoxic and are useful against Caco-2 cells that remarkably improved swelling and cohesive characteristics that are promising for dry mouth syndrome therapy where lubrication and mucoadhesiveness of mucosa is needed [9, 12, 20] than that of unmodified chitosan. About 10% of older people have dry mouth syndrome/xerostomia, i.e., not enough saliva/spit in the mouth. Treatment of dry mouth syndrome includes chitin-based products that moisten the mouth, e.g., electrospun chitosan fibers decrease microorganisms, molds, yeast, to yield lighter appearance, and less muscle denaturation in comparison with traditional dryageing. Test disks were compressed out of unmodified chitosan-TGA (thiomers) and/or TGA-MNA conjugates to investigate cohesive properties, cytotoxicity assays, and mucoadhesion studies. Immobilized-MNA achieved higher swelling and cohesion for chitosan-TGA-MNA conjugates compared to unmodified chitosan. Preactivated chitosan thiomers exhibited higher stability among all conjugates and nontoxic against Caco-2 cells.

11.16. Chitosan in gene silencing in disease vector mosquito larvae

The vector mosquitoes inflict diseases in humans, such as malaria, dengue, and yellow fever, which cause death of more than one million people per year compared to any other living organism. RNA interference mediated gene silencing/targeting the interested/responsible gene for disease using chitosan nanoparticles combined with food and ingested by larvae. Thus, a technically straightforward, high-throughput, and cheap methodology is compatible for mosquitoes, insects, agricultural pests, and nonmodel organisms deals with long double-stranded/small interfering RNA. Chitosan nanofibers can potentially inhibit gene functions in disease vector mosquitoes ingested by larvae when mixed with food [12, 20]. Chitosan/siRNA nanoparticles used to target semaphorin-1-a during olfactory system development in dengue and yellow fevers arise by vector *Aedes aegypti* mosquitoes. Chitosan/AgCHS-dsRNA-basenanocrystals own repression of AgCHS-1 and AgCHS-2 chitin synthase genes via feeding larval in *Anopheles gambiae*.

12. Conclusion

Chitin or chitosan has distinctive biological/physicochemical properties and are researched in the fields of biotechnology, medicine, cosmetics, food technology, and textiles. Marine crabs,

lobsters, shrimps, and mollusks are a resource of chitin as well as arthropod, crustacean, fungi, yeasts, algae, and squid pen exoskeletons. Comparatively, chitosan is a widely used in various industries, viz., biochemical, food, drugs, as dietary fiber, wastewater treatments, surgical threads, wound healing, immune response to allergy, plant immune inducer/defense against pathogens, and is also used in antimicrobial, anticholesterol, and antitumor activities. Chitosan alteration/designing via tissue engineering is also used in various areas such as bone scaffold, drug delivery, wound healing, and metal/dye absorbents. The marine crustacean shells are rich chitooligosaccharides with calcium carbonate (20–50%), proteins (20–40%), and chitin (15–40%), contents that can be separated by using an integrated biorefinery with mechano/chemical processes for their distinct uses. This chapter presents a variety of chitooligosaccharides with specific characteristics, such as skeletal modifications, biocompatibility, and antimicrobial and antiinflammatory activities, in relation to possible solution properties.

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