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MINI-REVIEW

Implications of molecular diversity of chitin and its derivatives

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Abstract Chitin is a long unbranched polysaccharide, made up of β-1,4-linked *N*-acetylglucosamine which forms crystalline fiber-like structure. It is present in the fungal cell walls, insect and crustacean cuticles, nematode eggshells, and protozoa cyst. We provide a critical appraisal on the chemical modifications of chitin and its derivatives in the context of their improved efficacy in medical applications without any side effect. Recent advancement in nanobiotechnology has helped to synthesize several chitin derivatives having significant biological applications. Here, we discuss the molecular diversity of chitin and its applications in enzyme immobilization, wound healing, packaging material, controlled drug release, biomedical imaging, gene therapy, agriculture, biosensor, and cosmetics. Also, we highlighted chitin and its derivatives as an antioxidant, antimicrobial agent, anticoagulant material, food additive, and hypocholesterolemic agent. We envisage that chitin and chitosan-based nanomaterials with their potential applications would augment nanobiotechnology and biomedical industries.

Keywords Polysaccharide · Chitosan · Chitinase · Chitin · Pharmaceutical materials · NanobiotechnologyFaez Iqbal Khan, Safikur Rahman, and Aarfa Queen contributed equally to this work.

Introduction

Chitin has emerged as an essential polymer with its ever growing use in pharmaceutical, cosmetic, biomedical, and food industries (Kobayashi 2007; Mano et al. 2007; Yang 2011). Chitin deposition is essential for fungal growth and molting in arthropods (Lenardon et al. 2010). Biosynthesis of chitin is based on the membrane-bound synthase enzymes which incorporates the UDP-*N*-acetylglucosamine from the cytosol to its nascent chain that is extruded outside the membrane (Martínez et al. 2001). Chitin-hydrolyzing enzymes such as chitinases regulate the biochemical and biophysical modes of action in a number of eukaryotes. Chitinolytic bacteria are active in scavenging or degrading a massive amount of chitin in marine and soil biomass, averting its accumulation and favoring its utilization as a renewable source of biomaterial (Khan et al. 2015a, b). Chitin is found in the cell walls of fungal mycelia and other invertebrates like crustaceans (Kurita 2006), and is considered to be a structural material (Azuma et al. 2015b).

Chitin has been used frequently as a potential biomaterial, but recently, several newer applications have emerged (Kaur and Dhillon 2014). Chitin, chitosan, and their derivatives are beneficial in wound healing (Azuma et al. 2015b; Thadathil and Velappan 2014), tissue regeneration, and cell culture, and as antimicrobial and dermal protection agents (Muzzarelli

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et al. 2014). Ngo and Kim (2014) suggested the roles of chitin, chitosan, and their derivatives for therapeutic purposes such as anti-inflammatory, antioxidant, antihypertensive, anticoagulant, antitumor, anticancer, antimicrobial, hypocho lesterolemic, and antidiabetic effects extending the applications from biophysical to biomedical areas.

With increasing knowledge of molecular diversity based on structural analysis and chemical modifications of chitin, chitosan, and their derivatives having newer applications for human welfare, a comprehensive literature survey is required, (Alves and Mano 2008; Hayes et al. 2008; Jain et al. 2013; Jayakumar et al. 2010; Park and Kim 2010; Prabaharan 2008; Prashanth and Tharanathan 2007). This review focuses on available data and elucidates industrial and biomedical applications of chitin and its derivatives.

Chemical structure

Chitin is an unbranched polymer of 2-acetamido-2-deoxy-D-glucopyranose (Fig. 1a). The chemical structure of chitin is regarded as a homopolymer but it does not exist in this form in nature (Hoffmann et al. 2010). The chitin crystal structure is composed of individual chains associated by C=O and H-N-groups forming hydrogen-bonded sheets. In addition, each chain involves intramolecular hydrogen bonding between the carbonyl group and the hydroxyl group on C_6 of neighboring sugar rings. Another hydrogen bond exists between the ring oxygen and the OH-group on C-3, similar to that observed in cellulose (Minke and Blackwell 1978). This hydrogen bonding accounts for the stiffness of the chitin chain (Fig. 1b).

Chitin possesses a highly ordered, crystalline structure and exists in three polymorphs, namely α, β, and γ (Hackman 1954; Hackman and Goldberg 1965). These variants differ in packing, size of the unit cell, number of chitin chains per unit cell, their degree of hydration, and polarities of adjacent chitin chains in successive sheets (Fig. 2) (Aam et al. 2010; Chen et al. 2010). Chitins have several functional groups which are available for chemical reactions. The sites on which chemical modifications can be done are illustrated in Fig. 3. It is interesting to note that –OH groups of chitin are the second essential function after $–NH_2$.

Natural forms of chitin

Chitin is the second most abundant biopolymer and aminopolysaccharide available in nature (Chandy and Sharma 1990; Synowiecki and Al-Khateeb 2003). In animals, chitin mainly exists in the shells of mollusks and crustaceans, in the backbone of squids, and in the cuticle of insects (Heath-Heckman and McFall-Ngai 2011). Calcium carbonates are deposited into the network contributing to the strength of the shells and the protection of the organism (Ghatak et al. 2013; Rahman and Halfar 2014).

α-Chitin is the most predominant form and is isolated from the exoskeletons of crustaceans, particularly shrimps and crabs. It is also found in fungal and yeast cell walls and in insect cuticles (Carlstrom 1957). β-Chitin is comprised of

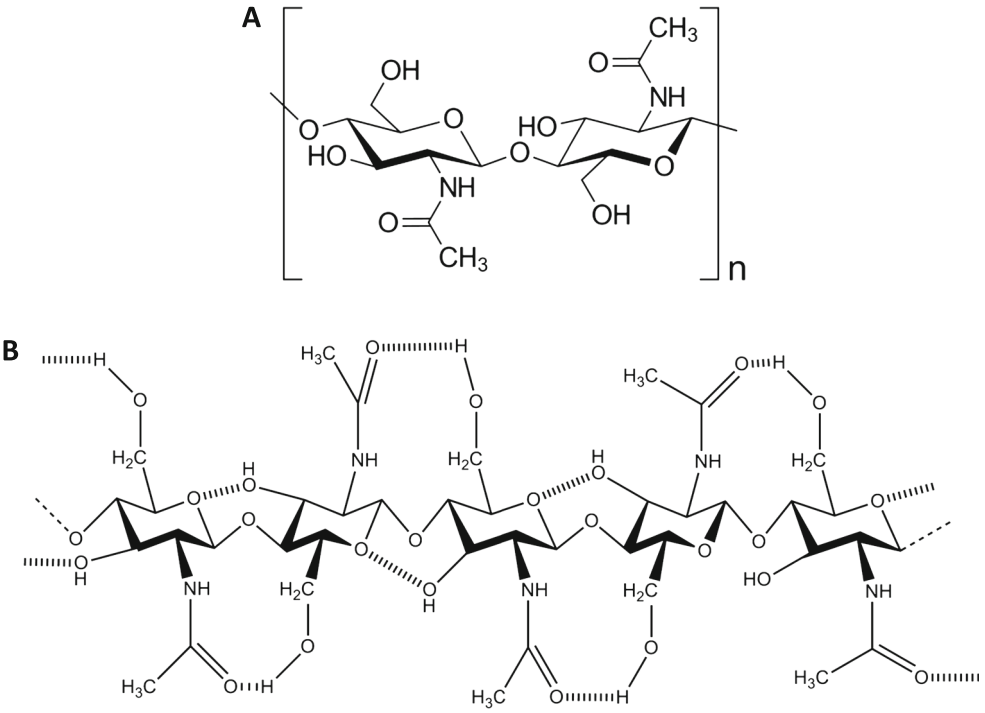


Fig. 1 **a** Primary structure of chitin. **b** Structure of chitin depicting its intramolecular hydrogen bonds between the neighboring sugars rings in chitin (source: https://commons.wikimedia.org/wiki/File:Chitin.svg)

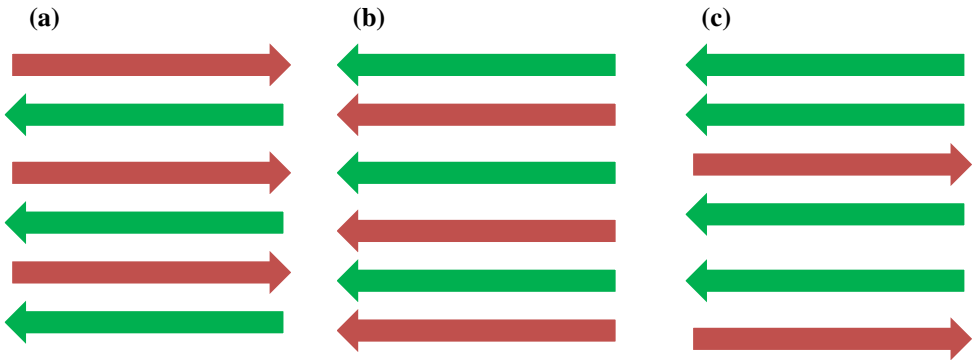


Fig. 2 Schematic representation of the three polymorphic forms of chitin: **a** α-chitin, **b** β-chitin, and **c** γ-chitin

parallel chain and its more reactive form possesses higher affinity for solvents (Kumirska et al. 2010; Park et al. 2015). In γ-chitin, two out of three chitin chains are arranged in parallel while the third one is oriented in the opposite direction. The γ-chitin is considered to be a combination of α and β structures. α-Chitin provides hardness (Deguchi et al. 2015), but β- and γ-chitin are meant for toughness, flexibility, and motility (Kaya et al. 2015; Ospina Alvarez et al. 2014). The extensive intermolecular hydrogen bonding explains the inability of α-chitin to swell upon soaking in water (Minke and Blackwell 1978), whereas β-chitin readily swells in water as it lacks these interchain hydrogen bonds (Blackwell 1969).

Chitin bears a crystalline structure and constitutes a network of systematic arrangement of fibers of sponges of phylum Porifera. Ehrlich et al. (2007) found that these fibers are arranged in layers with specific compositional variations in the composite of chitin/silica. They demonstrated that α-chitin is an important component of the skeletal structures of glass sponges. *Aplysina fistularis* of class Demospongiae is studied recently for having α-chitin in the skeleton scaffold by chitinase digestion test. Wysokowski et al. (2013a) studied nanostructured chitin scaffolds as a highly optimized structure. They found that *A. fistularis* act as filtering systems, for biomineralization and metallization which can be used in the production of novel biocomposite for tissue engineering (Wysokowski et al. 2013a).

Chitin acts as an important structural component of holdfasts of the endemic freshwater demosponge, *Lubomirskia baicalensis*. The chitin from the holdfast of *L. baicalensis* resembles more to α-chitin than to β-chitin. The chitinous holdfast is the oldest part of the sponge body (Ehrlich et al. 2013).

In another sponge *Ianthella basta*, a demosponge is composed of a composite material containing chitin-based

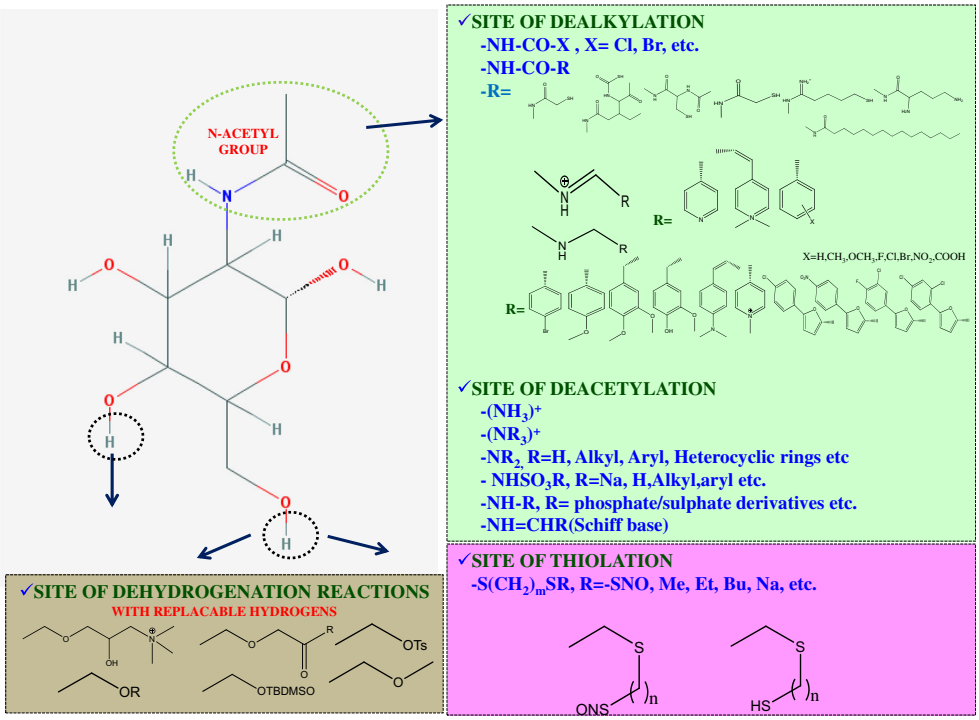


Fig. 3 Sites for chemical modifications in chitin

scaffold. Using isolation and purification technique based on treatment with alkaline solutions, these chitin-based scaffolds are isolated from the sponge skeletons. The spectroscopic signature of these chitin-based scaffolds in this sponge is closer to that of α-chitin than β-chitin. These fibers consist of loosely packed chitin with rough and deeply fissured surfaces. Since the chitin processing is difficult, the chitin-based sponge scaffolds may be of interest for various useful applications (Brunner et al. 2009).

Chemical properties

Chitin is a biopolymer having a linear structure and is water insoluble. It is soluble in concentrated acids and in some fluoro alcohols. Chitin is composed of 7 wt% biologically fixed nitrogen and useful in the synthesis of N-containing compounds. Upon pyrolysis (thermochemical decomposition at high temperatures) or radiolysis of chitin/chitosan, it results in the formation of volatile aromatic heterocyclic compounds such as pyridines, pyrroles, pyrazines, and furans (Chen et al. 2014; Einbu and Varum 2008; Kaczmarek and Zawadzki 2010). Due to its tough crystal structure having extensive inter- and intrahydrogen bonds within the polymer chains like cellulose, its conversion to form new derivatives holds immense possibilities (Fan et al. 2013).

Derivatives synthesized from chitin after chemical modifications are listed in Table 1. A number of phenylaminocarbonyl or benzoyl substituted chitosan were synthesized by Senso and Oliveros (1999). Hydrophilic modification to chitosan backbone has been employed for improving transfection efficiency for increasing water solubility at physiological pH (Wang et al. 2014). Recently, *N*-(2-(*N*,*N*,*N*-trimethylammoniumyl)acetyl)-chitosan chloride and *N*-(2-(1-pyridiniumyl)acetyl)-chitosan chloride derivatives are synthesized which have improved biological properties (Sahariah et al. 2014). Nitric oxide-releasing derivatives of chitin and chitosan were synthesized through conjugation of the symmetrical dithiols 1,2-ethanedithiol, 1,3-propanedithiol, and 1,6-hexanedithiol for biomedical applications (Lutzke et al. 2014). Apart from this, major derivatives of chitosan which possess unique properties and application are provided in Table 1 in detail.

Chitin is an inert biorenewable and biodegradable polymer having exceptional structural and functional properties (Table 1). Chitin forms microfibrillar arrangements in living organism. The hydroxyl and amino functional groups present in chitin and chitosan show significant adsorption capacity. This property of chitin is used in the removal of aqueous pollutants (Bhatnagar and Sillanpaa 2009). Chitosan membranes are used as artificial kidney owing to their mechanical strength, urea, and creatinine permeability. These act both as permeable and impermeable components to serum proteins, thus proving to be better hemodialysis membranes (Mollison and Graydon 1977). Chitosan and its derivatives are used as drug carriers because of membrane thickness, controlled release by changing the pH, and are sensitive to bile, urine, and pancreatic juices.

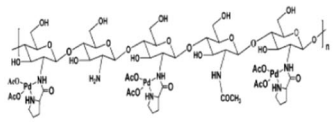
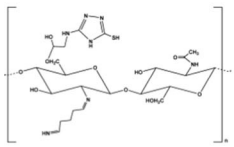
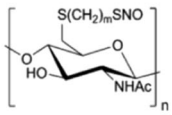
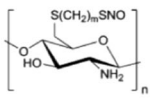
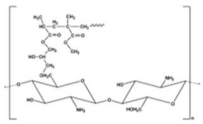
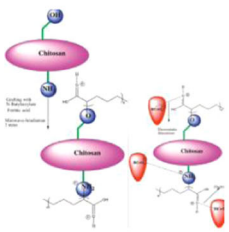
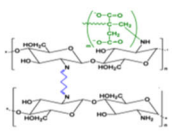
Chitin after deacetylation in alkaline medium or chitin deacetylase enzyme results in the production of chitosan. Chitosan is hydrophobic in nature and is employed for the construction of nanoparticles (NPs) by using simple methods instead of harmful organic chemicals. The chitosan NPs possess enhanced absorption properties, useful for site-specific drug delivery (Rajitha et al. 2016; Xue et al. 2015). In recent years, a large number of chemical modifications of chitosan are performed to improve its solubility and its enhanced applications. Chemical derivatization includes introducing small functional groups such as alkyl, carboxymethyl, hydroxyl, etc., to the chitosan structure (Alves and Mano 2008).

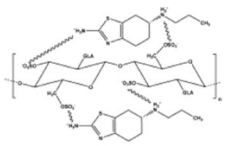
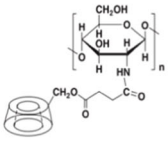
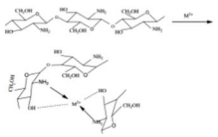
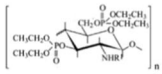
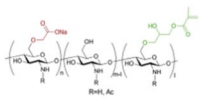
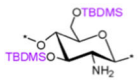
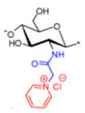
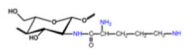
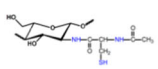
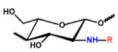
Immobilized silver NPs have been synthesized by the reduction of silver ion under microwave-assisted conditions in the presence of chitin nanocrystals (CNC). Due to exceptional surface properties of these immobilized silver nanoparticles (Ag NPs), they bear significant antimicrobial properties (Li et al. 2016b). Chitin nanofibers offer tensile properties, water vapor permeability, swelling solubility, and color properties of the silver NPs. Chitin nanofibers are used to improve the mechanical properties of silver NPs (Jafari et al. 2016).

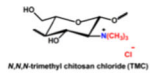
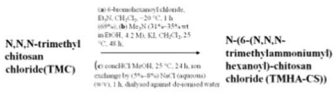
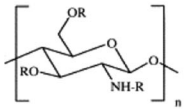
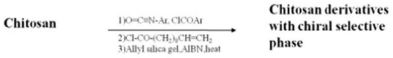
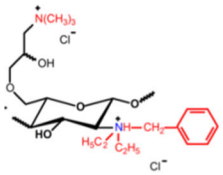
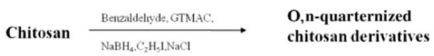
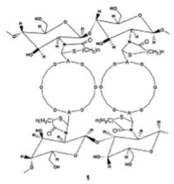
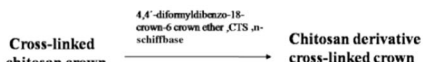
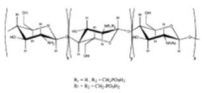
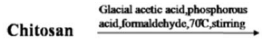
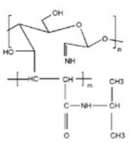
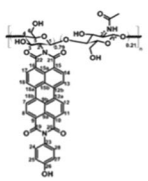
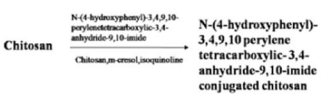
Bare gold NPs prepared by reducing gold solution through sodium borohydride were surface coated with chitosan through adsorption by incubating these gold NPs with chitosan. With the help of L-phosphatidyl choline and cholesterol, liposomes loaded with vancomycin were prepared using vesicular extrusion techniques. These gold NP-stabilized liposomes release the encapsulated vancomycin in 24 h in the presence of methicillin-resistant *Staphylococcus aureus* bacteria. The bacterial toxin leads to the release of drug from NP-stabilized liposomes which is an effective approach for the treatment of bacterial infections (Pornpattananangkul et al. 2011).

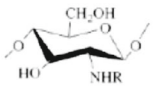
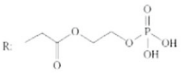
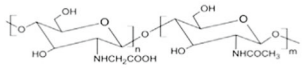
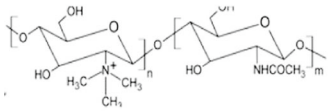
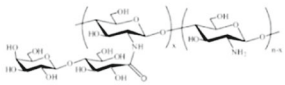
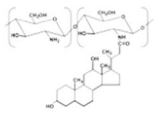
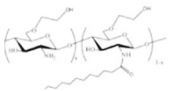
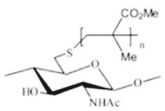
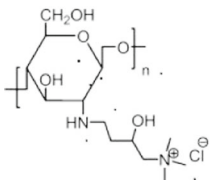
Chitin and chitosan are used in bioremediation. Novel processing for chitin and chitosan using the ionic liquid 1-butyl-3-methyl-imidazolium chloride was done for fixing CO_2. Chitin and chitosan solutions are efficient medium for reversible fixing of carbon dioxide and used in gas sensing and industrial exhaust management (Xie et al. 2006). Chitin nanofibers were synthesized by electrospinning chitin directly from an extract solution of shrimp shell. This method helps in the production of chitin fibers having high surface area and the ability to separate chiral compounds (Barber et al. 2013). The nanofibers of chitin transport the D-isomer of glutamic acid, phenylalanine, and lysine across the membrane from the

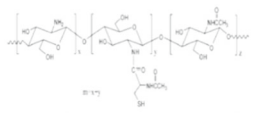
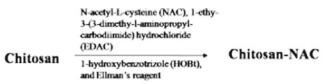
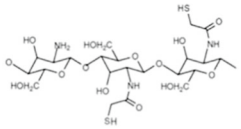
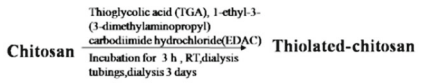
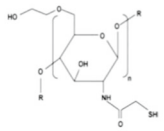
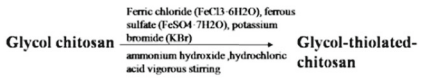
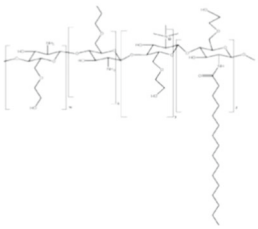
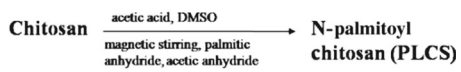
Table 1 Structures of chemical derivatives of chitin and their applications

S. no.	Derivatives	Scheme of synthesis	Application
1.		Chitosan —(Methyl prolinate, $Pd(OAc)_2$)→ Pd(II) functionalized proline chitosan	Heterogeneous catalyst in suzuki cross coupling reaction in organic chemistry
2.		Chitosan —(Glutaralddehyde, NH_4OH; resin based)→ Chitosan resin	Dye adsorbtion
3.		Chitin —(i) TsCl, TEA in DMA/LiCl, 24 h, 5 °C; (ii) $HS(CH_2)_mSH$ (where methylene units, *m*, are 2, 3, or 6), TEA in DMA/LiCl, 20 h, 60 °C, DTT, TEA in DMA, 1 h, RT.→ Thiolated chitin derivatives	Mucoadhesive properties, drug delivery, coating for stents
4.		Chitosan —(i) Phthalic anhydride in DMF, 8 h, 120 °C, (ii) TsCl, TEA in DMA/LiCl, 24 h, 5 °C; (ii) TsCl, TEA in DMA/LiCl, 24 h, 5 °C, (iii) $HS(CH_2)_mSH$, TEA in DMA/LiCl, $H_2NNH_2{\cdot}H_2O$, 5 h, 80 °C, TCEP·HCl in 1% AcOH, 1 h, RT→ Thiolated chitosan derivatives	Mucosal drug delivery system
5.		Chitosan —(i) Deacetylation,addition of bentonite, (ii) Addition of quarternary salt solution with strong stirring→ Chitosan grafted poly(methyl methacrylate)	For controlled release of ampicillin
			Removal of Cu(II) and Ni(II) from aqueous solutions
6.		Chitosan —(i)$ClCH_2COONa$,pH=7; (ii)CS_2,NaOH→ Xanthate carboxymethyl grafted chitosan	
			Absorption of chromium released from tannery
7.		Chitosan —(i) Grafting with n-butylacrylate formic acid,microwave irradiation 3 minutes; (ii)Electrostatic interaction with Cr(VI)→ Chitosan, *n*-butylacrylate and chromium(VI)	
			Adsorption of Pd(II) and Cd(II)
8.		Chitosan —(i)Cross linking glutaraldehyde; (ii)Grafting itaconic acid→ Poly(itaconic acid)-grafted chitosan	Environmentally adsorbent, drug delivery

9.		Chitosan —(i)Cross linking glutaraldehyde; (ii)Grafting with sulfonate groups (CsSLF) or *n*-(2-carboxybenzyl) groups (CsNCB)→ **Interactions between 2 molecules of pramipexole and chitosan grafted sulfonate group(CsSLF)**	
10.		Chitosan —(a) Phthalic anhydride, DMF, 130 °C, 15 h; (b) trityl chloride, pyridine, 100 °C, 20 h; (c) hydrazine, H2O, rfx. 20 h; (d) 6-monosuccinyl-β-CD, DCC, DMAP, DMF, r.t., 20 h; (e) Cl2CHCOOH→ **Cyclodextrin–chitosan adducts.**	Mask bitterness in food and drugs
11.		Chitosan —(i)Deacetylation,depolymerisation→ **Chitosan metal complexes**; (ii) Addition of metal ions (1 mole metal ions per 1 mole amine group of chitosan)	Antimicrobial agent
12.		Chitosan —(i) Mixed and stiorred with 45% NaOH→ **Chitosan alkyl phosphate**; (ii) Treated with Diethylchlorophosphate,stirred for 24 hr,washed with ether and dialysed in water	Textile membranes, medicinal aids
13.		Deacetylated Chitin —(i)Water,methanol,overnight stirring; (ii) 5.8 mole CH_3COOH,stirring,acetone,centrifugation, Glycidyl methacrylate (0.94 g), stirring for 24 h at room temperature→ **2-hydroxy-3-methacryloyloxypropylated carboxymethyl chitin (HMA-CM-chitin)**	Quick adhesion and induction of inflammatory cells
14.		Chitosan —(i) Mesylated,$MeSO_3H$; (ii) TBDMSCl,imidazole,dry DMSO→ **Di-tertbutyldimethylsilyl-chitosan**	Enhance aqueous solubility and biological activity
15.		Chitosan —((i)a) $MeSO_3H/H_2O$ (1:1), 10 °C, 1 h (90%); (b) tert-butyl-dimethylsilyl chloride (TBDMSCl), imidazole, DMSO, 25 °C, 24 h (96%); (c) bromoacetyl bromide, Et3N, CH_2Cl_2, −20 °C, 1 h (92%); (ii) (e) pyridine, 25 °C, 24 h; (f) conc HCl/MeOH, 25 °C, 24 h, ion exchanged by (8%) aqueous NaCl (w/v), 1 h, dialysed against de-ionised water, 48 h→ **N-(2-(1-pyridi(niumyl)acetyl)-chitosan chloride (PyA-CS) derivative**	Antimicrobial and dug delivery
16.		Chitosan —((i)a) $MeSO_3H/H_2O$ (1:1), 10 °C, 1 h (90%); (b) tert-butyl-dimethylsilyl chloride (TBDMSCl), imidazole, DMSO, 25 °C, 24 h (96%); (c) bromoacetyl bromide, Et3N, CH_2Cl_2, −20 °C, 1 h (92%); (ii) (d) Me_3N (31%–35% wt in EtOH, 4.2 M), CH_3CN, 25 °C, 12 h; (f) conc HCl/MeOH, 25 °C, 24 h, ion exchanged by (8%) aqueous NaCl (w/v), 1 h, dialysed against de-ionised water, 48h→ **N-(2-(N,N,N-trimethylammoniumyl)acetyl)-chitosan chloride (TMA-CS)**	Antimicrobial properties
17.		Chitosan —EDC/NHS,Arginine,MES buffer→ **Chitosan/arginine(CHT/ARG)**	Antimicrobial against gram negative
18.		Chitosan —EDAC/NAC→ **Chitosan/N-acetyl L cysteine(CHT/NAC)**	Mucoadhesive, eye drops, immunusuppresive
19.		Chitosan —NaOH,heat,R-X,X=Cl,Br,I→ **N-substituted chitosan**	Mucoadhesive, enhanced absorption, drug delivery

20.			Drug delivery, tissue engineering
21.			TLC separation layer
22.			Catalysis, antibacterial
23.			Adsorption of silver ions for antibacterial properties
24.			Enhanced solubility in water
25.			Dual stimuli responsive polymeric system used as delivery vehicles that can respond to pH, temperature conditions in vivo
26.			Photophysical and electrochemical properties, useful in medical and pharmaceutical and drug carrier application
27.			Antipolyelectrolyte effect and electrolyte effect, separation and purification of anionic proteins and pharmaceutical formulations

28.	 where 	Chitosan —(MAEP, phosphorus acid; acid aqueous solution)→ **Phosphonate functionalized chitosan**	High nerve cell affinity, good substratum for neuro-2a cells, modified drug delivery, apoptosis
29.		Chitosan —($BrCH_2COOH$,NaOH,iPrOH; AcOH)→ **Carboxy methyl chitosan**	Antibacterial activity, improved aqueous solubility
30.		Chitosan —(CH_3I,NaOH,NaI,NMP; NaCl)→ **N,N,N-trimethyl chitosan**	Gene delivery tool, drug delivery application
31.		Chitosan —(EDC,NHS,RT; Lactobionic acid,72 hr)→ **Galactosylated chitosan**	DNA delivery carrier, drug delivery application
32.		Chitosan —(Deoxycholic acid,EDC, 24 hr, NHS,RT; Methanol /ammonia solution,washed with methanol/ether)→ **Deoxycholic acid-modified chitosan (DAMC)**	Polysoap for drug delivery, delivery of hydrophobic drugs
33.		Glycol chitosan —(Palmitic acid n-hydroxy succinide ester)→ **Palmitoyl glycol chitosan**	Initiate graft copolymerization
34.		Chitin —(1.TsCl,Ac_2O,2.KSAc,NaOMe, 3.CO_2Me,DMSO)→ **MMA mercaptochitin graft**	Tissue engineering, wound dressing, drug delivery, drug diagnosis
35.		Chitosan —(O/W/O double emulsion, temperature-programmed solidification)→ **PTX-loaded CS nanoparticle (CS-NP:PTX)**	High loading efficiency, tumor inhibition, apoptosis

36.			Nasal absorption enhancement of insulin
37.			Mucoadhesive properties for biomedical applications
38.			Pulmonary delivery of calcitonin
39.			Stabilize liposome containing anti-tumor drug

racemic amino acid mixtures easily as compared to L-isomer (Ifuku and Saimoto 2012). Porous chitin-based materials were prepared by processing chitin using ionic liquid (1-butyl-3-imidazolium acetate) together with supercritical fluid technology. The formation of porous chitin structures serves as potential candidates for various biomedical applications (Silva et al. 2011).

Chitin is produced employing green solvents from biomaterials. The synthesis of such crystalline chitin films offers various applications fulfilling the requirement of a well-defined crystalline structure (Ramírez-Wong et al. 2016). Good solubility maximizes its utilization in biorefinery and "green processing" of the biopolymer for industrial applications (Sharma et al. 2013).

Chitin polymorphism and its functional attributes

Chitin serves as a new route for the production of a large number of bioinorganic composite materials which bear electrical, chemical, and mechanical properties (Wysokowski et al. 2015). The industrial uses of chitinous materials are mainly due to its chemical characteristics like high nitrogen content and unique biological properties, rather than its power to develop structural composites with novel mechanical properties (Fernandez and Ingber 2013). Chitin is found as α- and β-forms (Hajji et al. 2014). A third allomorph, chitin, has also been reported (Jang et al. 2004).

Thermally induced transition between anhydrous and hydrated forms of α-chitin was studied by differential thermal calorimetry and X-ray diffraction. At elevated temperature, α-chitin showed corresponding changes in d-spacing of chitin molecules. Thus, it is concluded that water is reversibly incorporated into the α-chitin crystal and that the temperature change induces transitions between anhydrous, monohydrate, and dihydrate forms (Saito et al. 2002). Water microdrops of about 50 μm in diameter, generated by an ink-jet system, have been used to hydrate fragments of Pogonophora tubes. X-ray microdiffraction with a beam size of 10 μm was used to follow the structural transformations that affected the crystalline α-chitin part of the specimens.

Whether the sheet-like hydration of α-chitin is likely to progress readily in a wedge-like fashion between chitin sheets, a more complicated system must occur in the columnar case. Setting aside hydration processes in solids, ink-jet technology in combination with μXRD or micro-X-ray small-angle scattering could find multiple other applications including fast mixing processes of microdrops (Rössle et al. 2003). With the help of X-ray diffraction, it was demonstrated that α-chitin formed an inclusion complex. α-Chitin complexes are developed by using cultured diatom specimen including the strong action of aliphatic amines. These complexes are used to develop novel materials and industrial processes (Noishiki

et al. 2003). Since α-chitin is selective for various amines, therefore, it forms a complex with high melting point compounds as intercalating uptake of small molecules by α-chitin has specific selectivity for guest species. This wide variety of guest species is useful in various applications like drug delivery or composite material preparation, practical applications such as template polymerization, composite material processing, or biomedical materials (Noishiki et al. 2004).

α-Chitin seems like a layered crystal, having stacked molecular sheets. It is formed of parallel chain that is firmed by intermolecular amide hydrogen bonding. A crystallosolvate is formed by insertion of small guest molecules (acrylic acid) between the molecular sheets. It is also useful in pharmaceuticals (Saito et al. 2007). β-Chitin is isolated from the bathophilous tubeworm *Lamellibrachia satsuma* and complexed with ethylene diamine. The complexed ethylene diamine molecule has a trans conformation. Ethylene diamine is an important reagent for studying the interactions between chitin complexes as it is liquid at ambient conditions (Sawada et al. 2013).

Intercalation complexes are formed by α-chitin with aliphatic alcohols, carboxylic anhydrides, and amines. Esterified chitin derivatives are prepared by treating these complexes at different temperatures which are useful in studying regioselectivity (Mine et al. 2009; Yoshifuji et al. 2006). Bathophilous tubeworm *L. satsuma* is used to obtain the complete crystal structure of dihydrate β-chitin through high-resolution X-ray and neutron fiber diffraction. It was found that two water molecules per *N*-acetylglucosamine residue are present in the structure and participate in hydrogen bond formation (Sawada et al. 2012).

Industrial production

The annual biosynthesis of chitin is estimated to be approximately 100 billion tons (Synowiecki and Al-Khateeb 2003b). The cuticles of various crustaceans obtained as a by-product in the seafood industry serve as the major source of raw material for industrial-scale production of chitin. Crustacean chitin is closely associated with protein, lipid, mineral, and pigments. The extraction process involves three basic steps: demineralization for removal of calcium carbonate, deproteinization for removal of protein, and decoloration for removal of pigments (Teng et al. 2001). Demineralization is generally carried out with 0.275–2.0 M HCl at a temperature of 0–100 °C for 1–48 h (Huang et al. 2005; Xu et al. 2013; Younes and Rinaudo 2015). Deproteinization is performed using 1.0 M NaOH for 1–72 h at 65–100 °C (Lodhi et al. 2014), and decoloration is attained by ethanol, acetone, or hydrogen peroxide (Laurienzo 2010).

Chitin production from fungal mycelium has increased due to significant advantages. Seafood waste supplies are limited by seasons and sites of the fishing industry, whereas fungal mycelium can be obtained easily by fermentation without any geographic or seasonal limitations (Cano-Canchola et al. 1992). Similarly, fungal mycelia contain lesser inorganic materials compared to crustacean wastes, thus requiring no demineralization treatment during the processing (Calonje et al. 2000). Apparently, fungal chitin is more effective in inducing the plant immune response and is a better candidate for agricultural application (Gramany et al. 2016; Khan et al. 2015a, b; Stephens et al. 2014; Wiesel et al. 2014).

Various enzymatic procedures for mold mycelia and deproteinization of the shells or for chitin deacetylation were also studied (Synowiecki and Al-Khateeb 2003a). Functional chitosomes from five diverse genera, namely: *Zygomycetes*, *Chytridiomycetes*, *Hemiascomycetes*, *Ascomycetes*, and *Basidiomycetes*, and three distinct developmental forms: hyphae, yeast cells, and basidiocarp demonstrate that chitosomes are the cytoplasmic mechanism. This reveals that chitin synthetase lies at the sites of microfibril assembly at the fungal cell surface. Thus, these can be harnessed for the production of chitin (Bartnicki-Garcia et al. 1978). 1-Ethyl-3-methyl-imidazolium acetate is used for the complete dissolution of raw crustacean shells. This leads to the recovery of a high purity, high molecular weight chitin powder (Qin et al. 2010). Chitin oligomers are prepared chemically by acid hydrolysis (Defaye et al. 1994; Rupley 1964). The conventional procedure of isolation is as follows: acid hydrolysis, neutralization, demineralization, charcoal-celite column fractionation, HPLC fractionation, and lyophilization (Takahashi et al. 1995). Defaye et al. (1994) had done fluorohydrolysis of chitin in anhydrous hydrogen fluoride that leads to the formation of chitin oligomers (Jeon et al. 2000).

Biotechnological applications

Chitin, both in its native and modified forms, exhibits a wide range of application in food industry, biotechnology, agriculture, drugs and pharmaceuticals, environmental science, and gene therapy (Prashanth and Tharanathan 2007). Because of its biocompatible nature, chitins are employed in the treatment of cancer and other lethal diseases and as artificial skin implants, as well as in ophthalmology, food engineering, and metal capture from wastewater (Table 1). Chitosan ascorbate is used for the treatment of periodontitis for reducing depth and tooth mobility and is synthesized by chitosan ascorbate gel (Muzzarelli et al. 1989). Chitosan-bonded hydroxyapatite is used as bone-filling paste and N-carboxybutyl chitosan is used for repairing meniscal lesions (Muzzarelli et al. 1993) and in the manufacturing of contact lens. N-

Table 2 Biotechnological applications of chitin, chitosan, and its derivatives

S. no.	Application	Forms	References
1.	Enzyme immobilization	Chitin	Wang et al. (2013)
		Naturally derived chitosan	Yong et al. (2015)
		Chitosan-grafted hydrogels	Facin et al. (2015)
		NPs	Deveci et al. (2015)
2.	Antioxidant	Chitin	Ngo and Kim (2014)
		Chitosan derivatives	Woranuch et al. (2015)
			Xie et al. (2014)
3.	Wound healing	Chitosan nanocomposites	Vedakumari et al. (2015)
		Bioglass-chitosan	Jebahi et al. (2015)
4.	Packaging material	Chitin/chitosan-derived films	Carneiro et al. (2015)
		Nanocomposite	Babul Reddy et al. (2015)
5.	Controlled drug release	CM-chitin	Wang et al. (2011)
		Chitosan derivatives	Rajitha et al. (2016)
		Nanocomposite	Ordikhani et al. (2015)
		Chitosan NPs	Assa et al. (2016)
6.	Biomedical imaging	Echo-CNPs	Min et al. (2015)
		Chitosan NPs	Scheeren et al. (2016)
7.	Antimicrobial property	Chitosan derivatives	Bigucci et al. (2015)
		Chitosan NPs	Tang et al. (2015)
			Martins et al. (2015)
		Nanocomposite	El-Nahrawy et al. (2016)
8.	Anticoagulant	Chitosan derivatives	Gao et al. (2014)
		Chitosan NPs	Ehmann et al. (2015)
9.	Gene therapy	Chitin	Li et al. (2015)
		Chitosan derivatives	Je et al. (2006)
		Chitosan NPs	Nam and Nah (2016)
10.	Agricultural materials	Chitin	Egusa et al. (2015)
		Chitosan	Devarayan et al. (2015)
11.	Food additives	Chitin	Irkin and Esmer (2015)
		Chitosan	Belanche et al. (2015)
		Chitosan hydrogels	Facin et al. (2015)
12.	Hypocholesterolemic agents	Chitin nanofibers	Azuma et al. (2015c)
		Chitosan derivatives	Zhang and Xia (2015)
13.	Cosmetic ingredients	Chitooligomer	Pei et al. (2016)
		Chitosan gels/films	Contri et al. (2016)
14.	Biosensors	Chitin derivatives	Jayakumar et al. (2010)
		Quantum dots	Liu et al. (2016)
		Chitosan NPs	Bao et al. (2015)
15.	Affinity chromatography column	Chitin	Gildemeister et al. (1994)
16.	Treatment of industrial pollutants	Chitin/chitosan derivatives	Daraghmeh et al. (2015)
17.	Treatment of periodontal bony defects	Hydroxyapatite-chitin-chitosan composite	Ito (1991)

carboxybutyl chitosan is employed in processing collagen bundles for tissue repair (Biagini et al. 1991). Examples of various uses of chitin are given in Table 2 and described here in detail.

Enzyme immobilization

Enzyme immobilization has enormous practical utility owing to enhanced catalytic potential under enhanced pH and temperature with prolonged reusability (Gomes et al. 2004; Kilinc et al. 2006). Chitin and its derivatives provide an excellent support material for the immobilization of numerous enzymes (Chern and Chao 2005; Kilinc et al. 2006; Onal and Telefoncu 2003; Wang et al. 2013). Naturally derived chitosan is used as an immobilizing agent because of its enzyme compatibility and stabilizing effect (Yong et al. 2015). Facin et al. (2015) have recently shown that chitosan-grafted hydrogels can be employed for the immobilization and controlled release of β-galactosidase. They proposed that chitosan-grafted hydrogels with immobilized enzymes are useful for the production of lactose-free food and controlled enzyme release with high performance.

Recently, several novel materials were synthesized by a combination of chitin and lignin for immobilization of lipase from *Aspergillus niger* (Zdarta et al. 2015). The immobilization process, using a cheap, nontoxic matrix of natural origin, provides potential application for wastewater treatment. Badgujar and Bhanage (2015) have synthesized a biocompatible hybrid blend of cellulosic polymers of hydroxypropyl-methyl-cellulose and chitosan for the immobilization of *Candida rugosa* lipase. They observed that immobilized lipase activity is three- to fourfolds higher in comparison to soluble enzyme. Long et al. (2015) synthesized hybrid magnetic carrageenan NPs from chitosan. They immobilized pullulanase enzyme and studied the behavior of pullulanase with chitosan as a function of pH and protein-polysaccharide ratio using turbidimetric titration. Their results indicated that immobilized pullulanase was efficient in terms of catalytic activity and can be applied to continuous starch processing applications in the food industry.

The stability of porcine pancreatic lipase was significantly improved by immobilization to the chitosan/TiO_2 composite beads for industrial usage especially for the production of biodiesel and dairy products (Deveci et al. 2015). Chitinase from *Thermomyces lanuginosus* was immobilized on glutaraldehyde cross-linked chitosan beads and it was found that the enzyme was stable at least for 1 month at 4 °C without any significant loss in activity (Prasad and Palanivelu 2015). De et al. (2015) designed nanocerium oxide-decorated reduced graphene oxide-reinforced chitosan nanocomposites as an effective enzyme immobilizer. Apart from these studies, a wide range of applications of chitin and its derivatives has been reported for enzyme immobilization (Chen et al. 2015b; ElMekawy et al. 2013; Salazar-Leyva et al. 2013; Wang and Esker 2014; Wang et al. 2013; Zdarta et al. 2015).

The properties of immobilized enzymes depend upon the properties of the enzyme as well as the supporting material (Tischer and Wedekind 1999). High affinity to proteins, availability of reactive functional groups for the reactions with enzymes, hydrophilicity for chemical modifications, mechanical stability and rigidity, biocompatibility, antibacterial properties, physiological inertness, nontoxicity, remarkable affinity to proteins, etc. are some of the important properties that make chitin and chitosan important for enzyme immobilization. Furthermore, chitin is also biodegradable, economical, and inexpensive (Krajewska 2004).

Antioxidant property

The demand for potent, naturally derived antioxidant molecules has seen an exponential increase over those of synthetic origin. Chitin/chitosan and its derivatives, being safe and nontoxic, provide protection against highly reactive free radicals, thus inhibiting the advancement of numerous chronic diseases. The molecular weight and viscosity of chitosan affects its antioxidant property (Jeon et al. 2002; Xie et al. 2001). Low-viscosity chitosan exhibits the greatest antioxidative effect (Chao et al. 2004). Recently, a novel recombinant biodegradable polysaccharide was synthesized by chemical modification of chitosan having a remarkable antioxidant activity (Guo et al. 2015). Woranuch et al. (2015) suggested that ferulic acid coupled onto chitosan can be used as an antioxidant for biodegradable active packaging film. These biodegradable films possess an improved oxygen barrier and radical scavenging and antioxidant properties.

Agarose-chitosan was implanted in the femoral condyle of rabbits that increased the angiogenesis with newly formed tissue during bone grafting (Jebahi et al. 2014). During this process, there were no inflammatory, necrotic, or fibrous tissues detected in the newly formed bone. These discoveries suggested that the agarose-chitosan biomaterial implantations are effective for treating trauma and bone regeneration. In another finding, grafting of gallic acid onto chitosan showed to have high viscosity and antioxidant capacity that could be used as potential biomaterial in the food industry (Xie et al. 2014). Recently, 6-amino-6-deoxychitosan and their 2,6-di-N-sulfonated derivatives were prepared which show appreciable reducing power, superoxide anion radical scavenging ability, and hydroxyl radical scavenging effect (Yang et al. 2015).

Ferulic acid coupled onto chitosan film showed a very high antioxidant activity. It was demonstrated that radical scavenging activity and reducing power of film containing ferulic acid-coupled chitosan were higher than those of film containing only ferulic acid (Woranuch et al. 2015). Apart from these findings, various studies have been carried out to show the antioxidant property of chitin and chitosan (Ngo and Kim 2014; Sedaghat et al. 2016; Younes et al. 2014; Zhang et al. 2012). Modified chitosan NPs with gallic acid and octyl gallate have been prepared (Abdel-Wahhab et al. 2016). These chitosan NPs possess scavenging activity due to the positive charge and are useful in the evaluation of ochratoxin A in catfish. Ochratoxin A causes biochemical disturbances and oxidative stress in the kidney and liver and also causes fragmentation of DNA in the kidney. Treatment with gallic acid

chitosan NPs results in the improvement of kidney tissues. Moreover, octyl gallate chitosan NPs possess less scavenging properties due to carboxyl group blocking in octyl gallate chitosan NPs as compared to gallic acid chitosan NPs.

Wound-healing property

Materials with an appropriate pore size, biocompatibility, and mechanical strength are essential for tissue engineering and wound healing. For this purpose, a novel chitosan membrane has been designed comprised of a macroporous sponge-like sublayer with a top layer of skin surface. This membrane exhibited controlled evaporative water loss and excellent oxygen permeability and promoted fluid drainage ability, inhibiting invasion of exogenous microorganisms at the same time (Mi et al. 2001). Chitosan-based wound dressing led to quick wound healing by enhanced epithelialization rate and well-organized dermal deposition of collagen. This resulted in reduced scar tissue (fibroplasias) by preventing fibrin formation in wounds and formed a protective film coating. Chitosan degradation products were internally absorbed being a lysozyme substrate, affecting the macrophage activity.

Vedakumari et al. (2015) prepared chitosan-fibrin nanocomposites as drug delivery and wound-healing materials with antibacterial activity against *Escherichia coli* and *S. aureus*. The antifibrotic effect of chitosan-aptamer has been demonstrated in a rat model, where chitosan gel may be considered to be a promising antifibrotic agent for local drug therapy (Zhu et al. 2015). Curcumin-encapsulated bioglass-chitosan might also have potential applications in wound healing (Jebahi et al. 2015). In one study using a rat model, it has been shown that the chitosan membrane may promote early wound healing and reduce inflammation when wounds were covered with chitosan membranes (Nordback et al. 2015). Various studies have shown that chitin and chitosan derivatives can be used as drug delivery, wound healing, and antibacterial substance (Azuma et al. 2015b; Izumi et al. 2015; Jang et al. 2012; Sudheesh Kumar et al. 2013; Shao et al. 2015).

Packaging material

Of late, the paradigm shift from synthetic packaging materials to biopolymer-derived biodegradable packaging films has opened up numerous opportunities for chitin/chitosan-derived packaging films. These have an advantage over the synthetic ones owing to their eco-friendly and user-friendly features, as the raw materials are generally obtained from renewable natural resources (Duran et al. 1975; Goldman and Vicencio 2012; Ruckenstein and Zeng 1997). Biopolymeric membranes prepared with chitosan/alginate combinations can be utilized to remove glyphosate herbicide from water (Carneiro et al. 2015).

Another advantage of chitosan as a packing material is its intrinsic antimicrobial activity and exceptional physicochemical properties (van den Broek et al. 2015). Chitosan is recognized as a natural alternative to chemically synthesized antimicrobial polymers. A multilayered film prepared from chitosan and alginate was found highly stable in a wide range of pH (Silva et al. 2015). In this regard, NPs have emerged as an excellent alternative because of their proportionally larger surface area, which favors the filler-matrix interactions and the performance of the resulting material (Ghanbarzadeh et al. 2015). Recently, a novel nanomaterial based on chitosan/poly(vinyl alcohol)/titanium NP was prepared which can be used as packaging materials for soft white cheese (Youssef et al. 2015). Another packaging material was prepared from a set of rectorite/chitosan bionanocomposite films by facile reaction of chitosan with ion-exchanged rectorite clay (Babul Reddy et al. 2015). Extrusion processability of thermoplastic starch film was enhanced by incorporating 0.37–1.45% of plasticized chitosan (Dang and Yoksan 2015). This type of films possessed better extrusion processability, increased tensile strength, rigidity, and thermal stability that are useful in the food industry.

Gul et al. (2016) prepared chitosan-Fe_3O_4 NPs cross-linked with graphene oxide composites for cleaning industrial wastewater by removing toxic anionic and cationic dyes. Tang et al. (2016) incorporated nanofillers into polymeric matrix chitosan/titanium dioxide to prepare a new nanocomposite. This resulted in improved mechanical properties as compared to cellulosic paper due to surface coating and TiO_2 NPs increase antibacterial properties. With an increase in TiO_2 NP concentrations, the dynamic viscoelasticity of the nanocomposite decreases. The mechanical properties and antibacterial activity of surface-coated cellulosic paper are improved which serves as antibacterial coating for paper packaging.

Controlled drug release

Chitosans are considered to be a potential carrier for drug and other biologically active molecules owing to its easy availability, nontoxicity, biocompatibility, biodegradability, broad range functionalities, and high drug-loading capacity (Rajitha et al. 2016). The drug release profiles of chitosan-alginate combination show a long period of induction followed by a rapid drug release phase in the artificial intestinal fluid. CM-chitin was modified selectively for obtaining antitumor drug conjugates (Wang et al. 2011). 5-Fluorouracil (drug of choice for colon carcinomas) and the D-glucose analog of muramyl-L-alanyl-isoglutamine, possessing immune-adjuvant activity, were grafted on CM-chitin utilizing a specific spacer and an ester bond. Sustained release of antibiotic oxytetracycline from chitosan microspheres for both oral administration and injection has been reported (Hou et al. 2011; Mi et al. 1997; Ohya et al. 1992).

Chitosan is an attractive natural biopolymer useful for drug delivery system in the form of chitosan NPs to enhance the

surface to volume ratio (Assa et al. 2016). Chitosan NPs possess outstanding physicochemical, antimicrobial, and biological properties. These unique properties make chitosan NPs a promising biopolymer for the application of the drug delivery system. Bioadhesive NPs prepared with chitosan-thioglycolic acid conjugate have shown to have improved controlled release, prolonged sustenance, and drug retention in case of superficial bladder cancer (Ay Senyigit et al. 2015). Recently, chitosan NPs were produced by cross linking chitosan with 3-methoxy-4-hydroxybenzaldehyde (vanillin) through a Schiff reaction. 5-Fluorouracil as a model of hydrophilic drug was successfully encapsulated, and it was found that its release from the NPs was constant and controllable (Li et al. 2016a). Moreover, in vitro cytotoxicity against HT-29 cells and cellular uptake of the chitosan NPs were also evaluated and suggested that chitosan NPs cross-linked with vanillin may be a promising vehicle for the delivery of anticancer drugs.

In one of the studies, it has been demonstrated that the chitosan-laponite-nanocomposite prepared by electrophoretic deposition technique exhibits improved cell viability and controlled drug release (Ordikhani et al. 2015). Recently, Duan et al. (2016) showed that folate-modified chitosan NPs coated with the *interferon-inducible protein-10* gene enhance the cytotoxic T lymphocytes' responses to hepatocellular carcinoma. The therapeutic potential of antitubercular drugs was analyzed by loading into natural polysaccharide comprised of galacto-mannan subunit in experimental tuberculosis in mice. It was suggested that guar gum-coated chitosan NPs may be a promising carrier for selective delivery of antitubercular drugs to alveolar macrophages for efficient management of TB with minimal side effects (Goyal et al. 2016).

Gold nanospheres (AuNS) are an extensively studied system for various biomedical applications like drug delivery, photomedicine, and bioimaging. However, chemically synthesized NPs are toxic and have a risk of bioaccumulation. Thus, chitosan-reduced AuNS (12.0 ± 1.99 nm) has helped out in overcoming this bioavailability and toxicity problem causing no subacute physiological damage even when tested at high concentrations and hence used for biomedical applications including targeted drug delivery (Hari and Kumpati 2016). Jin et al. (2016) synthesized chitosan nanoparticle-based drug carrier system using ursolic acid and folate. Although ursolic acid possesses antitumor effects and also has a broad spectrum, its poor solubility in water along with incompetent targeting limits its application for clinical use. Thus, the ursolic acid, folate, and chitosan nanoparticle drug carrier system is constructed to temper off-target and increase the concentrations of ursolic acid.

Biomedical imaging

Theranostic NPs like Echo-CNPs have proven beneficial in targeting tumor specificity of anticancer agents and imaging probes. Chitosan-based NPs comprise an outer hydrophilic glycol chitosan polymer and anticancer hydrophobic drug/PFP inner cores. Inner hydrophobic cores serve as potent reservoir for PFPs and chemodrugs, and the hydrophilic core of Echo-CNPs provides significant physicochemical properties like biodegradability and serum stability as well as tumor-homing ability. These Echo-CNPs have been employed in ultrasound-triggered drug delivery and cancer-targeted ultrasound imaging. Thus, Echo-CNPs bear selectively increased tumor-homing ability and less nonspecific particle uptake by other tissues via NP's enhanced permeation and retention effect (Min et al. 2015).

Chitosan and tripolyphosphate were used to synthesize NPs using opposite charge interactions (Scheeren et al. 2016). Bioactive adjuvant lysine-based pH-sensitive amphiphile (77KS) shows high ionization with pH. Thus, it is employed in designing pH-sensitive devices. Cytotoxicity experiments suggested that doxorubicin (DOX)-loaded CS-NPs are beneficial in killing HeLa tumor cells. These results show that pH-responsive CS-NPs are efficient in delivery systems to target tumor and DOX carrier systems and can prove beneficial in cancer therapy (Scheeren et al. 2016).

Also pH-responsive doxorubicin (DOX)-loaded chitosan-tripolyphosphate NPs (NPs) are hemocompatible and so suitable for administration to an intravenous environment. The endosomal acidity in combination with the potential endosomolytic capability of pH-responsive nanocarriers results in an increase in the delivery of doxorubicin intracellularly and results in an increase in its antineoplastic efficacy (Nogueira-Librelotto et al. 2016).

Antimicrobial property

In recent years, the antimicrobial property of chitin and its derivatives has received significant attention. Chitosan bears a broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative bacteria (Badawy et al. 2014; Bigucci et al. 2015; Vishu Kumar et al. 2005). Raafat et al. (2008) showed the antimicrobial mode of action of chitosan using combinatorial approaches. They suggested that the antimicrobial function of chitosan is because of interaction of the polycationic molecule with the negatively charged cell wall components (proteins and lipopolysaccharides) of the microorganism. This may result in leaky intracellular components owing to the modifications in permeability barrier. The other possibility is the prevention of nutrient uptake by cell or binding to DNA (upon entry into the cell) and thus inhibiting transcription and translation. The antimicrobial properties of chitosan depend on their molecular mass and degree of acetylation. Generally, chitosan with low molecular mass and high degree of acetylation is more effective on reducing microorganism growth and multiplication (Martins et al. 2014).

Chitosan formulations in the form of nanoparticles possess an excellent antimicrobial property due to its unique surface

characteristics. Immobilized silver nanoparticles were synthesized in the presence of chitin nanocrystals under microwave-assisted conditions exhibiting high effectiveness of antibacterial activity against *E. coli* or *S. aureus* (Li et al. 2016b). In a recent study, an improved antimicrobial property of iodine, by mixing N-(2-hydroxy) propyl-3-trimethylammonium chitosan chloride in ethanol solution, was reported (Tang et al. 2015). Silver NPs, prepared on chitin nanofiber surfaces by UV light, show a strong antifungal activity (Ifuku et al. 2015). Trimethyl chitosan prepared by the methylation process has shown to have killed *E. coli* due to a strong interaction with the cell envelope (Martins et al. 2015). The surface coating of mammalian cells by polymer N-[(2-hydroxy-3-trimethylammonium) propyl] chitosan chloride reduces the colonization by bacteria (Wang et al. 2015). Chitosan-based core-shell particle containing poly(n-butyl acrylate) has been used as a novel antibacterial coating agent for textiles. Cotton fabric treated with water-soluble carboxymethyl chitosan possesses admirable antimicrobial activity and improved wrinkle recovery (Costa et al. 2014; Sarwar et al. 2015; Yuan et al. 2015). Recently, mucoadhesive electrospun nanofiber mats have been developed using chitosan and thiolated chitosan for dental caries prevention and to maintain oral hygiene by reducing bacterial growth that causes dental caries (Samprasit et al. 2015).

Chitosan-based nanocomposites possess good antibacterial activities. Chitosan/calcium silicate nanocomposites doped with Ag (1, 2 mol%) nanocomposites show superior antibacterial activity against Gram-negative (*Pseudomonas aeruginosa*) and Gram-positive (*S. aureus*) bacteria and fungi (*Candida albicans*) (El-Nahrawy et al. 2016). Enterohemorrhagic *E. coli* cause zoonotic pathogenic infections. These infections cause hemolytic uremic syndrome causing death as well. Chitosan with its water-soluble derivative such as trimethylated chitosan is a mucoadhesive biopolymer which has been used for the preparation of nanovaccines by electrospraying technique (Doavi et al. 2016).

The antibacterial performance of inorganic-organic hybrid polymers of ZnO nanoparticles-chitosan with an average particle size of 40 nm has been studied against a Gram-negative bacterium *E. coli* and a Gram-positive *Micrococcus luteus*. The antibacterial activity of ZnO-chitosan NPs increases with the decrease in molecular weight of chitosan (Wysokowski et al. 2013b). AbdElhady (2012) synthesized chitosan/ZnO NPs using different concentrations of ZnO at varying temperatures. Synthesized NPs of ZnO/chitosan were in rod form (length = ~60 nm and width 5–15 nm). When different cotton swatches were treated with increasing concentrations of chitosan/ZnO NPs, excellent antibacterial activities were observed. It is interesting to note that the inhibition zone for *E. coli* is larger as compared to the inhibition zone for *S. aureus*, due to differences in cell wall structure. The antibacterial activity of the coated fabrics was also examined against both Gram-negative (*E. coli*) and Gram-positive (*Enterococcus faecalis*) bacteria. Zn-chitosan NPs showed higher antibacterial activity than nanostructured chitosan. Ultra-small ZnO NPs, less than 2.1 nm, have contributed to higher antibacterial activity (Perelshtein et al. 2013).

Anticoagulant activity

Blood coagulation is a phenomenon involving the sequential activation of a number of serine proteinases by generating thrombin and subsequent thrombin-catalyzed conversion of fibrinogen into insoluble fibrin. Several sulfated glycosaminoglycans show anticoagulant activity owing to their ability to interfere with the process of blood coagulation (Vongchan et al. 2002). Sulfated chitosan, for example, has been claimed to possess a high potency of anticoagulant as compared to the well-known antithrombic agent, heparin. Albuminal coating of rapamycin onto the endothelialization-accelerated chitosan stent is proven as an efficient treatment for tackling the late stent thrombosis with improved therapeutic effects (Gao et al. 2014). Gold NP core surrounded by chitosan sulfate shows both antibacterial and anticoagulant activities (Ehmann et al. 2015).

Gene therapy

Gene therapy involves delivering a gene into a cell exogenously with the aim of combating genetic disease, impending tumor progression, and fighting viral infections (Liu and Yao 2002). Chitin is a naturally occurring cationic biopolymer which has emerged as an alternative nonviral gene delivery system (Li et al. 2015). Its biocompatible and nontoxic nature with minimal side effects even at very high doses made it an excellent material for gene delivery (Gordon-Thomson et al. 2009). Chitosan facilitates the transport of various drugs across cellular membranes owing to its superior mucoadhesive properties (Je et al. 2006). Chitosan NP facilitates the delivery of desired gene to enhance antitumor activity.

A successful gene therapy approach can be utilized to prevent congenital and acquired diseases. Chitosan-based NP delivery of vaccine is being useful for tumor therapy (Yan et al. 2015). Recently, Nam and Nah (2016) demonstrated that HPOCP copolymer is a good candidate for gene delivery carriers for targeted gene therapy because it possesses low cytotoxicity, site-specific target function, and high transfection efficiency. Chitosan-methylprednisolone conjugate is used for gene therapy because of its anti-inflammatory and anti-apoptotic effects. The DNA conjugated to the chitosan-methylprednisolone NP showed reduced apoptosis and inflammation at the injury site, suggesting the utility of such NP as an effective gene delivery system (Gwak et al. 2015). Mucoadhesive conjugates of chitosan glutathione glycol chitosan and *N*-acetylcysteine polymer are used for formulating nano- and micro-NPs through the spray-drying technique.

These mucoadhesive conjugates are sensitive at pH = 5.0–7.0 and are useful in the treatment of local bladder diseases (Denora et al. 2016).

Agricultural materials

Chitin and chitosan play an important role in the defense mechanism of plants against microbial invasion (Egusa et al. 2015). The antimicrobial property has been improved by nanofibrillation of chitosan (NF-chitosan) which possesses high tensile strength. The NF-chitosan sheets showed strong mycelial growth inhibition against *Microsporum*/*Trichophyton* showing resistance to degradation by the fungi (Egusa et al. 2015). The effects of oral administration of chitin nanofibers on plasma metabolites were studied. It was observed that plasma levels of ATP and 5-hydroxytryptamine (5-HT) increase via activation of gut microbiota (Azuma et al. 2015a). Biocontamination within the international space station is ever increasing mainly due to human activity. α-Aminophosphonate chitosan significantly reduces fungal growth. The inhibition mechanism of the modified chitosan is exploited as disinfectant in space stations to remove fungal contaminants (Devarayan et al. 2015). The oleoyl-chitosan NPs show antifungal activity against several plant pathogenic fungi such as *Nigrospora sphaerica*, *Botryosphaeria dothidea*, *Nigrospora oryzae*, and *Alternaria tenuissima* due to a lower level of unsaturated fatty acid present in the plasma membranes of these fungi (Xing et al. 2015). Chitosan may also promote carrot somatic embryo survival, improvement of defense in tomato cells, and formation of nodule in soybean root.

Food additives

Chemical preservatives can be replaced by chitin-based compounds due to safer antimicrobial activity (Irkin and Esmer 2015). Chitosan can protect food products against microbial invasion as it could delay the growth of indigenous bacteria in food products. Vinegar products containing chitosan have cholesterol-lowering ability. Chitosan showed promising potential to improve rumen function (Belanche et al. 2015). Romanazzi et al. (2015) suggested that the shelf life of fresh fruits and vegetables can be increased by chitosan coating due to formation of a semipermeable film on the surface of fruit and vegetables, thereby delaying the rate of respiration. A novel amphipathic chitosan derivative, *N*-benzoyl-*O*-acetyl-chitosan showed both antibacterial and antifungal activities (Cai et al. 2015). Lopez-Moya et al. (2015) suggested that carbon and nitrogen limitation increases antifungal activity of chitosan in *Neurospora crassa* and fungal human pathogens. The chitosan-grafted hydrogels are useful for lactose-intolerant individuals due to controlled released of β-galactosidase. These hydrogels containing immobilized enzymes are employed to simulate the production of lactose-free food (Facin et al. 2015).

Hypocholesterolemic agents

Chitin and chitosan treatment is reported to reduce the amount of cholesterol in rats with no change in liver weight and appearance (LeHoux and Grondin 1993). It may be due to binding of chitin to cholesterol micelles or increasing the excretion of bile acid by which the amount of fecal fat increases (Burton-Freeman 2000; Gallaher et al. 2000). Azuma et al. (2015c) suggested that the administration of surface-deacetylated chitin nanofibers has hypercholesterolemic effect. Chitosan-covered poly lactic-co-glycolic acid NPs are promising agents to enhance the bioavailability and activity of poorly water-soluble compounds such as α-tocopherol and tocotrienols (Alqahtani et al. 2015). Zhang and Xia (2015) suggested that media milling chitosan enhances the lipid-lowering and antioxidant activities of chitosan due to its effect on strengthening the ability of chitosan in promoting fecal lipid excretions. Chitosan-oligosaccharide is potentially used to treat obesity due to its improved dyslipidemia and to prevent body weight gains by inhibiting the adipocyte differentiation in obese rats induced by a high-fat diet (Huang et al. 2015). Chitosan-oligosaccharide treatment attenuated atherosclerosis and decreased plasma non-HDL level, which may be due to enhanced expression of hepatic liver low-density lipoprotein receptor, scavenger receptor, and macrophage ATP binding cassette transporter (Yu et al. 2015).

Cosmetic ingredients

Chitooligomer prepared by degradation of high molecular weight chitosan with hydrogen peroxide followed by oxidation using a laccase-TEMPO system improved the moisture absorption, retention, and antioxidant abilities of chitooligomer (Pei et al. 2016). The resulting oxidized products with low molecular weight have potential application in the pharmaceutical and cosmetics industries. Rose hip oil has skin-regenerating properties with applications in dermatological and cosmetic areas. Its nanoencapsulation into chitosan gel and film shows an increased contact with the skin (Contri et al. 2016). The chitosan gel and film are considered as a better alternative for incorporating the nanoencapsulated rose hip oil, combining the advantages of the NPs to the advantages of chitosan. Incorporation of hydroxypropyl methylcellulose increases the physicochemical properties of chitosan hydrogel, enhancing the hardness, viscosity, as well as bioadhesion, and has improved antimicrobial effects (Chen et al. 2015a). Gelfuso et al. (2015) suggested the skin permeation and disposition of minoxidil sulfate which is used in the treatment of alopecia.

Biosensors

Chitin and its derivatives are extensively used in the development of biosensor (Jayakumar et al. 2010; Liu et al. 2013). Lectins possess stereospecificity for some carbohydrates including sugar residues. This protein-carbohydrate interaction is beneficial in monitoring various pathophysiological infections (like viral and bacterial) inflammation and cancer metastasis. Keeping in mind a highly selective and sensitive sensing system has been developed by integrating carboxymethyl chitosan (CM-CHIT) and CuInS2 quantum dots (QDs) with Au NPs. After synthesizing CuInS2 QDs hydrothermally with surface bearing (COO^-) groups, these carboxyl groups interact with CM-CHIT polymeric chains having the amino groups (−NH2), carboxyl groups (−COOH), and hydroxyl groups (−OH) through hydrogen bonding and electrostatic interactions to form CM-CHIT-QD assemblies. In the absence of lectin, with the introduction of Au NPs in the CM-CHIT-QD system results in quenching of fluorescence of CMCHIT-QDs with the transfer of energy and electron transfer. When lectin is present in the above system, it significantly binds to CM-CHIT-QDs due to its specific carbohydrate-protein interaction resulting in the inhibition of transfer of electron and energy between Au-NPs and CM-CHIT-QDs. Thus, the fluorescence of CM-CHIT-QDs is successfully "turned on." This chitosan-based biosensor is used for determining lectin in fetal bovine serum samples (Liu et al. 2016).

Chitosan-based biosensors are used for pesticide detection in agriculture. Organophosphate pesticides which are neurotoxic to humans are detected by chitin-based biosensors. Bao et al. (2015) designed an esterase-chitosan/gold NPs-graphene nanosheet (PLaE-CS/AuNPs-GNs) biosensor for detecting malathion and methyl parathion selectivity. Esterase enzyme produced from plant was employed in preparing the highly sensitive PLaE-CS/AuNPs-GNs nanocomposite biosensor; this biosensor is used in organophosphate detection in food and agriculture (Bao et al. 2015).

Apetrei and Apetrei (2016) developed thick-film biosensors of diamine oxidase (DAO)/platinum NPs (nPt)/reduced graphene oxide (GPH)/chitosan for the sensing of histamine level in freshwater fishes. Due to the synergistic effect of GPH and nPt during electrochemical detection of H_2O_2, DAO/nPt/GPH/chitosan-based biosensor showed a sensitive amperometric response with histamine (Apetrei and Apetrei 2016). Similarly, chitin-based nanosensors have been used in different types of electrochemiluminescent/electrochemical detection reactions as a tracer tag even to detect dopamine (Shirazi et al. 2016; Stewart et al. 2015).

Miscellaneous applications

Chitin has been used in the preparation of affinity chromatography column for isolation of lectins and determination of their structure (Gildemeister et al. 1994; Peumans et al. 1985). Chitin and 6-O-carboxymethyl chitin have been found to activate peritoneal macrophages in vivo and elicit nonspecific host resistance against *E. coli* infection (Lee 2009; Li et al. 2013; Muzzarelli 2010). Chitin and chitosan derivatives are capable of adsorbing silver thiosulfate complexes, thus are also used for the treatment of industrial pollutants and actinides (Badwan et al. 2015; Daraghmeh et al. 2015). Regenerated chitin derivative fibers find their use in the paper making process as binders (Younes and Rinaudo 2015). Another interesting application is in the treatment of periodontal bony defects as a hydroxyapatite-chitin-chitosan composite bone-filling material, which forms a self-hardening paste useful for guided tissue regeneration (Ito 1991).

Conclusions and future directions

Chitin, chitosan, and their derivatives have been considered as useful biopolymers because of their potential uses. Research and development in this area have been directed both at the industrial and laboratory levels. The physiological properties and biological function of chitins depend on their molecular mass, chain length, and chemical derivative attached. Chemically derived oligomers may have extra advantage than chitin and chitosan as a biopolymer for their industrial uses in human health. In recent years, biodegradable chitosan derivatives have been widely used in the medical industry. However, there still is a challenge whether these biopolymers may have the potential to influence physiological functions or metabolism in the human body. Studies are required to determine the mechanism of chitin functioning on the human body to provide a better understanding of how they may be manipulated in the creation of better quality chitosan-derived biomaterials. Finally, chitin may be made more robust to the extent that the same may be used for protection. This is possible because insects with chitin shield can withstand an extremely high dose of radiation.

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