JOTCSA Journal of the Turkish Chemical Society Section: A Chemistry

TURKISH CHEMICAL SOCIETY

Chitosan, Its Derivatives, Sources, Preparation Methods, and Applications: A Review

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Abstract: Chitosan is a type of biopolymer that can be derived from various natural sources, including animals and marine organisms. When determining its quality, molecular weight, crystallinity, and degree of deacetylation of chitosan are considered. Biocompatibility, bioadhesive, solubility, and polycationic character are all based on these traits. Chitosan's characteristics make it a good and appealing material for a variety of physical and chemical alterations. This review talks about the structure of chitosan and its properties. It also covers how chitosan is extracted from different sources. Special emphasis is placed on its utilization in the formation of metallic nanoparticles, drug delivery, and wastewater treatment.

Keywords: Chitosan, Biopolymer, Extraction, Applications.

Submitted: August 1, 2023. **Accepted:** December 9, 2023.

Cite this: Hemmami H, Ben Amor A, Zeghoud S, Ahmed S, Alnazza Alhamad A. Chitosan, Its Derivatives, Sources, Preparation Methods, and Applications: A Review. JOTCSA. 2024;11(1):341-64.

DOI: https://doi.org/10.18596/jotcsa.1336313

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1. INTRODUCTION

Chitin is a polysaccharide composed of β-(1-4) N-acetyl-D-glucosamine units. Cellulose, being the most prevalent biopolymer globally, is followed by this particular biopolymer as the second most abundant (1). Chitin serves as the primary constituent of the exoskeleton in crustaceans like crabs and shrimp, as well as the skeletal framework of insects. Additionally, it is present in the cellular walls of fungus (2). Because of its non-toxicity, antioxidative nature, biocompatibility, biodegradability, and renewability, this substance finds use in several domains, including food science, agriculture, cosmetics, biotechnology, and pharmaceuticals. Chitosan (CS), a polysaccharide derived from the deacetylation of chitin, has a wide range of applications across several industries (3).

Chitin and its derivatives are commercially obtained from the exoskeletons of various crustaceans like crab, shrimp, crayfish, and krill (4). Following the 1970s, chitin, chitosan, and its derivatives gained prominence in Various applications, such as water treatment for the removal of dyes, proteins, and metal ions (5). Additionally, these compounds are used in the food business for purposes such as weight management, nutritional supplementation, and as antioxidant coatings. They are also often used in industrial sectors such as the paper and textile industries (6). Crustaceans, including crab, lobster, and shrimp, possess a composition characterized by around 30-50% calcium carbonate, 30-40% protein, and 20-30% chitin inside their exoskeleton. In the process of chitin manufacturing from shell wastes, the wastes undergo treatment with alkali and acid solutions to eliminate protein and mineral components. As a result, it is possible to get chitin of superior quality from shells, as well as chitosan derived from this chitin, using appropriate treatment techniques (4). The chitin concentration of blue crab is around 14% (7).

It is economically feasible to turn food waste from crab shells into chitosan. Crabs, shrimp, desert locusts, honey bees, beetles (8), crayfish, corals,

fungi (9, 10), and cockroaches (11) could be exploited for the commercial production of CS (12, 13).

This review aims to provide a comprehensive exploration of chitosan and its derivatives, delving into the origins of this biopolymer and the different methods used to extract and modify it. The variety of sources from which chitosan can be extracted will be examined, ranging from crustaceans such as shrimp and crab to other marine organisms and even fungi. Furthermore, we will delve into preparation methods, including traditional chemical processes and contemporary enzymatic methods, highlighting the most important developments in recent applications of chitosan.

2. STRUCTURE, PRIMARY SOURCES, AND CHARACTERISTICS OF CHITOSAN

2.1. Chemical Structure

Chitin, which serves as the precursor of chitosan, is the most prevalent biopolymer in nature, second only to cellulose. It is abundantly present in several including insects, crustaceans, and fungi (14). Chitin is a biopolymer composed of N-acetyl-D-glucosamine units. When subjected to deacetylation, the acetyl functional groups are removed, resulting in a polymer largely consisting of β-1,4-D-glucosamine units. This polymer is called chitosan (Figure 1) (15). The degree of acetylation (DA) is defined as the mole fraction of the N-acetylated repeating units, while the degree of deacetylation (DD) is defined as the percentage of the repeating units of β-1,4-D-glucosamine in the polysaccharides (15).

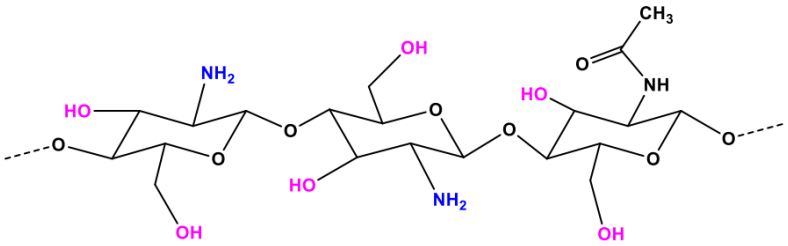

Figure 1: Structure of chitosan.

2.2. Sources

Among the various sources available for chitosan production, *shrimp* is one of the most promising and much discussed, and many other species, such as beetles and insects, have also been used, according to Figure 2 (4).

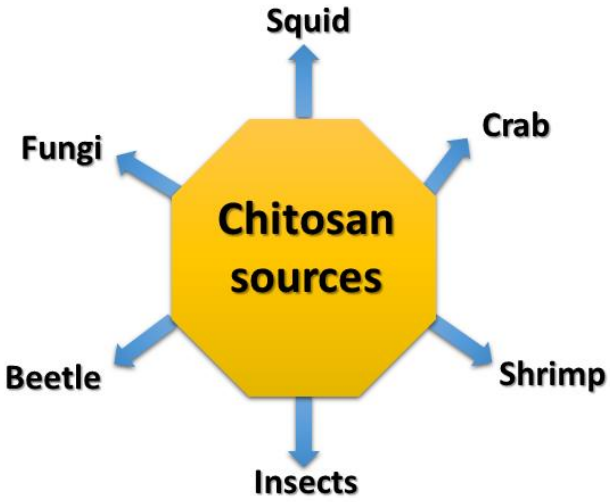

Figure 2: The most significant chitosan sources.

2.2.1. Crustaceans

Crab and shrimp waste are the main sources of chitosan for industrial production (16). Chitin, a substance found in the exoskeleton of these crustaceans, is used to make chitosan. Exoskeletons are waste from the fishing industry. Depending on the crustacean species, the chitin concentration in dried exoskeletons is between 5% and 42% (17, 18). In summary, chitosan derived from crab and shrimp waste is particularly attractive as these sources are readily available, renewable, and less expensive. In addition, it is an alternative method for the proper disposal of solid waste in the fishing industry.

2.2.2. Insects

Insects have emerged as a viable alternative supply of chitosan; nevertheless, this development has only occurred in recent times, and studies have only been conducted on a laboratory scale. Kaya et al. (19) reported that chitosan was obtained from the Colorado potato beetle (larvae and adults). The chitin concentration in larvae and adult beetles was determined on a dry weight basis to be 7% and 20%, respectively. Furthermore, it was shown that adult beetles yielded a chitosan production rate of 72%, while larvae exhibited a slightly lower rate of 67%. The use of insects to produce chitosan is based on

biodiversity, with insects representing 95% of all animal species. In addition, insect cuticles contain less inorganic material compared to crustacean shells, which facilitates demineralization treatment (5). Another advantage is the control of insects in agricultural land (20).

2.2.3. Mollusks

Mollusks provide an additional source of chitosan. The use of species such as *Sepia kobiensis*, *Sepia spp*, *Loligo lessoniana*, and *Loligo formosana* has been seen in this regard (20, 21). *S. kobiensis* cuttlebone was used to make chitosan, which had an 85.55 % deacetylation rate, a molecular weight of 322.04 kDa, and good antioxidant qualities (22). Chitosan and chitin were also extracted from the Chiton, and the antioxidant activity of the extracted chitosan was higher than that estimated for commercial chitosan (23).

2.2.4. Fungi

Compared to crustaceans, fungi are a source of chitosan and chitin that is not seasonal and not influenced by geographical factors. Chitin extraction from this source requires less use of chemicals, as there is usually no need for mineral removal and decoloration. In fungal chitin and chitosan, there are generally no heavy metal contaminants or allergenic proteins that can be found in marine sources (24). Furthermore, fungal chitin and chitosan have more consistent characteristics and properties due to their production by controlled fermentation, and they seem to be more suitable for agricultural applications in enhancing plant immune response. Despite these advantages, the availability and quantity of fungal biomass for the production of chitin and chitosan are much lower than marine sources. Furthermore, the extraction process has not yet been optimized for fungi, and lower yields are obtained (24).

The major components of the fungal cell wall are chitin and chitosan, glucans, glycoproteins, and mannans. Although not ubiquitous in the fungi kingdom, chitin is widely distributed in many fungal classes, including *Basidiomycetes*, *Ascomycetes*, *Zygomycetes*, and *Chytridiomycetes*, comprising 1-15% of the cell wall mass (25). The components of the fungal cell wall are all covalently cross-linked to each other. Chitin forms interchain hydrogen bonds with glucans, creating a glucan/chitin matrix that can assemble into microfibrils that form a scaffold around the cell (25). Different from crustaceans, chitosan can also be directly extracted from the cell walls of some species of fungi. For this purpose, the most investigated species include Mucor rouxii, Absidia spp., and *Rhizophus oryzae*, all belonging to Zygomycetes, *Aspergillus niger* (Ascomycetes) and *Lentinus edodes* (Basidiomycetes).

Three categories of potential fungal sources for the commercial production of chitosan and chitin have been described: waste biomass from biotech industries, fungus fermentation, and exploitation of existing mycothec products. Biotech industries annually generate thousands of tons of waste fungal biomass residue from various processes, including the production of bread, beer, antibiotics, and other drugs, enzymes, and the cultivation of edible mushrooms. From the latter activity, for instance, around 50,000 tons of waste mushroom stalks and irregular fruit bodies are produced every year (26). Additional 80,000 tons of waste biomass are derived annually from the cultivation of A. niger to produce organic acids, and more than one billion tons of fungal waste is generated annually from the penicillin production process. These huge amounts of biomass usually are disposed of in landfills or incinerated. By exploiting them for chitin and chitosan production, waste from biotech industries could be turned into a profitable solution to waste management (4).

For the commercial production of chitosan and chitin by fermentation, several fungal species have been evaluated. Different results in terms of yields and polymer characteristics are obtained using different fungal growth mediums. Moreover, different forms of mycelia (e.g., aerial mycelia for sporulation and submerged mycelia for absorption of nutrients) with different chitosan and chitin content are produced by single filamentous fungi. Experimentation focuses mainly on zygomycetes because of the potential to extract chitin and chitosan directly. Analysis of the cell wall of several Zygomycetes conducted by Campos-Takaki and co-workers to evaluate the most promising species for industrial production of these polymers showed an average chitin content of 10-16% of the cell wall and 26-28% chitosan. The species analyzed were Gongronella butleri, Absidia blakesleeana, Mucor javanicus, Rhizopus arrhizus, Syncephalastrum racemosum, and Cunninghamella elegans. A. blakesleeana and R. arrhizus had the highest content of chitin plus chitosan (43% of the cell wall) (27). Chitosan content in Zygomycetes generally ranges from 1 to 10% of the cells' dry weight. However, fungal chitin and chitosan yields vary depending on fungus strain, type of cultivation (solid or submerged fermentation), growth rate and nutritional requirements of fungi, and extraction process.

In another study, chitosan and chitin were extracted from the biomass of the fungal Termitomyces titanicus, and the chitin extraction rate reached 38.04% (28).

Finally, it is worth mentioning that the production of fungal chitosan and chitin is not completely free of risk. Some genera of Zygomycetes used to extract these polymers (Absidia and Rhizopus) include pathogenic species to humans or animals. For example, Rhizopus oryzae can cause pulmonary mucormycosis in humans, and some species of Absidia cause abortion in domestic animals. Therefore, specific safety measures should be adopted when handling these potentially pathogenic fungi to prevent their dispersal (29).

2.3. Properties of Chitosan

2.3.1. Molecular weight (Mw)

One of the most fundamental properties of a macromolecule is its Mw (21). Understanding the Mw of polysaccharides is crucial to understanding their functions and roles in biological systems. The molecular weight of CS can be measured using gel

permeation chromatography, light scattering (30), and viscometry, which is highly dependent on the deacetylation conditions. The simplest and most widely used technique for estimating Mw of CS is viscometry. However, because it is based on a correlation between intrinsic viscosity and molecular weight data, the problem with this technique is that it needs to be more absolute.

2.3.2. Determining molar mass

Estimating molar mass is one of the most significant analyses in the evaluation of CS since it defines the polymer's biological activity. According to a significant study, chitosan activity rises when molar mass and degree of deacetylation(DD) (31, 32). In medical CS, where the link between biological function and molecular structure appears to be crucial, determining molar mass is critical. It enables researchers to explore the biochemical processes generated by chitosan in cells (33).

2.3.3. Viscosity

From a technological point of view, the viscosity of polymers is a parameter of great interest because high-viscosity solutions are difficult to control. Although not an exact method and therefore requires the identification of solvent-specific constants, viscometry is an effective tool for determining the molecular weight of chitosan. The Mark-Houwink-Sakurada equation connects average molecular weight to intrinsic viscosity:

$$\eta = KM_v{}^{\alpha} \qquad (1)$$

where K and α are parameters to be determined experimentally, different K values have been reported depending on ionic strength, pH, and solvent composition (15). The viscosity of chitosan is affected by the Mw of the polymer, DD, and the viscosity of chitosan increases with increasing concentration and molecular weight. Viscosity increases with the extent of deacetylation. Due to charge repulsion within the molecule, high and low deacetylation chitosan exhibits various conformations in aqueous solution. When chitosan is significantly deacetylated, the chain is more flexible, and the conformation stretches. At low levels of deacetylation, the CS molecule adopts a spiral or rod shape due to the low charge density in the polymer chain. Temperature and concentration factors can affect the viscosity of CS solutions. The viscosity increases with decreasing temperature and increasing CS content. Due to depolymerization, the CS viscosity decreases with increasing demineralization time. The intrinsic viscosity of chitosan can be affected by physical factors (ultrasonic, milling, autoclaving, heating) and chemical (ozone) processes. Chitosan concentrated solutions with various levels of deacetylation differ in their viscosity and flow characteristics. As the DD of chitosan increases, there is a corresponding increase in the viscosities of the solutions and the manifestation of non-Newtonian flow characteristics. Conversely, the addition of salt decreases the viscosity and alters the non-Newtonian flow properties of the chitosan solution (34).

2.3.4. Deacetylation degree (DD)

The ratio of glucosamine groups to the total number of glucosamine and acetylglucosamine groups gives DD. The DD value of a polymer identifies if it is chitosan or chitin. If a polymer has a DD value of more than 60%, it is considered to be chitosan (35). Infrared spectroscopy (36), UV spectroscopy, near-infrared spectroscopy, potentiometric titration (37), and magnetic resonance (38) are a few of the analytical methods used to determine DD.

In Catharsius molossus, the chitosan DD was 94.9 %; in locusts, honeybees, and beetles, 80.96% (39); in Zophobas morio, the chitin DD was 86%, 133%,121%, 120%, 117%, and 86% in Anaz imperator, Ranatra linearis, Notoneeta glauca, Hydrophilus piceus, Agabus bipustulatus, and Asellus aquaticus, respectively (40). Several techniques have been developed to measure the amount of DD found in insect chitosan and chitin. Among them, the FT-IR, the conductometric, the acid-base, and the potentiometric titration methods are useful for completely soluble compounds. Fish, shrimp, and crab shells yielded chitosan with DDs of 75%, 78%, and 70%, respectively. According to earlier research, a greater DD represents a noteworthy advancement in chitin that may be applied to scaffolds and implantations in the biomedical industry (41).

2.3.5. Crystallinity

One of the most important physical properties that determine the functionality of chitosan is its crystallinity. In the solid state, CS molecules often self-assemble into highly ordered crystallites within large amorphous domains. There are two primary crystal polymorphs of CS (42). The most common polymorph is the "tendon chitosan" polymorph, which is a hydrated form. The anhydrous crystal form is referred to as the “tempered polymorph”. Two antiparallel chitosan molecules with a double helix shape supported by hydrogen bonds form the crystal cell in both polymorphs. The presence of water molecules between the crystal cells stabilizes the structure through multiple hydrogen bonds, resulting in differences between the polymorphs (43). X-ray diffraction (XRD) is used to measure the crystallinity of chitosan, which detects and analyzes the pattern created by X-ray diffraction through a dense atomic lattice in a crystal.

2.3.6. Complex formation with metals

Under near-neutral conditions, metal cations can be absorbed by chelating the amino groups of CS. The sorption of metal anions in acidic solutions is caused by the electrostatic attraction of the protonated amino groups. On the other hand, the effectiveness of the sorption (sorption isotherm) and the absorption process (the chelation mechanism could become an electrostatic attraction mechanism if the metal speciation is disturbed) is significantly influenced by the presence of ligands and the pH value (44). In addition, CS can bind metal ions more effectively than chitin. It chelates various transition metal ions and has a reactive amino and hydroxyl group. Chelation is influenced by the distribution of the amino groups and their content. The nature of the cation is crucial in the interaction mechanism.

Various processes have been proposed as mechanisms for the formation of complexes between CS and metal ions, including adsorption, chelation, and ion exchange. Both metal and pH influence the type of interaction that takes place (45).

3. EXTRACTION OF CHITOSAN

Chitosan is obtained from the shells, fungi, and exoskeletons of insects. Shrimp shell wastes and crabs are currently the most common industrial biomass source for large-scale chitosan manufacturing. To extract pure chitosan, a variety of techniques have been proposed and tested. In general, chemical procedures could be used to conduct both demineralization and deproteinization. For the extraction of CS, these traditional chemical procedures (Figure 3) are used because they are both simple and economical. In this article, the chemical extraction of CS from a variety of sources is detailed in Table 1.

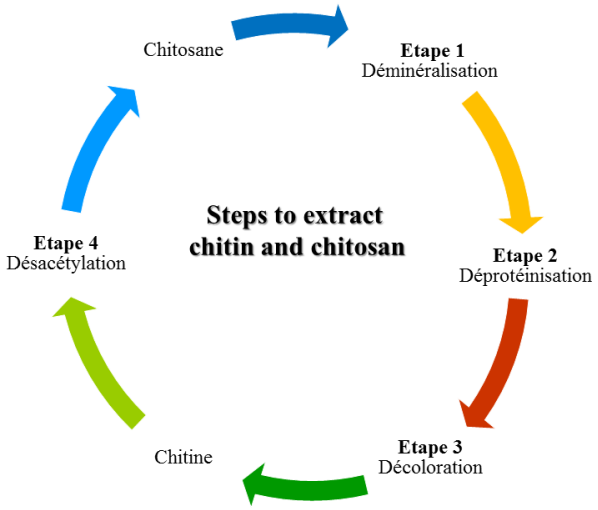

Figure 3: Chitin and chitosan extraction technique.

Table 1: Extraction techniques and characterization of CS from many sources.

Source	Demineralization	Deproteinization	Decoloration	Deacetylation	Yield Chitosan (%)	Characterization	Ref.
Shrimp	1M HCl	24 hours of 1 M NaOH	$KMnO_4$ and Oxalic acid	50% NaOH	-	FT-IR, TGA, SEM	(43)
	4% HCl for12 h	24 hours with 4% NaOH at ambient temperature	1% $KMnO_4$ and 1% oxalic acid for 30 mins to 2 hours	65% NaOH for three days	46	FT-IR, XRD, SEM	(44)
Crab	1 N HCl for 6 hours	3 hours of NaOH at 100°C	1% $KMnO_4$ for 1h, 1% oxalic acid for 1h	40% NaOH for two h at 105°C	32.2	XRD, SEM, TGA,	(45)
Tenebrio molitor	3 hours for 2 N HCl at 20°C	3 hours for 5 % NaOH at 95°C	-	50% NaOH for 3 h at 105°C	10.20		(46)
Catharsius molossus	30 minutes at 80°C and 1.30 M HCl	4 M NaOH for 6 hours at 90°C	3% $KMnO_4$ for 30 min and 2% oxalic acid for 30 min at 70 °C	24 hours of 8 M NaOH at ambient temperature	24	XRD, FT-IR, TGA, SEM	(47)
Leptinotarsa decemlineata	2 M HCl at 65–75 °C for 2 h	80-90°C for 2 M NaOH	methanol, water, and chloroform in a 1:2:4 ratio for one hour	3 hours at 100 °C with 50% NaOH	-	SEM, XRD, FT-IR, TGA,	(19)
Goliathus orientalis Moser,	1M HCl for two h at 95°C	36 hours for 2 M NaOH at 95°C	H_2O_2 (50%) for 4 hours at 25°C	50% (w/w) NaOH at 95°C	80	FT-IR, TGA, SEM	(48)
Mealworm Beetle	7% HCl at 25 °C for 24 h	10% NaOH at 80 °C for 24 h	-	9 hours for 55% NaOH at 90°C	83.37	FT-IR, XRD	(49)
Clanis bilineata	7% HCl at 25 ◦C for 24 h	10% NaOH at 60◦C for 24 h	-	4 hours for 55% at 120°C	95.9	HPLC	(50)
Bombyx mori	HCl for 20min at 100°C	24 hours for NaOH at 80°C	0.4% Na_2CO_3	NaOH (40 %), with NaBH	88.40	C NMR, SEM	(51)
Ganoderma Lucidum Mushroom	1M HCl	4 M NaOH at 50 °C		2 hours for 60% NaOH at 50°C	-	H-NMR	(52)
Grasshopper	1 M HCl in 30◦C for 2 h	1 M NaOH in 90 °C for 2 h	2 hours for 2 % $KMnO_4$	8 hours for 60% NaOH at 100°C	5.7	SEM, FT-IR, TGA, XRD	(53)
Hermetia illucens	2 hours for 2% HCl at 20°C	NaOH for 2h at 50 °C	-	NaOH at 100◦C for 2	32	NMR, FT-IR	(54)

3.1. Demineralization

Not all species of crustaceans have the same mineral composition in their exoskeleton. To dissolve calcium carbonate as $CaCl_2$, demineralization is typically performed using acids like hydrochloric acid (HCl), nitric acid, and acetic acid in concentrations up to 10 % at 25°C with continuous stirring. Although it is employed at a concentration of 0.2-2 M for 1 to 48h at temperatures ranging from 0 to 100°C, HCl is the preferred acid. Calcium chloride is produced in significant volumes when minerals are demineralized for 1–3 hours at room temperature using diluted (1–8%) HCl (1). The typical solid-to-solvent ratio is 1:15; an indication of how well the demineralization process worked is the amount of ash in the demineralized shell (15).

3.2. Deproteinization

Chitin naturally exists in conjunction with protein. Stable complexes are created when the protein forms covalent connections with chitin via aspartyl, histidyl, or both residues (57). Alkaline treatment is typically used to deproteinize chitin. The shells are subjected to potassium or sodium hydroxide treatments at temperatures between 65 and 100°C with a minimum shell-to-alkali ratio of 1:4 for between 1 and 12 hours. When these circumstances exist, the protein separates from the solid portion of the shrimp waste. To improve the deproteinization efficiency, solid-to-alkali solution ratios of 1/20 or 1/10 are utilized in conjunction with appropriate agitation. The process is typically carried out in a nitrogen environment and with sodium borohydride present to avoid oxidation of the products ($NaBH_4$). The protein hydrolysate is simply removed when the deproteinization step is finished by separating the particles from the protein slurry by filtration. Depolymerization and deacetylation are the results of protracted alkaline treatment under difficult circumstances. Table 2 summarizes the results of chemical deproteinization.

Table 2: Deproteinization processes involving chemicals.

Technique	Source types	Concentration	Temperature /Duration	Residual Protein /Chitin Yield	Ref.
NaOH	Lagoon crab (Callinectes amnicola)	2.39 M	70 ° C for 2 h	19.36 % / -	(47)
NaOH	Rock lobster (Jasis lalandii)	5%	80–85 °C for 2 × 30 min	24.0% /-	(48)
NaOH	White shrimp (Litopenaeus vannamei)	0.68 M	Ambient for 24 h	-/0.92 – 0.96%	(49)
Boiling water under pressure	Gray shrimp (Crangon crangon)	-	180 °C for1 h	-/4.7%	(50)

3.3. Decoloration

Chitin is a colored substance that is produced during the demineralization and deproteinization of shell debris. The chitin must be bleached or decolored to produce cream-colored chitin powder for commercial use (62). Chitin and the pigment found in crab shells combine to produce complexes. (63)discovered three 4, 4'-dike to-ß-carotene derivatives and one 4-keto-ß-carotene derivative securely attached to the red kelp crab's exoskeletal chitin. The degree of chitin and pigment connection varies among crab species. The leftovers are dyed using oxidants or solvents. The chemical that is employed during the decolorization process shouldn't have an impact on the physicochemical or functional characteristics of CS and chitin. Based on a dry shell, (64)were able to create a near-white crawfish chitin by extracting it with acetone, drying it for two hours at 25°C, and then bleaching it for five minutes with a 0.315% NaClO solution (carrying 5.25 %available chlorine).

3.4. Deacetylation

The process of deacetylation involves the removal of the acetyl group from chitin, resulting in the conversion of chitin into chitosan. The alkali concentration and duration of deacetylation, temperature, previous chitin isolation techniques, atmosphere, density, the ratio of chitin to alkali solution, and the size of the particle are just a few of the significant factors that significantly affect DD. The ideal deacetylation process condition should produce CS that is not damaged and is soluble in diluted acetic acid in the shortest amount of time (2), taking into account all of these prerequisites. Alkaline techniques must be used for N-deacetylation because the polysaccharide cannot be hydrolyzed without the N-acetyl groups being removed (65). The trans arrangement of the C2-C3 substituents in the sugar ring imposes a resistance of groups that necessitates severe alkaline hydrolysis processes. With a solid-to-solvent ratio of 1:10 (w/v), it is typically accomplished by treating the polymer with concentrated Na or KOH solution (40-60%), typically for 30 min at 80-140 °C or more (57). As an alkali, sodium hydroxide is chosen. After deacetylation, CS is thoroughly washed to remove any alkali that may have remained, and it is then dried to produce flakes. Ash and protein levels should be low in the substance. Chitosan is produced chemically, which has many drawbacks, including environmental contamination, variable degrees of acetylation, and molecular weights.

4.CHITOSAN DERIVATIVES

Despite being widely and effectively employed in several industrial applications and biomedical, CS has several disadvantages, including the fact that it

is insoluble at physiological pH. When protonated, CS is soluble and works as a permeation enhancer in an acidic environment. As a result, several alkylated derivatives of CS have been created. These partly quaternized chitosan derivatives have been employed in place of chitosan because they exhibit strong water solubility across a wide pH range.

The chemical alteration may readily improve the structural features of chitosan for a specific application. Fortunately, CS is open to chemical modification. Due to the presence of acetamido, amine, and hydroxyl functional groups, changes result. Because of this, chemical modifications would preserve the original biochemical and physicochemical properties of CS and would not alter its basic structural components.

4.1.Enzymatic and Chemically Modified Functional Chitosan Derivatives

By directly altering the reactive amino and OH groups with a limited number of chemical processes, a wide variety of CS derivatives with various functional substituents have been produced. Using chemocatalytic or moderate and selective enzymatic conversion, it is possible to make chitosan derivatives that are highly cationic and quaternized, anionic with arylated or carboxyl, sulfate groups, hydrophobic, or nonpolar.

4.2.Derivatives of Anionic Chitosan

Cationic and polyelectrolytes are anionic CS derivatives with acidic groups on the polymer backbone. The charge density and level of substitution may have an impact on the pH-dependent behavior of these derivatives. Typically, carboxymethylation with monohalocarboxylic acids is utilized to produce carboxyalkyl CS derivatives that have both O and N substituted to achieve N/O selectivity (66, 67).

Carboxypropyl chitosan, N/Oand O-carboxymethyl CS, and carboxybutyl CS derivatives [16], with antimicrobial characteristics, have been produced using this technique. Using reduced-oxidant amination with glyoxylic acid and 2carboxybenzaldehyde (68), respectively, glycine and carboxybenzyl pending group-containing derivatives of carboxyalkyl CS have been created. N-carboxymethyl CS is appropriate for food and cosmetics because it can form films and gels, has a high viscosity, has a large hydrodynamic volume, and is soluble in water (66). Using cross-linking glutaraldehyde, a pH-responsive hydrogel for colon-specific drug delivery, n -n-carboxybenzyl CS is created (69).

Using N / O acylation with glutaric, and succinic anhydrides, CS compounds with anticoagulant and antiplatelet action have been produced (69, 70). A recently developed sophisticated and gentle chemoenzymatic method for the selective oxidation of the C6-hydroxyl group, which is used to create carboxyl chitosan derivatives (71), and controlling the reaction conditions led to the production of a variety of oxidized CS derivatives with various levels of oxidation and characteristics. These compounds displayed reduced viscosity and higher solubility in solution. A cross-linked CS derivative that may create a self-assembling pH-responsive hydrogel was created when CS was disintegrated in weak hydrochloric acid before TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) laccase oxidation (71). The developed pH-responsive CS derivative had a sol-gel transition that was roughly at physiological pH (7.4) and had the potential to be used as a platform for the transport of medicines to the stomach.

4.3. Hydroxyalkylchitosans

In a popular process for modifying polysaccharides, such as cellulose and starch, hydroxyalkyl CS, also known as hydroxypropyl CS, glycol CS, and hydroxyethyl CS, are created using reacting alkyl epoxides (such as propylene oxide, butylene oxide, and ethylene oxide) with glycidol. The reaction conditions can be exploited to regulate the selective synthesis of different process temperatures and catalysts employed for O- or N- hydroxyalkyl derivatives. Water-soluble hydroxyalkyl chitosans have the potential to be used as temperature-sensitive injectable carriers for cells (72) and, additionally, as self-assembled nanoparticles for use in drug delivery (73). They also exhibit antibacterial capabilities.

4.4. Chitosan Derivatives That are Quaternarized and Water Soluble

For chitosan, solubilities at pH levels lower than six are not preferred. Its derivatives are used in food, medicine, and cosmetic products (74). To increase its solubility at a neutral pH, it is first derivatized with quaternary amino group substituents, then carboxymethylated, and then sulfonated by adding a highly hydrophilic substituent. Trimethyl ammonium salt is chitosan's most basic by-product. Chitosan was treated with NaOH, chloride ion, and methyl iodide in N-methyl-2 pyrrolidone to produce the trimethyl ammonium salt of CS, which has a high degree of substitution. Iodide must undergo anionic modifications with chloride ions to stabilize, producing a product that is water soluble at a pH of 7 (75).

4.5.Some Chitosan Derivatives

4.5.1. Chitosan-grafted copolymers

In recent years, there have been notable advancements in the field of chitosan-grafted copolymers, marking a significant stride in the realm of biomaterials and polymer science (76). Chitosan, a biodegradable and biocompatible biopolymer, has been ingeniously modified through grafting with various copolymers to enhance its properties and widen its scope of applications. For instance, chitosan-grafted polyethylene glycol (PEG) copolymers have shown great promise in drug delivery systems, improving drug solubility and bioavailability. Additionally, chitosan can be reductively aminated using PEG-aldehyde to add PEG(54). Polypeptides have been bonded by reacting with N-carboxy anhydrides of amino acids to produce new biomaterials (55). These copolymers can be tailored to achieve controlled release of pharmaceuticals, making them pivotal in precision

medicine and cancer therapy (77). This is just one example among many, demonstrating the versatility and potential of chitosan-grafted copolymers, which hold the key to numerous innovations in areas such as tissue engineering, biomedicine, and environmental remediation (78).

4.5.2. Alkylated chitosans

As polysaccharide-based amphiphilic polymers, alkylated chitosans play a crucial role. Highly substituted derivatives with poor regularity were produced on CM-chitosan using carboxylic anhydrides with various chain lengths. They had a reduced capacity for biodegradation and were insoluble in water (79).

The properties of alkylated chitosans with high solubility under acidic situations are particularly fascinating. They are initially evaluated against equivalent low molecular weight surfactants based on surface activity (80). They then greatly enhance the stability of the interfacial coating while having a negligible effect on the lowering of surface tension (81). A basic surfactant and modified chitosan display radically distinct behaviors, as has been demonstrated (82). Second, due to interactions between hydrophobic chains, a physical gel is produced; the creation of this gel depends on the pH and salt concentration. These gels result from a delicate balance between hydrophobic attraction caused by alkyl chains, particularly about their length, and electrostatic attraction between positively charged CS chains (6).

Because it has been shown, it is important to remember that alkyl chitosan works with both neutral and cationic surfactants and that cationic surfactant adsorbed on the alkyl chain grafted on chitosan increases its solubilization (83).

4.5.3. Chitosan 6-O sulfate

In recent years, there have been notable developments in the field of biopolymers, especially in the case of chitosan 6-O sulfate. This modified form of chitosan has received significant attention due to its unique properties and diverse applications. For example, chitosan 6-O sulfate has shown great potential in the development of wound healing materials, as it can promote tissue regeneration and reduce inflammation. In addition, it has shown promising results in the field of drug delivery, where it can serve as a carrier for controlled and targeted release of pharmaceutical compounds. The latest developments in 6-O chitosan sulfate highlight the ongoing innovation in biopolymers, with the potential to impact various industries such as medicine, biotechnology, and pharmaceuticals.

A recent study published by Bolshakov et al. (84)explored the optimization of chitosan 6-O sulfate synthesis. The researchers used a method of quaternizing chitosan with sulfate-containing ingredients to produce a product with a high percentage of sulfate groups.

In a study conducted by Samet et al. (85), it was found that sulfated chitosan oligomer (ShCsO) is a heparin mimetic. The researchers modified chitosan oligomers into ShCsO and studied its chemical composition and biological properties. Chitosan 6-O sulfate was used in developing composite scaffolds for cartilage tissue engineering. A study reported that the coupling of dermatan sulfate (DS) and chondroitin-6 sulfate (CSC) with chitosan scaffolds could improve chondrocyte culture, extracellular matrix (ECM) production, and chondrogenesis. It was reported that the high molecular weight of 6-O chitosan sulfate can effectively reduce the infectivity of porcine virus type 2 (PCV2) in PK15 cells (86). These recent developments demonstrate the potential of 6-O chitosan sulfate in various applications, including biomedical applications, tissue engineering, and inhibition of viral infection.

4.5.4. O-and N-Carboxymethyl chitosan

Carboxymethyl chitosan, a soluble polymer that is amphoteric and varies on pH, and which can be converted to O- and N-carboxymethylation in a well-regulated process (with sodium monochlorocetate when NaOH is present), is the chitosan derivative that has been the subject of the most research. Phase separation was observed because of the balance between the negative and positive charges on the polymer at pH values of 2.5 to 6.5, which extends the pH range in which CS is water soluble. NMR was used to calculate the yield of the three locations' substituted compounds (35).

The process of making N-carboxymethyl chitosan from glyoxylic acid in the presence of a reducing agent is the most intriguing. By using ^{1}H and ^{13}C NMR, it was possible to determine the disubstituted ($-N(-CH_2COOH)_2$) and distribution of monosubstituted ($-NH-CH_2COOH$) groups.

O-carboxymethyl chitosan has demonstrated its potential as a drug delivery system, effectively delivering therapeutic agents to target sites, while N-Carboxymethyl chitosan has proven its worth as a wound healing material, facilitating tissue regeneration. These latest developments underscore the ongoing evolution of chitosan-based materials, offering innovative solutions with the potential to improve drug delivery and medical treatments, as well as enhance food safety and quality in various applications (87).

4.5.5. N-methylene phosphonic chitosan

These intriguing anionic derivatives, which exhibit certain amphoteric properties, were created under diverse circumstances and shown effective complexation with cations, for example, Ca^{2+} and transition metals (Cd, Zn, Cu, etc.) (88, 89). Metal surfaces are protected from corrosion by the complexation (90). Additionally, these compounds were altered and grafted with alkyl chains to provide amphiphilic qualities that may be used in cosmetic applications (91).

4.5.6. Trimethyl chitosan ammonium

This cationic derivative was thoroughly described by NMR (92)and is generated by quaternizing chitosan with CH_3I in NaOH under experimental conditions. It is soluble in water over the entire process pH range.

Under all of the investigated circumstances, a significant reduction in molecular weight is seen during this process. With kaolin dispersions, these polymers exhibit effective flocculating properties, indicating potential applications in paper manufacturing. It has been claimed that additional quaternized derivatives have antistatic properties (93).

4.5.7. Chitosan chains with nanosheets of graphene oxide (GO)

The latest developments in materials science have seen a fascinating collaboration between chitosan chains and graphene oxide (GO) nanosheets, offering a range of interesting applications. GO has high mechanical strength, and when combined with chitosan, it can enhance the overall mechanical properties of the material. Adding GO to chitosan can reduce electrical impedance, making it suitable for applications that require conductivity, such as tissue engineering scaffolds (94). For example, Researchers have successfully designed chitosan-GO nanocomposites for drug delivery systems, taking advantage of chitosan's biocompatibility and GO's excellent drug-loading capabilities. These nanocomposites can efficiently deliver therapeutic agents to targeted sites in the body, potentially revolutionizing the field of pharmaceuticals. Moreover, this innovative combination has also proven beneficial in water purification processes, as GO nanosheets enhance the adsorption capacity of chitosan to remove heavy metals and organic pollutants from contaminated water sources due to its high adsorption capacity and biodegradability. These pioneering developments promise to address critical challenges in healthcare and environmental sustainability and demonstrate the exciting potential of chitosan-GO composites (95, 96).

5. STRUCTURAL CHARACTERIZATION

Scanning electron microscopy, x-ray diffraction, thermogravimetric analysis, nuclear magnetic resonance spectroscopy, and Fourier transform infrared spectroscopy were used to characterize the structure of chitosan and chitin.

5.1.Scanning Electron Microscopy (SEM)

One useful technique for visually verifying the shape and physical condition of the chitin surface is scanning electron microscopy. The surface shape of chitin and chitosan varies depending on the source species. Table 3 lists the surface morphologies of insect chitin and chitosan as nanofibre, nanofibre, nanopores without nanofibres, nanopore, nanofibres without nanopores, smooth surface, and (VI) rough surface. Both nanofibre and nanopore structures are seen in the chitin of house crickets, grasshoppers, orthopteran species, and crickets (11) (Figure. 4). The chitosan of aquatic insects, water-scavenger beetles, desert locusts, and Colorado potato beetles is nanofibrous. According to a few studies, the chitin of black army flies, and cockroaches exhibited both nanopores without nanofibres and nanofibres without nanopore structures (97). Furthermore, the surface morphologies of the chitosan from *Catharsis molossus* and the chitin from *Zophobas morio* and *Holotrichia parallela* were both smooth and rough (98). In this regard, Anand et al. (98) stated that chitin from crabs and squillas was shown to have a morphology similar to that of sponges and cauliflower leaves. Conus chitin's microfibrillar crystalline structure and porosity were revealed via SEM investigation. The chitin derived from krill, shrimp, and lobster shells likewise showed closely spaced fibers. Additionally, microfibril and porous structures were revealed by SEM study of P. monodon's chitin and chitosan surface morphologies (67). One of the key characteristics that influence how well chitin and chitosan are used is their surface shape. Chitin and chitosan in their nanofibre and nanopore forms have potential uses in food, medicine, and textiles.

Table 3: Surface morphology of chitin and chitosan (SEM analysis).

Species	Surface morphology				References
	Chitin	Pore diameter	Chitosan	Pore diameter	
Ranatra linearis	Nanofiber	NA	Nanofibre	NA	(20)
Chrysomya megacephala	NA	NA	Fine regular fibril structure	NA	(88)
Brachytrupes portentosus	Nanopores, thread-like fibrous	0.30–0.89 μm	Big pores and fibres	72.1 nm to 0.12 μm	(89)
Calliptamus barbarus and Oedaleus decorus	Smooth surface	NA	porous and nanofibrillar structure	100–200	(11)
Ephestia kuehniella	Pores and parallel nanofibers	5.2 μm NA	NA	NA	(90)
Hermetia illucens	Honeycomb structure and no porosity	NA	NA	NA	(86)

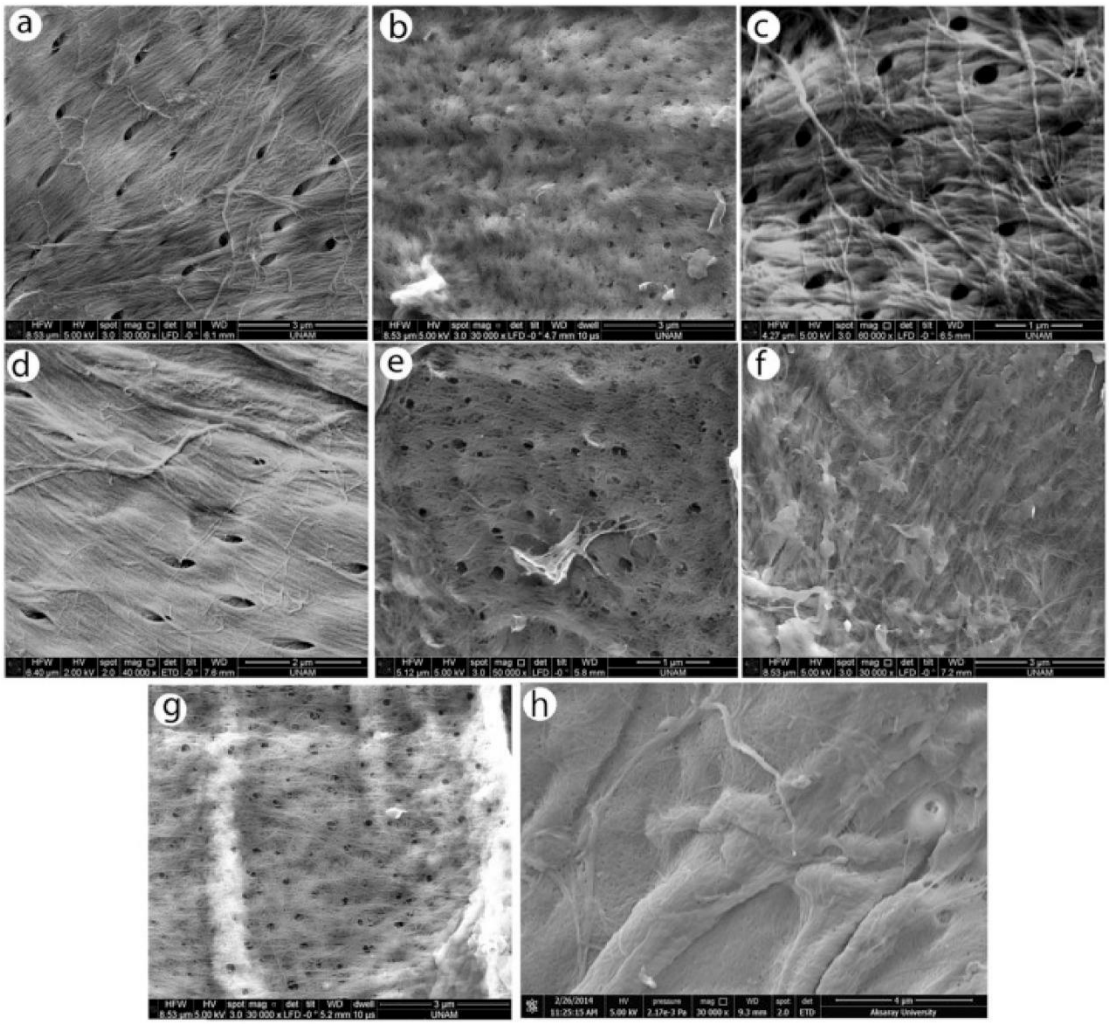

Figure 4: Electron microscopy images of seven different species of grasshoppers (a. Ailopus simulatrix chitin, b. Ailopus strepens chitin, c. Duroniella fracta chitin, d. Duroniella laticornis chitin, e. Oedipoda miniata chitin, f. O. caerulescens chitin, g. Pyrgomorpha cognata chitin and h. Commercial chitin). Reprinted with permission from Kaya et al. (20).

5.2. Fourier Transform Infrared Spectroscopy (FT-IR)

Generally speaking, organic sample identification is done using FT-IR spectroscopy. Chitin comes in three crystalline forms: beta, alpha, and gamma. However, not much is known about the gamma form. The amide I band's existence or absence may be used to distinguish between the α- and β-forms utilizing FT-IR spectra. The amide I band in the α-form splits into two bands at around 1650 and 1620 cm^{-1}, but in the β-form, the 1656 cm^{-1} area has just one amide I band. α- chitin is found in the order Arthropoda, whereas beta chitins are found in squid pens. The amide I band in the FT-IR spectra of the chitin and chitosan extracted from different insects (Figure. 5) is split at 1654 cm^{-1}, 1663 and 1618 cm^{-1}, 1647 and 1654 cm^{-1}, 1654 and 1621 cm^{-1}, 1654, 1617 and 1550 cm^{-1}, and 1656 cm−1, respectively. These insects include *Zophobas morio* (51),*Hermetia illucens* (97),*Periplaneta americana* (12), and *Apis mellifera* (102). Chitosan isolated from crab, conus shell, squilla, krill, lobster, and shrimp has an amide I band whose FT-IR spectra are separated at 1643 cm^{-1}, 1634 cm^{-1}, 1625 cm^{-1}, 1628 cm^{-1}, and 1667 cm^{-1}, respectively (103-105). These findings demonstrate that the α-form of chitin and chitosan is extracted from insects and crustacean shell debris.

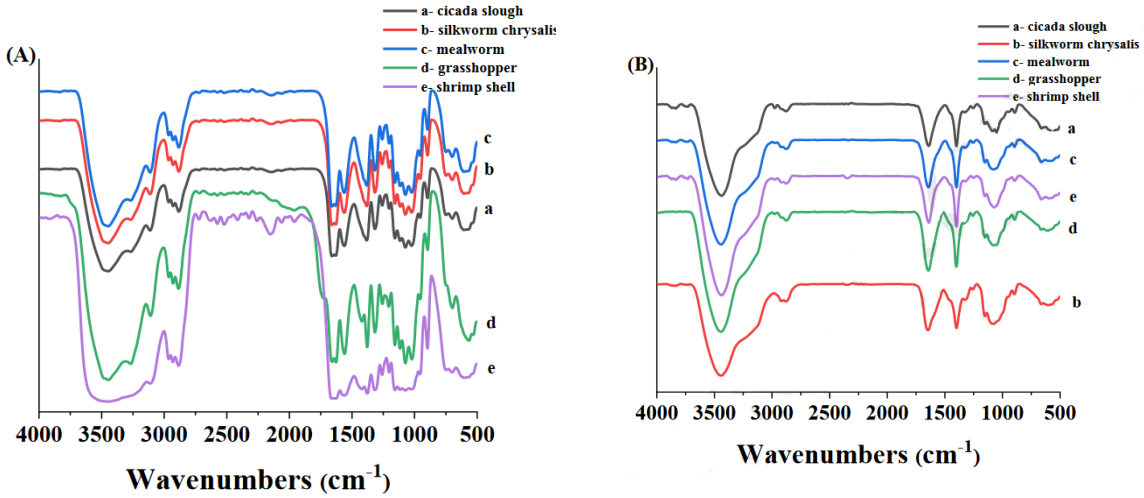

Figure 5: FTIR spectrograms of chitosan and chitin, respectively, taken from five different sources. .Reprinted with permission Luo et al., (96).

5.3. Crystalline Properties

Because they rely on whether chitin and chitosan are crystalline or amorphous, the CrI values of these substances are important in identifying possible application regions. One may use X-ray diffraction to identify this. However, the crystalline structure also symbolizes the size and purity of the biopolymer's crystals. As observed in earlier research, chitin from Hermetia illucens in the larval (33.05%) and prepupal (35.14%) stages has a low crystalline index (CrI%) (106). Nonetheless, significant CrI values have also been reported for the same species' puparium (68.4%) and adult (87.92%) stages. It has been discovered that high molarity (2 M) NaOH increases the amorphous character and decreases the crystallites of insect chitin during the deproteinization process (106). Additionally, compared to the higher CrI that had a rough and uneven surface, the resulting chitin's surface morphology had a lower CrI with an amorphous area and a porous surface. Park et al. (107) state that the ratio of the crystalline contributing area to the overall area was used to calculate the CrI. Likewise, Agabus bipustulatus and Brachytrupes portentosus yielded seven and ten different peaks at 2θ, respectively, with the highest CrI values of 90.6% and 88.02% among the total XRD peaks. This result also shows the impurity of the chitin that was extracted with N-6.02% from B. portentosus. The crystallinity indices of the chitosan from mealworms, shrimp shells, and grasshoppers were comparable, and the CrI values of the chitosan from *silkworm chrysalises*, *cicada slough*, *grasshoppers*, and mealworms were found to be 32.9%, 64.8%,51.9%, 49.1%, and 50.1%, respectively (Figure 6). Anand et al. (98) reported that the chitosan derived from crab and squilla had two distinct crystalline peaks at 2θ = 10.3° and 19.2° and 2θ = 10.2° and 19.5°. These peaks were slightly moved to a higher diffraction angle and demonstrated semi-crystalline chitosan. Six crystalline peaks with a CrI between 69 and 76% were shown by *Vespa orientalis*, *Vespa crabro*, *Vespula Argynnis Pandora*,*germanica*, and Ailopus simulatrix (12).

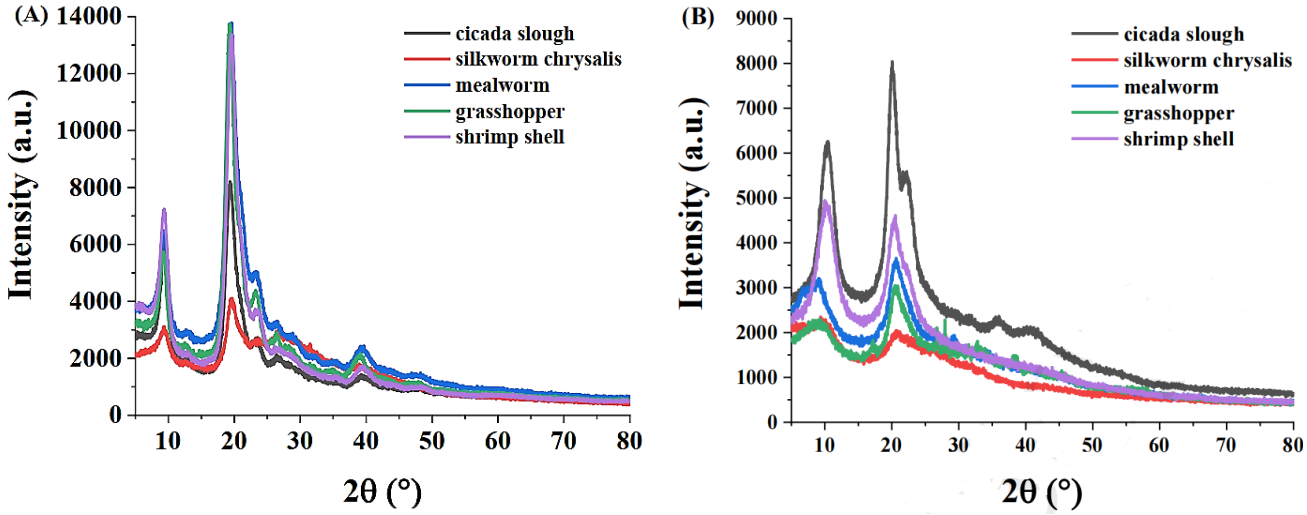

Figure 6: XRD of (A) chitin and (B) chitosan extracted from five sources: shrimp shells , mealworm, grasshopper, silkworm chrysalis, and cicada slough. Reprinted with permission Luo et al., (96).

6. APPLICATIONS OF CHITOSAN

Chitosan has garnered considerable scientific and commercial attention due to its macromolecular structure, biodegradability, biocompatibility, bioactivity, and other intrinsic functional features. CS has practical applications in the cosmetology industry, food, paper industries, textile, agriculture, sludge dewatering, and wastewater treatment (108). Figure 7 lists the main uses of chitosan. The most significant and recent uses of chitosan are highlighted in this section.

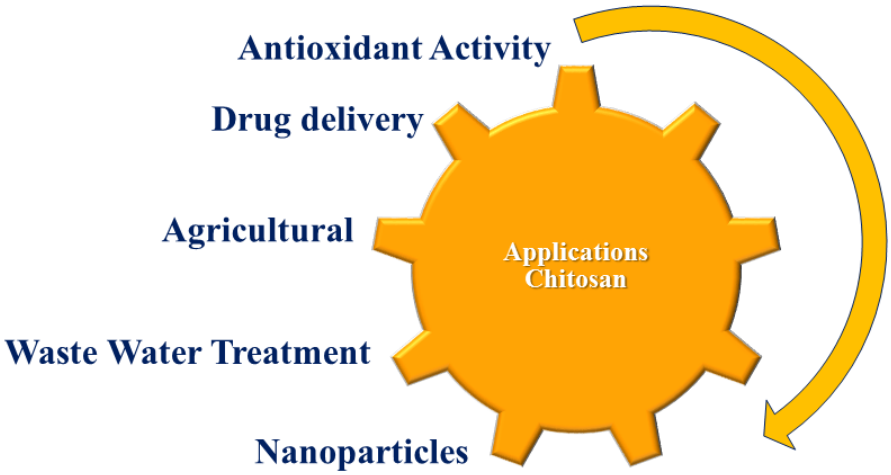

Figure 7: Different applications of chitosan.

6.1. Chitosan's Influence on How Metal Nanoparticles are Formed

CS can be utilized as a multipurpose agent in the environmentally friendly manufacturing of metal nanoparticles. CS can have an impact on metal nanoparticles both during the production and functionalization processes. Chitosan, which has a positive charge, interacts electrostatically with nanoparticles, which have a negative charge (which have the negative capping agent) occurs when the cationic polymer CS is introduced to the reaction solution (109, 110), or CS is absorbed on the surface of the metal nanoparticles, as shown in Figure 8 (111), resulting in a CS shell surrounding the nanoparticles. The CS can be added either before or after the nanoparticles are created, depending on the production procedure. As a result, CS directly affects how nanoparticles are made. Therefore, CS has a direct impact on how nanoparticles are produced. CS can function as a reducing, stabilizing, and size-controlling agent for the synthesis of metal nanoparticles. CS is used to modify the surface of nanoparticles during the functionalization process to enhance their biocompatibility and drug-carrying capabilities. The harmful effects on the environment and human health can be mitigated by using CS in the production of metal nanoparticles (112, 113).

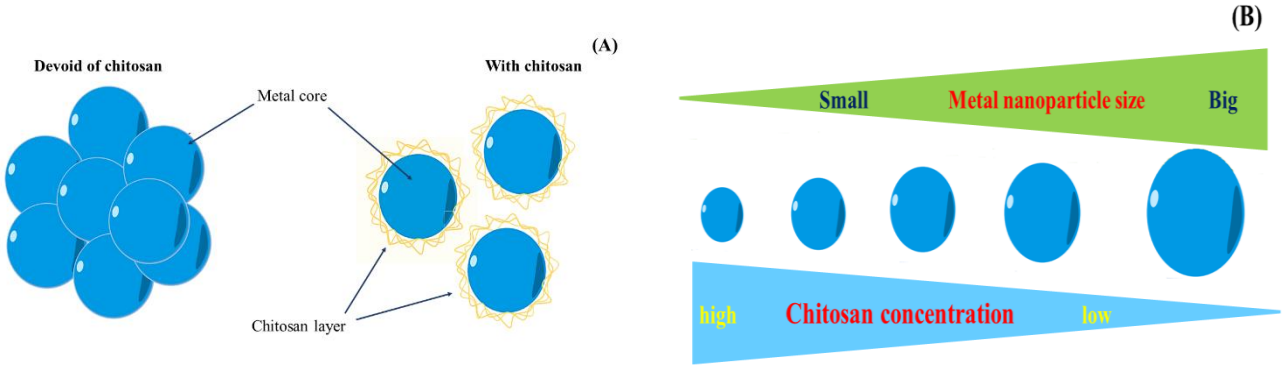

Figure 8: Influence of CS capping on the dispersion of NPs (A) and The relationship between chitosan concentration and the size of NPs (B).

6.2. Application of Chitosan in Agriculture

Plant diseases can be prevented and treated in agriculture with chitosan. They are effective against bacteria, viruses, fungi, and other pests in the soil. Adding chitosan changes the rhizosphere and phyllosphere's environmental conditions, tipping the microbial balance in favor of beneficial organisms and against plant pathogens. It is known that chitosan fragments in host plants cause the accumulation of phytoalexins, lignin synthesis, callose formation, and proteinase inhibitors, among other defense responses. Chitosan and its derivatives also exhibit antiviral and antibacterial properties. In soil, parasitic nematodes have been successfully

eliminated by using these polysaccharides. Chitosan film provides antibacterial protection and increases the fruits' and vegetables' storage life (114). Chitosan and its derivatives positively impact the metabolism of fruits and plants. This leads to increased crop yields and germination.

6.3. Food Industry

Enclosing beef in electrospun chitosan fibers while it is being dry-aged for up to three weeks produced superior outcomes than conventional dry-aging in terms of lower counts of bacteria, lighter look, molds, yield, yeasts, and less muscle denaturation. While lactic acid bacteria formation was seen, wet-aging of beef had low weight and trimming losses (115).

6.4. Waste Water Treatment

Water pollution is caused by a variety of harmful elements, for example, heavy metals, dyes, aromatic chemicals, etc (116). There is a significant environmental problem that could have serious health implications (117). As a result, chitin and chitosan, which are both inexpensive, are now extensively suggested for wastewater treatment. Giabl et al. (118)investigated the effects of chitosan characteristics on heavy metal, dye, and organic chemical adsorption. Chitosan-based materials can be used to remove anionic dyes, as Crinni and Badot have discovered. Chitosan has been applied to the treatment of aquaculture effluent as a coagulant, adsorbent, and bactericide. Low molecular weight and high DD chitosan samples increase the effectiveness of chitosan in coagulating and flocculating organic solutions at pH levels close to neutral and with little ionic strength (119).

Chitosan has emerged as a prominent solution for the mitigation of heavy metal contamination. Numerous studies have shown that chitosan can effectively remove Cr (VI), As (III), As (V), heavy metal oxyanions (Cu (II), Pb (II), Cd (II), Hg (II), Pd (II) and Pt (IV) (120). According to Ghinia et al. (121), chitosan has demonstrated significant efficacy as an adsorbent for zinc and many other metal ions present in wastewater, with the added advantage of being recyclable. For use in composites, the mechanical properties of chitosan are stabilized and improved by grafting, cross-linking, and functionalization. In contrast to poly (4-vinyl pyridine) modified activated carbon (53.7 mg/g) and ethylenediamine-functionalized Fe_3O_4 (61.35 mg/g). Effective elimination of Cr(VI) (67.66 mg/g) was demonstrated in another investigation by Li et al. (45).

The occurrence of water pollution due to metal ions is widespread and commonly attributed to industrial activities. Toxicity is a characteristic shown by certain substances, which can have detrimental impacts on organisms. Water and wastewater can undergo the process of biosorption utilizing chitosan to facilitate their removal. Heavy metal (including Pb, Cu, Ag, Ni, Cr, As, and others)adsorption has been demonstrated for chitosan and its derivatives, precious metals (such as Pd, Au, and Pt), as well as radionuclides.

In their study, Li et al. (45) synthesized a magnetic-cyclodextrin-chitosan (CC) material that exhibits enhanced separation properties and increased adsorption capacity. Furthermore, the incorporation of graphene oxide (GO) into the carbon composite (CC) was utilized to enhance the adsorption competence for metal elimination by chemical bonding. The findings of the study revealed that the adsorption capacity of magnetic-cyclodextrin-chitosan/graphene oxide (CCGO) for Cr(VI) exhibited a higher removal efficiency (67.66 mg/g) compared to other sorbents like poly(4-vinyl pyridine) modified activated carbon (53.7 mg/g)and ethylenediamine-functionalized Fe_3O (61.35 mg/g). The observed phenomenon can be attributed to the augmentation in the surface area resulting from the greater abundance of hydroxyl and amino groups, in addition to the magnetic characteristics shown. The findings of the study indicate that the efficacy of removal was greater under conditions of low. Additionally, it was observed that the adsorption equilibrium of CCGO followed the Langmuir isotherm model.

6.5. Antioxidant Activity

CS and its derivatives have been shown to have powerful antioxidant effects. By scavenging free radicals, they can lessen lipid oxidation thanks to their ability to bind metals. Molecular weight, viscosity, and DD all have an impact on the antioxidant properties of CS and chitin (122).

6.6. Chitosan as Lipid-Lowering Agent

Because of its capacity to lower serum cholesterol, chitosan is utilized as a dietary additive. It decreases lipid absorption by forming hydrophobic interactions with neutral lipids like cholesterol and other sterols. Chitosan works in the digestive system as a fat scavenger, excreting fat and cholesterol as a result of its inhibitory effect on fat absorption. Chitosan satisfies dietary fiber requirements such as high viscosity, non-digestibility, and lower GI tract water-binding ability. From a physiological standpoint, the primary role of dietary fiber is to reduce cholesterol levels and promote weight loss by reducing intestinal lipid absorption. Its positive ionic charge distinguishes it from other dietary fibers, allowing it to chemically bind with fats, bile acids, and negatively charged lipids.CS has an LD_{50} (median lethal dosage) of roughly 16 $g.kg^{-1}$, which is equivalent to salt and glucose values, indicating that it is safe to use for lengthy periods (123).

6.7. Delivery of Drugs

The goal of drug delivery systems is to enable controlled drug release, increase delivery time, increase target specificity, and reduce drug dose and time. These systems are considered a breakthrough in the pharmaceutical industry and are designed for the delivery of active ingredients, peptides, vaccines, proteins, and genes (124). Due to their degradability, natural polymers, in particular chitosan, offer a wide range of vehicles for drugs. Other advantages of CS as a drug carrier are its good biocompatibility and low toxicity. CS can be formulated in various ways depending on the management and the goals of the function. In addition, the protonated amino groups of D-

glucosamine in the chitosan structure allow it to adhere to negatively charged mucus layers and penetrate deep layers of the epithelium through electrostatic contact. CS has been used as a vehicle for drug delivery via the nasal, buccal, pulmonary, and ocular routes because of its mucoadhesive effect (125, 126). Chemical modifications such as carboxymethylation, acetylation, thiolation, quaternization, and others affect the problem of the insolubility of chitosan under physiological conditions, which is disadvantageous for successful drug delivery (127). N, N, N-Trimethyl-CS (TMC), thiolated CS obtained by exchanging amino groups with thioglycolic acid, N-acylated CS products, and carboxymethylated CS are examples of quaternary ammonium chitosan derivatives with permanent positive charges. They are known for their high solubility over a wide pH range, thereby increasing the mucosa (128). Growth factors, anti-inflammatories, antibiotics, vaccines, and chemotherapeutic agents have been delivered to target cells using CS-based drug carriers in micro/nanoparticles, gels, films, sponges, and fibers. In dentistry, CS-based drug delivery systems are used to treat periodontitis, root canal treatments (endodontics), and dental caries and to administer long-acting local anesthesia (129).

Chitosan derivatives have been used in targeted drug delivery systems to improve treatment outcomes and reduce side effects. Colon-specific delivery systems have been developed for diseases like Crohn's disease, ulcerative colitis, and irritable bowel syndrome. These systems use water-soluble amphoteric chitosan derivatives and o-carboxymethyl chitosan to prevent drug degradation in the stomach and small intestine. Spherical microcapsules have been used for intestine-targeted drug delivery, improving bioavailability and stability. Liver-targeted delivery systems use reticulated endothelial passive capture microparticles or active targeting based on liver receptor recognition. Insulin administration using fatty-acid-modified quaternary ammonium chitosan derivative nanoparticles has shown improved anti-diabetic effectiveness and increased hepatocyte absorption. Ferulic acid has been delivered to the liver using modified chitosan nanoparticles and glycyrrhizic acid. Acetylated low molecular weight chitosan is used in kidney and lung-targeted administration to facilitate renal medication delivery. The potential of a newly synthesized folic acid-grafted polyethylene glycol chitosan copolymer to lessen the adverse effects of very hazardous medications has been shown.

Chitosan derivative nanoparticles have the potential to improve drug delivery and transport by improving bioadhesion and permeability. These nanoparticles are used in targeted drug preparation, sustained release, and increasing drug absorption. Delivery carriers of chitosan include microspheres, nanoparticles, micelles, and gels, with particle sizes ranging from 1–500 μm. These nanoparticles can pass through biological barriers and provide better stability, tissue permeability, and sustained drug-release properties (83).

Chitosan derivative nanoparticles are also being researched for controlled drug delivery, as some drugs have short release times and require more doses to maintain plasma balance. The continuous delayed release of chitosan derivative nanoparticles may increase bioavailability and therapeutic effectiveness while lowering negative effects. Protein drugs are preferred due to their targeting and biocompatibility, but they have drawbacks such as enzyme degradation, low permeability in the intestinal epithelium, and poor oral absorption (130).

Peptide-loaded nanoparticles with improved thermal stability and controlled in vitro release are produced when chitosan derivative nanoparticles interact with peptides via hydrogen bonds and static electricity. Insulin-loaded quaternary ammonium chitosan nanoparticles modified by fatty acid have shown excellent loading capacity and efficiency (131, 132).

Gene therapy is a promising strategy for challenging diseases, and a safe and effective gene delivery system is critical for successful application. Non-viral vectors offer advantages such as ease of production, high yield, and low cost, making them suitable for gene delivery (133).

The mucosal immune system, which includes lymphoid tissues in the respiratory, gastrointestinal tract, genitourinary mucosa, and some exocrine glands, plays a crucial role in preventing infectious diseases. Mucosal vaccines have shown potential in enhancing mucosal immunity, as local antibodies work faster than serum antibodies and have a longer maintenance time. The process of immunity is shown in Figure 9 (134).

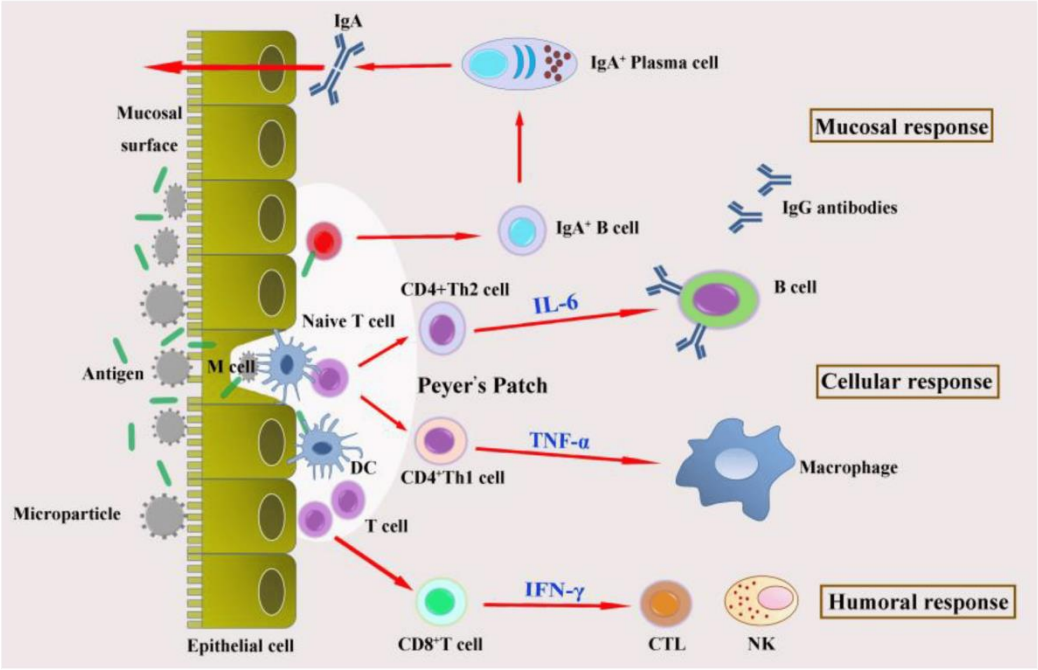

Figure 9: The generation of antibodies is immune-related. Reproduced with permission from Wang et al. (72).

Chitosan derivative nanoparticles can facilitate transmembranal drug delivery and have better water solubility, mucoadhesivity, and antigen absorption. They can serve as vaccine adjuvants or delivery carriers for mucosal immunity. Composite biological nanomaterials have been synthesized to achieve a higher mucosal immune effect. Intranasal immunization with chitosan nanoparticles induced stronger cellular, humoral, and mucosal immune responses than commercially available vaccines. Chitosan-coated PLGA nanoparticles have also been shown to induce humoral, stronger cellular, and mucosal immune responses than plasmid DNA alone. These results imply that, in the case of DNA vaccines, chitosan-coated nanoparticles may serve as an effective mucosal immunization delivery mechanism (135, 136).

6.8. Antimicrobial Activity

In recent years, there have been exciting developments in the understanding and application of the antimicrobial activity of chitosan (137). The ability of chitosan to inhibit the growth of various microorganisms, including bacteria and fungi, has drawn great attention in the fields of medicine, food preservation, and agriculture. For example, chitosan has been used as a natural, environmentally friendly antimicrobial agent in food packaging materials, extending the shelf life of perishable goods and reducing the need for chemical preservatives. In healthcare, chitosan-based wound dressings have been developed to prevent infection and speed up the healing process. As antibiotic resistance becomes a growing concern, exploring and utilizing chitosan's antimicrobial properties represents a promising avenue for infection control health promotion and sustainability in diverse industries (138).

6.9. Other Applications

6.9.1. Cosmetics

Chitosan has excellent film-forming abilities and a bioadhesive nature. Thus, it can function either as a delivery system or as an active component, prolonging the contact time of an active substance with the dermis and enhancing the penetration of active compounds in a regulated and long-term manner. These are the two main uses in cosmetic and cosmetic products. Essential oils and, for example, active ingredients, antioxidants, enzymes, and vitamins are partly contained in cosmeceuticals, with chitosan as the main component. Due to its antibacterial properties, CS is often used in dental care. In toothpaste, it can slow down the growth of oral germs and stop tooth erosion (139). Additionally, it can be used as a healthy substitute for traditional preservatives. CS is also an effective ingredient for hair care. Increases hair softness and flexibility, reduces static electricity, removes oils and sebum, retains moisture in the hair, fights dandruff fungus, and stimulates hair growth.

6.9.2. Tissue engineering

It is the process of improving or replacing biological functions by combining cells, artificial materials, and appropriate biochemical variables. It can be applied to several things, including partial or complete tissue replacement or repair (for instance, muscle, bone, blood vessels, skin, the bladder, and cartilage) (140). With recent significant advancements, chitosan-based biomaterials have emerged as a key area of study in tissue engineering. It gives the restored tissues certain mechanical and structural qualities that allow them to function properly (140).

Chitosan-based biomaterials have shown promising potential in skin tissue engineering due to their biodegradable, non-toxic, and biocompatible properties. These materials can be modified to

develop multifunctional structures with a morphology similar to the natural matrix (141).

Several studies have explored the potential of chitosan-based membrane formulations in skin tissue engineering. For example, one study designed a chitosan coating using titanium dioxide nanoparticles, which demonstrated potential structural and functional regenerative properties. The membranes also exhibited antibacterial activities against Staphylococcus aureus and showed rapid growth and reduced oxidative stress and apoptosis when applied to L929 mouse fibroblast cells (142).

Another study prepared chitosan membranes loaded with glycerol and antibacterial agents, which provided long-term stability and antibacterial activity against the growth of *S. aureus* and *E. coli*. An in vitro culture test of dermal fibroblasts showed enhanced proliferation of fibroblast cells on membranes, suggesting that these membranes could be used as an antimicrobial dressing system to treat skin burns (143).

In a different study, the combined use of ibuprofen and chitosan-polyvinyl alcohol membrane was examined for its capacity to cure wounds. The drug release was shown to be maintained, and normal human dermal fibroblasts were not adversely affected. Additionally, biocompatible microfibre membranes made of silk and chitosan demonstrated improved mechanical qualities and increased cell proliferation (144).

Another study examined the anti-inflammatory performance of the chitosan-hyaluronan-edaravone membrane during wound healing, which resulted in a lower inflammatory response and supported the migration of fibroblasts, keratinocytes, and endothelial cells, effectively promoting wound healing (144).

Another study prepared iodine-sodium alginate complex systems based on hydroxylated lecithin and chitosan and tested them on burn wound rat models. The fabricated membranes showed superior repair properties in deep, partial-thickness rat burn models, with high vascular endothelial growth factor expression observed (144).

Chitosan-based hydrogels have gained great interest in skin tissue engineering due to their high porosity, water absorption, swelling ability, satisfactory mechanical properties, biocompatibility, and biodegradability. These hydrogels have been widely reported for their skin rejuvenation potential. However, since chitosan hydrogels have poor mechanical strength, mixes of chitosan with other natural or synthetic polymers work better. Hydrogels based on chitosan may also have their mechanical strength increased by cross-linkers (144).

Several studies have investigated the use of chitosan-lignin hydrogels, which have shown improved cell growth capabilities and increased fibroblast penetration. Chitosan gelatin loaded with human dermal fibroblasts has also been investigated for its wound-healing potential in mice. The scaffold was highly porous and cross-linked, with human dermal fibroblasts showing attachment and migration onto the scaffold. In vivo experiments in mice demonstrated enhanced re-epithelialization of a skin wound treated with a transdermal fibroblast-loaded hydrogel (145).

When the regeneration capacity of chitosan hydrogel made with oxygenated fluorinated methacrylamide was evaluated, it revealed higher collagen fiber contents, better re-epithelialization, and enhanced vascularization. Another study examined alginate-chitosan hydrogel synthesized with hesperidin on injured mouse models, which demonstrated biodegradability and bactericidal properties. It has been discovered that the hydrogel reduces inflammation and encourages fibroblast growth, which speeds up the creation of epidermal layers, tissue granulation, and remodeling (145).

A chitosan-polyethylene glycol hydrogel impregnated with silver nanoparticles has been tested for the treatment of chronic diabetic wounds. The hydrogel showed high porosity and swelling properties, increased antimicrobial activity against *E. coli*, Pseudomonas aeruginosa, *Bacillus subtilis*, and *S. aureus*, and strong antioxidant activity. In investigations on wound healing, the hydrogel outperformed the control group in terms of keratinocyte migration, re-epithelialization, and wound contraction (146).

7. CONCLUSIONS

In this comprehensive review of chitosan, its sources, properties, extraction methods, derivatives, structural characterization, and wide-ranging applications are explored. From the depths of crustaceans to the intricacies of fungi, we have navigated through various sources, revealing the unique qualities of chitosan, including its molecular weight, viscosity, degree of deacetylation, crystallinity, and its interesting ability to form complexes with metals. The extraction process, which includes demineralization, deproteinization, decolorization, and deacetylation, is dissected to highlight methods that unleash chitosan's potential.

Furthermore, the article highlighted the diversity of chitosan derivatives and provided insight into their structural characterization. By exploring the applications of chitosan in diverse fields, from pharmaceuticals to agriculture, the study underscores the importance of this biopolymer in addressing contemporary challenges.

In concluding this review, it is clear that chitosan, with its countless properties and applications, represents a promising and sustainable material for future progress. The journey through its complexities invites researchers and practitioners alike to further explore and harness the potential of chitosan for innovative solutions in many industries.

8. CONFLICT OF INTEREST

The authors possessed no relevant financial or non-financial interests.

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