Review Article

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Polymer Sciences
ISSN 2471-9935

2019
Vol.5 No.1:3

Water Soluble Chitosan Derivatives and their Biological Activities: A Review

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Abstract

Recently, numerous scientific articles related to water soluble chitosan (WSC) have been released. Since the solubility of chitosan is restricted to acidic media, and there is an increasing demand against to the derivative of the chitosan polymer, which is mainly to obtain a material both having solubility in aqueous media and also being chitosan property. One of the benefits of synthesis of water soluble chitosan is to obtain a water soluble polymer is easily miscible with a variety of compounds in aqueous solutions. In this review, water soluble chitosan derivatives are principally examined in terms of their biological and other applications. Biological activities of WSC derivatives are analyzed in the sense of antioxidant, antimicrobial and anticancer activity, respectively. Thereby, the collected data may be useful to compare novel synthesized water soluble chitosan derivatives with alternative structures.

Keywords: Water soluble chitosan; Antioxidant; Antimicrobial; Anticancer; Activity

Received: May 06, 2019; **Accepted:** June 03, 2019; **Published:** June 10, 2019

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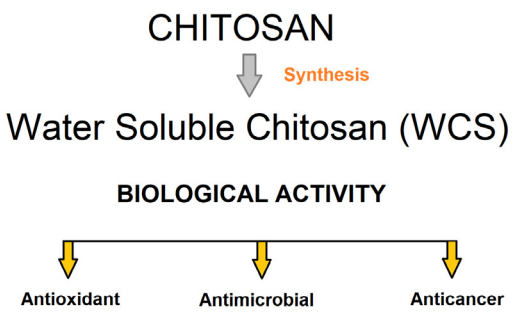
Citation: Kahya N (2019) Water Soluble Chitosan Derivatives and their Biological Activities: A Review. Polym Sci Vol.5 No.1:3

Introduction

Chitosan is a linear polysaccharide composed of β-(1-4)-linked 2-amino-2-deoxy-D-glucose and 2-acetamido-2-deoxy-D-glucose units. Chitosan is obtained from chitin, which is the second most common natural polysaccharide after cellulose, by acetylation of 2-amino-2-deoxy-D-glucose unit of chitin in alkali media [1]. **Figure 1** shows the structure of chitin and chitosan.

Chitosan has been commonly used in many applications through its biodegradability, biocompatibility and non-toxicity [2]. These unique properties enable to produce various chitosan based materials which are used in drug delivery [3], adsorption [4], food packaging [5], food additive [6], and in agriculture [7]. Chitosan is soluble in acidic media. The polymer chains are charged positively when it is dissolved in an aqueous solution of pH<6.5. Commonly used acidic solutions for dissolving chitosan are acetic acid, lactic acid, formic acid, and hydrochloric acid [8]. However, this cationic charged polymer usage is limited in some aspects due to it cannot be dissolved easily in aqueous media [9]. Water soluble chitosan is produced generally by substituting hydrophilic groups onto chitosan. Water soluble chitosan derivatives have been synthesized in a variety of structures [10,11].



Adding water soluble functional groups on chitosan's back bone, converts the polymer in an expedient form for many biological applications such as being antioxidant [12], antimicrobial [13], and anticancer agent [14]. Due to such properties, water soluble chitosan attracts many researchers' attention under the favour of its being highly soluble in aqueous solutions. **Figure 2** shows the total number of publications on water soluble chitosan between 1983 and December 2017. As it is seen from **Figure 2**, number of Web of Science (WOS) articles also in a balanced level showing the validity of topic in recent ten years. There has been a significant difference in publication number in comparison to last twenty years articles since from as known first article reported in 1983 [15]. In this review, synthesis routes of several water soluble chitosan derivatives are discussed. This review aims to collect

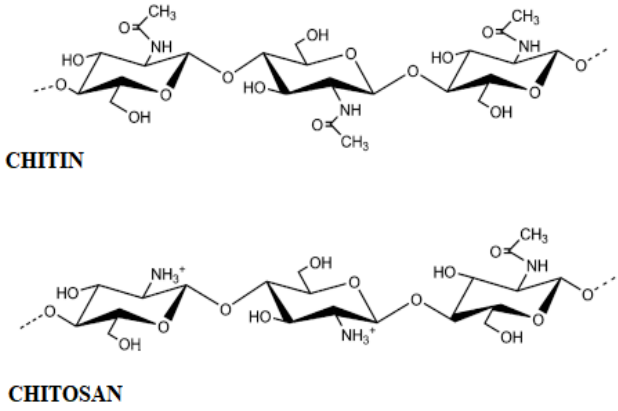


Figure 1 Chemical structures of chitin and chitosan.

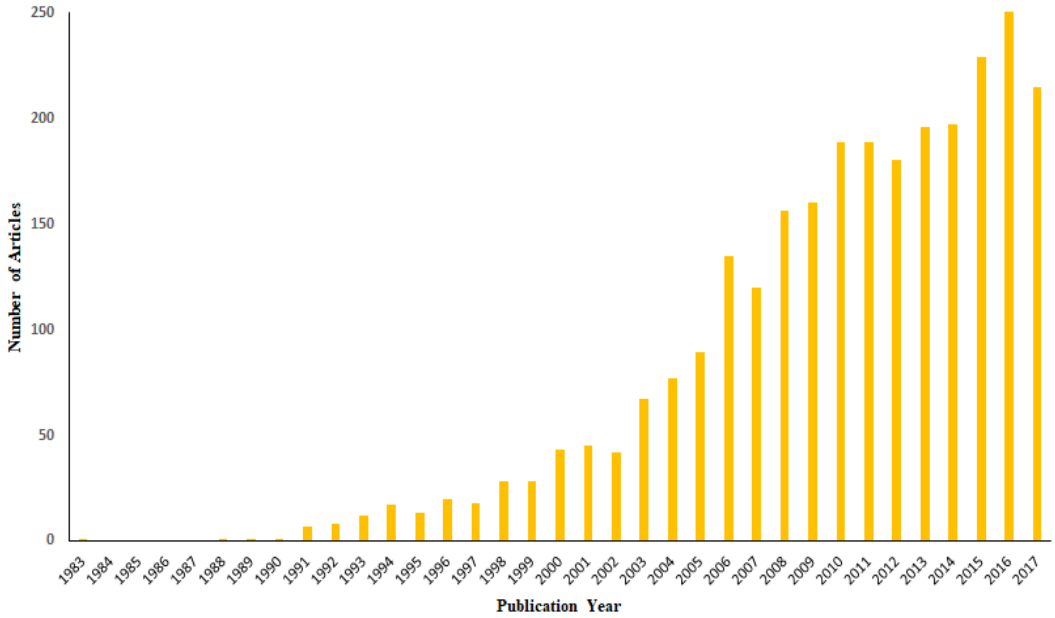


Figure 2 Number of WOS articles on water soluble chitosan between January 1983 and December 2017.

a wide range of published articles on water soluble chitosan as concentrating on its biological applications of antioxidant, antimicrobial, and anticancer, respectively. Furthermore, water soluble chitosan or WSC based material's usage is compared to exhibit their possible applications in different scientific fields.

Synthesis of Water Soluble Chitosan Derivatives

Water soluble chitosan derivatives are obtained by the addition of a variety of functional groups, which helps to make chitosan soluble in aqueous media, onto chitosan backbone. Chemical modification of chitosan enables to produce water soluble products that are useful for many further applications [16]. In literature many studies showed that synthesis of water soluble chitosan has been performed mostly modification of chitosan's backbone chair structure via modification of the chains with chemically proper compounds. It is quite common method to modify the side chain structure of chitosan via gaining the polymer a water soluble property.

A novel water soluble chitosan with both quaternary and NH_2 groups on its glycosidic units, trimethyl quaternary derivative of chitosan, was prepared through protection-deprotection strategy. Trimethyl chitosan (TMC) derivative was synthesized by the multi-step way as it can be seen from **Figure 3**. Firstly, amino groups in chitosan were protected. Then, hydroxyl groups of glycosidic units were enabled via converting them to phenyl carbonate ester groups. After a few more steps related with nucleophilic addition or substitution, finally protected-deprotected synthesis of quaternary chitosan derivatives was done by removing functional groups protectors [17].

Producing water soluble chitosan was done by enzymatic hydrolysis of chitosanase via breaking down polymeric chain of the polymer. In this enzymatic hydrolysis method, chitosanase from Streptomyces sp. N174 was used. Chitosanase enzyme

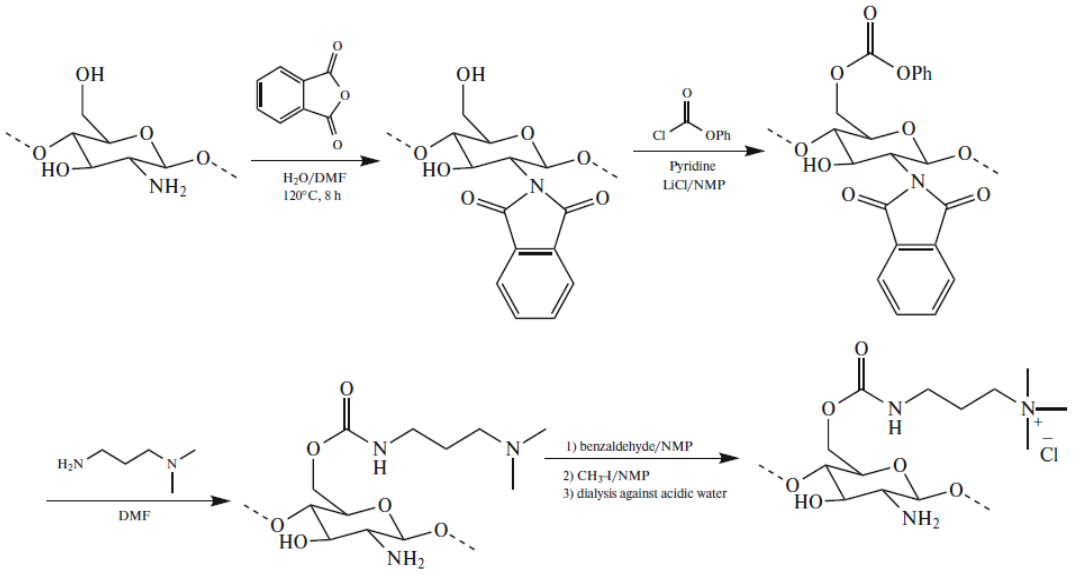


Figure 3 The scheme showing the steps of synthesis of trimethyl chitosan (TMC) derivative. (It is adapted from Seidi et al. [17]).

decreased the molecular weight of chitosan and particle size, curtailed the polymer chain, and significantly improved the water solubility of chitosan [18]. In some literature studies, the water soluble chitosan was prepared practically by hydrolysis of chitosan with commercial α-amylase [19,20]. Enzyme catalyzed production of WSC was obtained by chitosanolytic enzyme which was isolated from the soluble part of jelly fig latex. The jelly fish latex chitosanase was used to hydrolysis of chitosan derivatives, as ethylene glycol (EG) chitosan, carboxymethyl (CM) chitosan and aminoethyl (AE) chitosan [21].

A novel water soluble chitosan derivative (DCDA-g-CS) was prepared by graft polymerization of dicyandiamide. Characterization studies showed that DCDA-g-CS has a higher solubility in water by means of decreased crystallinity of chitosan after grafting. The aim was to improve solubility of chitosan via grafting DCDA onto chitosan by using potassium persulfate as initiator at 60°C. In this way, the free amino groups of chitosan bonded with double bonds to dicyandiamide and it was resulted in triple bonds which will allow further polymerization [22]. Linear and water soluble poly(butylene tartrate) (PBT) was grafted onto chitosan (CS-g-PBT) via the coupling reaction. **Figure 4** shows the synthesis procedure of CS-gPBT. After synthesis of PBT, the coupling reaction were occurred between the carboxyl group of PBT and amino groups of chitosan mediated by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC). For the coupling reaction a green solvent 3-methylimidazolium trifluoromethanesulfonate ($BSMIM.CF_3SO_3$) were chosen. Novel water soluble CS-g-PBT copolymer had good solubility in deionized water [23].

Two novel water soluble O-carboxymethyl chitosan Schiff bases named as OCMCS-5 and OCMCS-6a were synthesized. The prepared mono imine Schiff bases were obtained by condensation reaction of 2,6-diacetylpyridine with aniline orisopropyl aniline (1:1 mole). Monochloroacetic acid treatment of Schiff bases provided total water solubility [24].

Another way to synthesize water soluble chitosan is hydrolysis of the polymer using hydrogen peroxide. The present work represented hydrolyzing of chitosan using H_2O_2 under the catalysis of phosphotungstic acid. The content of the water soluble chitosan in the product and the yield were 92.3% and 94.7%, respectively [25]. Besides, different water soluble chitosan derivatives were synthesized in varying molecular weights (MW) via oxidative degradation assisted microwave irradiation. After dissolution of chitosan in acetic acid, H_2O_2 was added to the mixture. Microwave assisted degradation was performed at a power of 600 W at 70°C for different time intervals. Ethanol was used to precipitate the products. Lastly, the collected samples were centrifuged and lyophilized to obtain powdered WSC derivatives. The produced WSC derivatives associated with MW displayed excellent fat- and cholesterol binding capacities [26]. Another study investigated the oxidative degradation of chitosan using two peroxo species as $(TBA)_3\{PO_4[WO(O_2)_2]_4\}$ and $K_2[W_2O_3(O_2)4]$. It was found that both species were efficient catalysts for the oxidative degradation of chitosan. Moreover, as a novel catalyst, reusable $(TBA)_3\{PO_4[WO(O_2)_2]_4\}$performed a high degradation ratio of 96.2% even after 7 times usage [27].

N-(2-hydroxy) propyl-3-trimethylammonium chitosan chloride (HTCC) was synthesized as a water soluble chitosan derivative by the reaction of chitosan with glycidtrimethyl ammonium chloride in neutral aqueous condition. FTIR results showed that the characteristic bands of amine NH vibration of chitosan was disappeared at HTCC because of quaternary ammonium salt formation in the chitosan and the change of primary amine to secondary amine [28].

O,N-(2-sulfoethyl) chitosan with degrees of substitution up to 130% was prepared by reacting chitosan with sodium 2-chloroethanesulfonate in isopropanol in the presence of NaOH. Additionally, sulfoethylation of chitosan favorably occurred between at hydroxyl groups and some extent at amino groups [29].

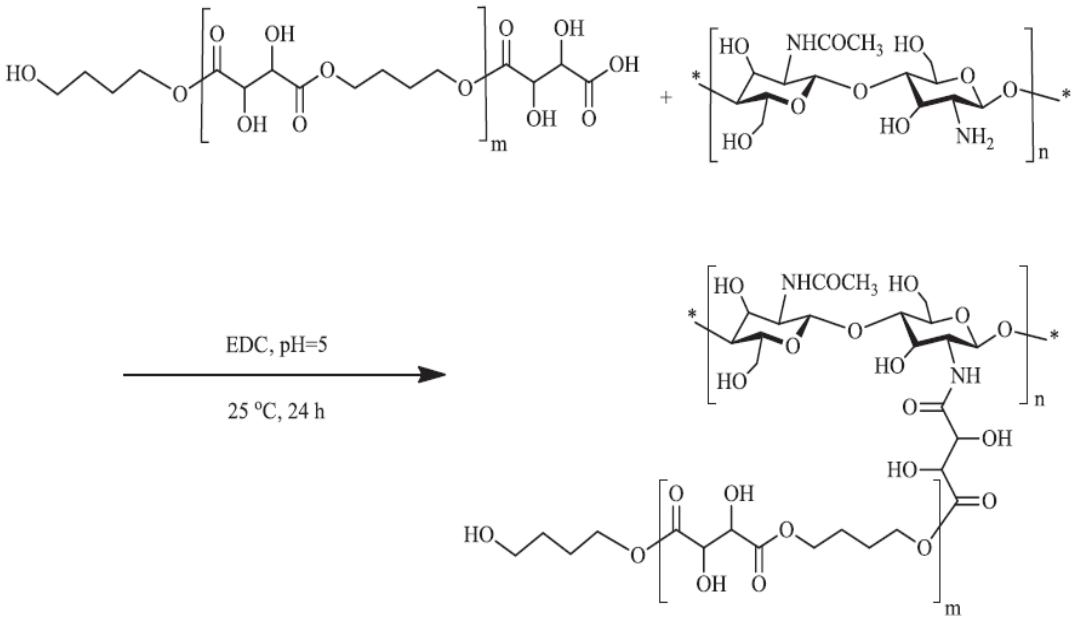


Figure 4 The synthesis procedure steps of poly(butylene tartrate) (PBT) grafted chitosan. (It is adapted from Chen et al. [23]).

Water soluble chitosan ammonium salts with different halogens were also produced. In that paper, some ammonium salts of chitosan including chitosan-bromoacetate (CSB), chitosan-chloroacetate (CSC), chitosan-dichloroacetate (CSDC), chitosan-trichloroacetate (CSTC), and chitosan-trifluoroacetate (CSTF) were successfully synthesized via one step reaction. The targeted chitosan ammonium salts are expected to have beneficial features such as being water soluble and having antifungal activity [30]. Different urea groups such as BCTCS, 2CBCTCS, 3CBCTCS, and 4CBCTCS were included into the chitosan derivatives with quaternary ammonium salt (CTCS) and four water-soluble chitosan derivatives were designed. At the final stage of synthesis, these substituted urea groups, which are used to improve the antifungal properties of chitosan, were attached to chloracetyl chitosan derivative with a quaternary ammonium salt (CTCS) [31].

Hydroxyethyl chitosan (HE-chitosan), a water soluble derivative of chitosan, was prepared by linking hydroxyethyl group to C6. In this synthesis, firstly chitosan was treated with sodium hydroxide, and then C_2H_5ClO was added to the mixture. After dialysis and freeze drying under vacuum processes, HE-chitosan product was attained eventually [32].

Water soluble chitosan was prepared from α- and β-type chitosan through Maillard reaction. Regarding the solubility, it was found that α-type chitosan is more suitable for preparing water-soluble chitosan than β-type chitosan. The optimum reaction set was constructed by adding different saccharides (glucose, glucosamine, maltose, and fructose) to the constant amount of α-type chitosan at 1% (w/v). With respect to several factors such as yield, solubility, degree of deacetylation and pH stability, the most potentially water-soluble chitosan was the chitosan-glucosamine derivative [33].

Water-soluble chitosan-isoniazid conjugates were synthesized. One of the methods is the carbodiimide method which uses isoniazid (INH) and N-(2-carboxyethyl) chitosan (CEC), and the other is the reaction between INH and N-(3-chloro-2-hydroxypropyl) chitosan (CHPC) [34].

Several acryl reagents such as DMMA, NIPAM, acrylic acid (AA), MAA, and hydroxyethyl acrylate (HEA) were reacted with chitosan under moderate reaction conditions and N-alkylated chitosan derivatives were synthesized. The obtained products from the Michael addition reaction were named as DMMA-CS, NIPAM-CS, AA-CS, MAA-CS, and HEA-CS, respectively. The modification of chitosan with these reagents gave differently soluble products in water [35].

Biological Activities of WSCs

In recent years, chitosan has generated great interest in various fields, especially in biological applications in terms of its biocompatibility and non-toxicity. Nevertheless, the most important disadvantage of chitosan is its being insoluble in water. In order to achieve that many chitosan derivatives have been synthesized based on modification of some functional groups in chitosan back bone. After production of water soluble chitosan, it has been to use in such important biological activities, as antimicrobial, antioxidant, and anticancer activity agent. Some scientific reports have been released on the biological activities of water soluble chitosan derivatives with respect to its usability in medical and pharmaceutical fields [36]. Examined biological properties either antioxidant, antimicrobial, and anticancer activities of various water soluble chitosan derivatives in this review article were represented in **Table 1**.

Antioxidant activity

Self-antioxidant property of chitosan can be brought to higher

Table 1 Biological activities of water soluble chitosan derivatives.

Chitosan Derivative	Biological Activity	Potential Usage/Application Field	References
Silk peptide modified carboxymethyl chitosan (CMC-SP)	Antioxidant	Wound healing material	[42]
Phenolic acid functionalized chitosan derivatives (Ga-Ch, Va-Ch, Fe-Ch, and Co-Ch)	Antioxidant	Functional food	[43]
Phenolic acids (Gallic acid (GA), caffeic acid (CA) and ferulic acid (FA)) grafted N,O-carboxymethyl chitosan (NOCC)	Antioxidant	Antioxidant agents	[44]
Phenolic acids (Caffeic (CA) and ferulic (FA)) grafted chitosan	Antioxidant	Antioxidant agents in food and pharmaceutical industries	[45]
Gallic-Acid-Grafted Chitosan	Antioxidant	Food industry	[46]
Monomethyl fumaric acid (MFA) modified chitosan	Antioxidant	Food preservative and packaging material	[47]
Quaternized carboxymethyl chitosan (QCMC) conjugated with collagen peptide (COP)	Antioxidant	Pharmaceutical and food industry	[48]
Polyethylene glycol (PEG)-grafted chitosan	Antioxidant	Treatment of immune-mediated liver injury	[49]
N-succinyl-chitosan (NSC)	Antimicrobial	Wound dressing material	[54]
O-fumaryl ester (OFTMCS) of N,N,N-trimethyl chitosan (TMCS)	Antimicrobial	Food products and biomedical science	[55]
Water-soluble chitosan (WSCh)	Antimicrobial	Carrier material for bioactive compounds	[56]
Sulfopropyl chitosan (SP-CS)	Antimicrobial	Water-soluble antimicrobial	[57]
N-(maleoyl) chitosan	Antimicrobial	Controlling the plant pathogens, crop and vegetable protection	[58]
N-benzyl-N,N-diethyl chitosan quaternary ammonium salt (BDCQA)	Antimicrobial	Cotton textile	[59]
O-quaternary ammonium salt-chitosans (QAS-CS)	Antimicrobial	Primary additive agent of self-owned intellectual band-aids	[60]
Carboxymethylated chitosan (CMC) based copolymer (DCMC)	Anticancer	Induction of apoptosis in Ehrlich ascites tumor cells (EAC)	[66]
Tanshinone I grafted low molecular chitosan	Anticancer	Cytotoxic activity against the tested two human cancer cell lines	[67]
Water-soluble chitosan (WSC)	Anticancer	Inhibits cell proliferation and induces apoptosis in human leukemic cells	[68]
Water soluble chitosan (WSC)	Anticancer	Adjuvant therapy against liver cancer	[69]
Water-soluble low-molecular-weight (LMW) chitosan	Anticancer	Inhibited the growth of S180 tumor cells in the mice	[70]

degrees with introducing a water soluble form of chitosan and different compounds which shows already antioxidant ability. In literature, many studies investigated the antioxidant activity of water soluble chitosan derivatives that even in pure forms or incorporated with any other compounds [37-41].

Carboxymethyl chitosan (CMC) modified with silk peptide (SP) was examined in terms of antioxidant activity. The studies demonstrated that CMC-SP showed strong antioxidant activity in various tests, such as DPPH, hydroxyl radical, H_2O_2 scavenging activity and total reducing power analysis. As a result of antioxidant property and biocompatibility evaluation of the enzymatic grafted CMC-SP, it was found appropriate to be used as an antioxidant at wound healing [42].

The water soluble (1.0-4.5 mg/mL) chitosan-phenolic acid conjugates were synthesized. The novel conjugates of chitosan from vanillic acid and coumaric acid were prepared by grafting, and the antioxidant properties of synthesized chitosan derivatives were compared with ferulic acid and gallic acid grafted chitosan. The highest antioxidant activity was reached by Ga-Ch and the order was followed by Va-Ch, Fe-Ch and Co-Ch. This reason was explained by a higher grafting ratio of gallic acid to chitosan than other conjugates and increased the antioxidant activity [43].

In another study, three phenolic acids (gallic (GA), caffeic (CA), and ferulic (FA)) were grafted onto N,O-carboxymethyl chitosan. *In vitro* antioxidant activity of water soluble chitosan grafted copolymer samples decreased in order of GA-g-NOCC > CA-g-NOCC > FA-g-NOCC > NOCC > chitosan. Phenolic acid grafted NOCC is proposed to be used in the development of effective antioxidant agents [44]. Similar results were also observed in another study. Water soluble chitosan derivatives were prepared by grafting caffeic acid (CA) and ferulic acid (FA) onto chitosan. The antioxidant activity of chitosan derivatives was determined and it vitro studies were proved that he antioxidant activity decreased in the order of CA-g-chitosan>FA-g-chitosan>chitosan. These derivatives are indicated a potential in the development of novel antioxidant agents [45]. As another example of gallic acid incorporation to chitosan also exhibited almost the same results which were observed by showing that gallic acid increased the antioxidant activity of water soluble chitosan. Water soluble chitosan derivative that was produced by green synthesis was proposed for food industry [46]. Fumaric acid was incorporated with chitosan similarly to phenolic acids. It was observed that all synthesized chitosan derivative were soluble in water and could swell in some organic solvents. The antioxidant activities of all chitosan derivatives were significantly higher than chitosan.

Monomethyl fumaric acid modified chitosan derivatives are presented as potential food preservative and food packaging material [47].

Quaternized carboxymethyl chitosan (QCMC) has been incorporated with collagen peptide (COP). Since COP has antioxidant capacity, collagen peptide modified QCMC was aimed to be the potential material which could be applied in pharmaceuticals and food industry. Firstly, QCMC was synthesized, and then fish collagen peptide was conjugated to the backbone by carbodiimide method. Antioxidant activity was expressed as the percentage inhibition of H_2O_2 using spectrometric method. COP introduction to QCMC significantly increased the hydrogen scavenging activity. The obtained results also showed that antioxidant activity was affected by degree of substitution, molecular weight and concentration [48].

Plasticizer polyethylene glycol (PEG) was used to investigate water solubility and antioxidant activity of chitosan derivatives. PEGylated chitosan derivatives were produced by grafting different molecular weight chitosans (CS1, CS2, and S3) with monomethyoxypolyethylene glycol (mPEG). The antioxidant property of materials was studied with three different methods. The most effective behavior was belonging to the low particle sized derivative. *In vivo* studies were applied to liver of mice. The findings suggested that mPEg-CS1 could be used in the treatment of liver injury that are linked with a high antioxidant activity [49].

Antimicrobial activity

Chitosan as an antimicrobial agent has been widely researched in increasing its applications and functionality. Subsequent to the synthesis of water soluble chitosan, the interaction of these conjugates with a variety of compounds were investigated in terms of benefits to antimicrobial ability [50-53].

A water soluble derivative of chitosan was synthesized as N-succinyl chitosan (NSC) from succinic anhydride, hydrochloric acid, and alkaline chitosan. The results showed that the solubility of NSC with comparison to chitosan was increased, also it was non-toxic and had good antibacterial activity. An application area of the NSC was chosen for wound healing material [54].

O-fumaryl ester (OFTMCS) of N,N,N-trimethyl chitosan (TMCS) was synthesized in order to obtain a water soluble derivative of chitosan with an enhanced antibacterial activity. It was seen that the antibacterial activity of OFTMCS against *S. aureus* and *E. coli* were greater than both of unmodified chitosan and TMCS. It is possible to enhance antibacterial properties of chitosan by including additional antibacterial groups to structure. OFTMCS is proposed as an antimicrobial agent in food products and biomedical field [55].

A study showed that water soluble chitosan (WSCh) is synthesized through Maillard reaction of glucosamine with low and medium molecular weight chitosan. In this way, solubility of chitosan was increased six times relative to neat polysaccharide. The study showed that prepared WSCh derivatives showed larger solubility than chitosan. Moreover, they almost comparable or enhanced antioxidant and antibacterial activities with comparison to neat chitosan [56].

In order to improve solubility and antibacterial activity of chitosan, sulfopropyl derivatives of chitosan can be prepared. Another study investigated the antibacterial activity of sulfopropyl chitosan (SP-CS) with various degrees of substitution (DSs). It was resulted that the SP-CS aqueous solution exhibited good antibacterial activity. The antibacterial effect of chitosan derivatives also raised in between SP-CSs when concentration and DS was increased [57]. Different degrees of substitution effected antibacterial activity of N-(maleoyl) chitosan. Chitosan derivative was synthesized by grafting maleic anhydride onto chitosan backbone via open-chain reaction mechanism. The obtained chitosan originated product was found soluble in aqueous media. With increase of the DS in between water soluble chitosan derivatives these products became more active in terms of antibacterial activity [58].

A novel water soluble chitosan derivative was prepared by introducing 1,3-propane sulfone to amino groups of chitosan under slightly acidic conditions. Via addition of a sulfonic group onto chitosan chains, chitosan solubility in water increased and higher antibacterial activity was gained against *Escherichia coli* and *Staphylococcus aureus*. Moreover, sulfonated chitosan (SCS) showed selective antifungal behavior, which is important in terms of the possible controlled biological applications. A water soluble derivative of chitosan was synthesized via Schiff's base intermediate. N-benzyl-N,N-diethyl chitosan quaternary ammonium salt (BDCQA). BDCQA-cotton exhibited well antibacterial activity and high stability against large spectrum bacterium, such as Gram-positive, Gram-negative and drug resistant. The cotton textile field was proposed as an application area of BDCQA to be using it a potential new material in cotton textile field [59]. Five O-quaternary ammonium salt-chitosan were prepared (QAS-CS). Derivatives of QAS-CS displayed high solubility not only in water, but also polar organic solvents such as methanol, DMSO, DMF. Among these derivatives –dodecyl and –tetradecyl radical groups containing types were chosen the best in case of antibacterial ability. Increased water solubility, low toxicity and better antimicrobial ability made these two types potential candidates for additive agent of self-owned intellectual band-aid [60].

Water soluble chitosan was used to improve antimicrobial activity and solubility of other materials. Primarily, being a self-antimicrobial agent property of chitosan was combined with silymarin to increase its solubility and antimicrobial activity using chitosan's water soluble form. Silymarin nanoparticles were prepared using water-soluble chitosan (WCS) and poly-γ-glutamic acid (γ-PGA) were suggested to application area of antimicrobial food additives and food packing [61].

Anticancer activity

It has been reported that water soluble chitosan has been used in many anticancer drug delivery studies in literature [62-64]. Thanks to solubility of water soluble chitosan and its variety of derivatives, they have been seen as potential candidates at chitosan property antitumor agent in the future. Also, it was proposed that the properties of chitosan including average molecular weight and the degree of acetylation could be important factors to exhibit antitumor activity *in vitro* [65]. A study revealed that new carboxymethyl chitosan based copolymer considerably inhibited

the growth of the tumor *in vivo* [66].

In this report, a water soluble chitosan derivative was prepared via Vilsmeier reaction which the first step is preparing Vilsmeier reagent made with N,N-dimethylformamide (DMF) and $POCl_3$ in 3:1 ratio. Tanshinone I (TanI), which is a diterpene derivative isolated from Salvia miltiorrhiza and is a well-recognized herb in traditional Chinese herb, was grafted onto low molecular chitosan (LMC). A novel antitumor agent was developed from water soluble LSC and TanI. The results showed that incorporation of TanI to chitosan w enhanced the anticancer activity of LMC [67].

Another study searched whether water soluble chitosan has pro-apoptotic activity against some types of human leukemia cells (U937, K562, HL60 and THP-1). Anticancer efficiency of WSC was investigated in the presence of Akt and B-cell lymphoma 2 (Bcl-2) protein which acts as anti-apoptotic. The results demonstrated that WSC induced the apoptosis that is related to occur via inhibition of Bcl_2 and Akt pathways in leukemic cell [68].

The anticancer effect of water soluble chitosan was examined mouse liver cancer H22-bearing mice. The oral administration of WSC was found efficient and reducer to the tumor growth and no acute body weight loss was observed by oral administration of chitosan [69]. Also in another report, positive results were seemed with the oral administration of WSC decreases the weight of the tumor. The antitumor activity of WSC was studied in the tumor cells in the mice after the preparation of water soluble low molecular weight chitosan the enzymatic hydrolysis with efficient hemicellulase. The providing of LMW chitosan and its N-acetyl product in intraperitoneal way inhibited the growth of S180 tumor cells in mice [70]. In another study, water soluble chitosan derivatives were synthesized by oxidative degradation of H_2O_2. The samples were tested against sarcoma 180 tumors. Results showed that water solubility of chitosan with high molecular weight positively affected to inhibition of tumor *in vivo* [71].

The water-soluble chitosan and chitin derivatives (CM-chitosan, CM-chitin) were synthesized by carboxymethylation reaction. The antioxidative and matrix metalloproteinase-2 and -9 (MMP-2 and -9) inhibitory effects of derivatives were examined in HT1080 human fibrosarcoma cells. This study demonstrated the neutraceutical properties of CM-chitosan and –chitin is effective and they could be potentials as an antioxidant and MMP inhibitor agent rather than their original usage as a food source [72].

Other Applications of Water Soluble Chitosan

Previously, chitosan and its derivatives were used as a support material in many different biological applications. Several scientific reports the usage of water soluble chitosan was found effective and beneficial when incorporated with targeted material. **Table 2** shows the various applications of water soluble chitosan included material in different fields.

Table 2 Further application areas and usage fields of water soluble chitosan based materials.

Water Soluble Chitosan Based Material	Application Area	The Aim of Usage	References
Water-soluble chitosan-based core-shell particles	Adsorption	Remove hazardous gas and heavy metal ions	[74]
Water Soluble Amino Chitosan (Amino-CS)	Transport	Carrier for CO_2 separation from CH_4/CO_2 mixed gas	[75]
Water soluble folate-chitosan nanogels	Drug delivery	Nanodevices for targeted anticancer drug delivery	[76]
Folate conjugated carboxymethyl chitosan–manganese doped zinc sulphide nanoparticles	Drug delivery/Bioprobe	Targeted anticancer drug delivery	[77]
PLA NPs bearing a combinatorial coating of WGA and WSC	Mucosal delivery of other drugs and proteins	Mucosal delivery of b-galactosidase	[78]
Water-soluble chitosan-coated nanoceria	Chitosan as a coating layer	Synthesis of nanoceria particles	[79]
Water soluble chitosan stabilized gold nanoparticles	Electrode modifier	Detection of UA in human urine and serum samples	[80]
Water-soluble acetylated chitosan-stabilized gold nanosphere	Bioprobe	Detection of UA in human urine and serum samples	[81]
Quaternary ammonium salt of chitosan and reactive red x-3b	Wood dyeing	Antimicrobial biopolymer dye synthesis	[82]
Water-soluble chitosan dye of Reactive Blue 19	Wood dyeing	Antimicrobial dye synthesis based on chitosan	[83]
Water-soluble chitosan linked fluorescent material	Fluorescent probe	Detection of chromium(VI)	[84]
Water-soluble chitosan and herbal honey compound	Medicine or functional cosmetic material	Treatment of AD-like lesion	[85]
Water-soluble chitosan from Clanis bilineata larva skin	Antioxidant/Antiageing agent	High antioxidant activity in vitro and antiageing activity in D–gal-induced mice	[86]
Water-soluble chitosan (WSC) in combination with glutathione	Antimicrobial and antioxidant agent	Prolong the shelf life of prolong the shelf life of pen shell adductor muscles	[87]
Sodium alginate-water soluble chitosan (WSC) hydrogel particles	Adsorbent/Carrier	Adsorption of heavy metal ions, acidic and basic gas/Encapsulation of hemoglobin	[88]
Tartrate/Tripolyphosphate crosslinked water soluble chitosan microparticles	Protein antigen delivery	Encapsulation of Bovine serum albumin (BSA) and Tetanus toxoid (TT)	[89]

In literature, a WSC based material was used for the removal of carbon dioxide, lead and copper heavy metals. The adsorbent, which was a strength-enhanced WSC-based core shell particles, was prepared using a facile ionic crosslinking and freezing thawing technologies. The particles were bound efficiently to carbon dioxide [73]. The WSC is sufficient to interact with acidic gases such as carbon dioxide. Another study investigated the transfer of CO_2 by WSC derivative from the CO_2/CH_4 gas mixture. A novel amino chitosan derivative was synthesized via Michael addition reaction, and it was successfully used as fixed carrier for CO_2 transportation in a mixed gas containing CO_2 and CH_4 [74]. In a similar way, it was observed that incorporation of water-soluble derivative of chitin on amylose films increased permeability of films to N_2, O_2, CO_2 and C_2H_4 gases [75].

Water soluble chitosan are used in drug delivery applications. Water soluble folate-chitosan derivatives as nanogels were prepared and genipin, a natural crosslinker, was used to crosslink the nanogels. The drug release behavior of chitosan derivative nanogels was investigated by 5-fluorouracil release. Nanogels exhibited high encapsulation in aqueous media and proposed to be a nanodevices for a targeted anticancer drug delivery [76]. In another study, novel folic acid (FA) conjugated carboxymethyl chitosan coordinated to manganese doped zinc sulphide quantum dot (FA–CMC–ZnS:Mn) nanoparticles were developed. The anticancer drug 5-Fluorouracil was chosen as a model drug. Although multi-functional nanoparticles were found effective for targeted delivery, 5-FU encapsulated nanoparticles were found to be toxic to breast cancer cell line MCF-7. The nanoparticles without drug encapsulation were suggested a potential bioprobe [77]. Novel poly(lactic acid) nanoparticles coated with combined wheat germ agglutinin (WGA) and water soluble chitosan (WSC) were used for mucosal drug delivery. The combining of nanoparticles with WGA and WSC in this work provided to nanoparticles a dramatic positively charged surface and high suspension stability [78].

Water-soluble chitosan-coated nanoceria particles (CNPs) were synthesized in s simple way. The coating of chitosan provided the nanoceria a good water-solubility, without interfering its antioxidative activity. Future application of nanoceria in biomedical and biotechnological fields was clarified with the help of chitosan coating [79]. Water soluble chitosan using as stabilizing and reducing agent was included to synthesis of gold nanoparticles (Au-NPs). The nanoparticles were used to design a modified electrode which was effective for detection of uric acid in human urine and serum samples [80]. Au nanoparticles in water were synthesized using water-soluble chitosan as a stabilizer and reducing agent. Water-soluble chitosan polymers produced from N-acetylation. The acetylated chitosan-stabilized gold nanospheres are recommended as bioprobes to detect selectively various biochemical agents of melamine, bacteria, and uric acid [81].

A novel biopolymer dye was synthesized by the reaction of quaternary ammonium salt of chitosan and reactive red x-3b. The quaternary ammonium salt of chitosan was produced by grafting glycidyltrimethylammonium chloride on chitosan which was chosen to improve the water solubility and antibacterial property of chitosan in this study. Wood dyeing used in hospital and other unique environment was found suitable for the dye [82]. Another study investigated the synthesis of a water-soluble chitosan dye obtained from the reaction of Reactive Blue 19 and previously hydrolyzed chitosan. Moreover, compared with Reactive Blue 19, the antibacterial property of chitosan dye increased. The results showed that development of antibacterial dye is useful for wood dyeing applications [83].

A novel water-soluble chitosan linked fluorescent carbon dots and isophorone diisocyanate (FCDs–IPDI–CTS) fluorescent material was produced from the NCO-capped intermediate and chitosan via reacting –NCO groups with the hydroxyl and amino groups in chitosan polymeric chains. The FCDs–IPDI–CTS material exhibited good fluorescence properties and stability. Since the fluorescence of the FCDs–IPDI–CTS could be quenched by chromium (VI), the material is seen a potential sensor to detect Cr (VI) in water and soil samples [84].

Low-molecular weight water-soluble chitosan and herbal honey (AMCH) were combined in an antimicrobial moisturizing cream formulation to treat Atopic dermatitis (AD)-like lesions. The together activities of chitosan and AMCH were successful to alleviate the symptoms of AD-skin lesions in NC/Nga mice [85]. Clanis bilineata larva skin was used to produce water soluble chitosan (CBLCWSC). The obtained product was tested in terms of its antioxidant and anti-ageing activities. Since CBLSWSC showed high antioxidant activity *in vitro* and anti-ageing activity in D–gal-induced mice, it is proposed to be used as a promising antioxidant and anti-ageing medicine [86].

Water-soluble chitosan in combination with glutathione was investigated to exhibit the quality of pen shell adductor muscles. Usage of WSC in combination with glutathione displayed slower bacterial growth, lower pH increasing, lower basic nitrogen, and higher overall acceptability scores of PSAM during frozen storage. The present study showed that the fresh PSAM which were treated with WSC in combination with glutathione could be stored frozen for ten months [87].

Sodium alginate-water soluble chitosan (WSC) hydrogel particles were prepared at acid free media via crosslinking. The novel particles exhibited a high adsorption capacity against too heavy metal ions (Cu^{2+} and Pb^{2+}), acidic gas (H_2S) and basic gas (NH_3). Moreover, the particle encapsulation efficiency for hemoglobin (HB) was 100%. The release of HB from the particles was found was pH-sensitive. These kinds of particles are proposed promising adsorbent or carrier [88]. Sodium potassium tartrate (SPT)/Sodium tripolyphosphate (TPP) crosslinked water soluble chitosan microparticles were synthesized and were used for encapsulation of Bovine serum albumin (BSA) and Tetanus toxoid (TT). The present study investigated also the crosslinking degree and characterization of chitosan microparticles either using ionic crosslinkers TPP and SPT as alone or SPT/TPP as co-crosslinkers for encapsulation of BSA and TT [89].

Conclusion

Natural source polysaccharide chitosan is researched for its applicability in a wide range of fields. Since this biopolymer is tended to dissolve in acidic media such as acetic, lactic and formic

acids, its applications are limited due to many compounds are not soluble in acidic medium. This problem could be exceeded by producing chitosan derivatives, which are soluble in water. Water soluble chitosan is incorporated in various formulations to investigate its similar features to chitosan such as being antimicrobial, antioxidant, and anticancer. In this review, the derivatives of water soluble chitosan either alone or together with appropriate compounds are investigated with subject to their synthesis ways, biological abilities, and possible further usability in miscellaneous fields in science.

Conflict of Interest

The author declares no conflict of interest.

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