Chitosan nanoparticles as practical biomedical tools in cancer therapy

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Abstract

Cancer is the leading cause of death throughout the world, next to cardiovascular diseases. Although various conventional modalities have been applied for cancer therapy, such as surgery, chemotherapy, and radiotherapy, their considerable drawbacks have limited their applicability and cancer eradication. Therefore, there is a fundamental requirement for the fabrication and development of breakthrough technologies in cancer therapy. The chitosan (CS) nanoparticle-based nanotechnology is one of the most prominent tools for the treatment of cancer, which has received deep attention from researchers and clinicians. The CS nanoparticles have potential physicochemical properties, such as stability and surface functional groups, which improve their practicality in the development of novel drug delivery systems (DDSs) against cancer. Moreover, these nanoparticles have various biomedical properties that have made them potent candidates for cancer treatment, including biodegradability, mucoadhesivity, biocompatibility, nontoxicity, antioxidant activity, immunomodulatory function, hemostatic and blood clotting, and macrophage activation. Moreover, these nanomaterials can be applied to the passive and active DDSs against cancer. Totally, the CS-based DDSs would be remarkable tools for cancer therapy.

Keywords: Chitosan; Nanotechnology; Drug delivery system; Biomedical sciences; Cancer

1. Introduction

Cancer has a high rate of prevalence and mortality worldwide. This disorder, as the second leading cause of death, has posed considerable challenges for human beings [1]. There is a wide reason for prevalence of cancer, including genetic disorders, inheritance, air pollution, chemicals, alcohol consumption, smoking, mutagenic high-energy irradiations, abnormal diet, and lifestyle, etc. [1, 2]. According to the reports, cancer resulted in over 19.5 million mortalities across the world in 2025. Predictions indicate that cancer will account for 35.3 million new cases and approximately 18.5 million deaths by 2050 [3, 4]. Although there are several modalities for cancer treatment, such as surgery, chemotherapy, and radiotherapy, they have remarkable disadvantages that restrict their treatment efficiency. To put it in a more vivid picture, surgery is associated with damage to healthy tissue, thereby forming a lesion after the operation [5]. The chemotherapy uses the chemotherapeutic agents which have lots of drawbacks; for instance, chemotherapeutics has low stability, weak solubility, immunogenicity, systemic toxic shock, and so forth. Moreover,

radiotherapy side effects are hair loss, inducing genomic disorders, mutagenicity, anorexia, nausea, and weak penetration into the deeper organs in the human body [6, 7].

As a result, there is a fundamental requirement for the development of cutting-edge technologies in cancer therapy. Nanotechnology is a promising field of science by which breakthrough tools could be fabricated [8, 9]. The use of nanoparticles in the development of nanocarrier/drug delivery systems (DDSs) has been extensively used for various goals in the biomedical and pharmaceutical sciences, including prognosis, diagnosis, and treatment of cancer. Among nanoparticles, biopolymers have received deep attention from scientists and clinicians over the last few years. Chitosan (CS) nanoparticles, as one of the FDA-approved biomaterials for biomedical applications, are environmentally sustainable "green" nanomaterials [10, 11]. CS nanoparticles, owing to the abundance, ease of extraction, stability, affordability, reliable surface modification/engineering, controlled/sustained drug release, and unique physicochemical features, are located at the top list of various industrial sectors, including food, chemical, physical, electronics, cosmetics, pharmaceutical, and biomedical engineering industries [12, 13]. Among various industries, the pharmaceutical and biomedical sectors are of great importance due to their association with human health. Fig. 1 presents some applications of CS nanoparticles in biomedical and pharmaceutical sciences. In this paper, the properties and applications of CS nanoparticles in biomedical and pharmaceutical sciences have been reviewed based on the latest updates.

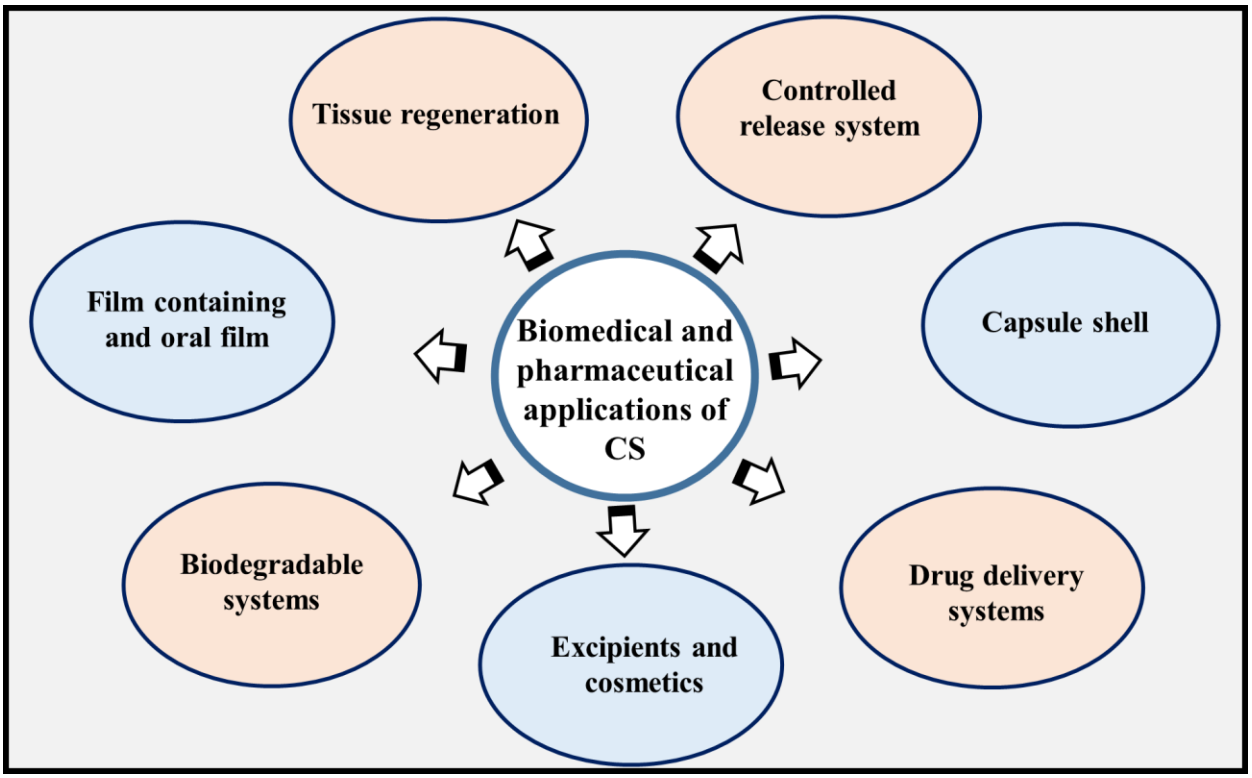

Fig. 1. Various pharmaceutical and biomedical applications of CS.

2. Properties of CS NPs

2.1. Physicochemical characteristics

CS nanoparticles possess unique physicochemical aspects, such as appropriate solubility, stability, various molecular weights, deacetylation degree, mechanical strength, and manipulability. These nanoparticles have a high drug loading capacity (incorporation and absorption of drug) due to the long-chain hydrocarbon backbone and various nanocarrier preparation approaches. On the other hand, these nanoparticles have a controlled/sustained drug release profile, which takes place through three mechanisms, including diffusion, swelling, and erosion [14]. The diffusion rate, solubility, type of crosslinker, and size of CS nanoparticles could either directly or indirectly affect the release rate of CS-based DDSs. The physical stability and surface positive charge of these NPs are directly associated with the agglomerations, coagulation, and bridging flocculation of them, whereas the pH of the solvent, temperature, and molecular weight of CS nanoparticles are linked to the chemical stability [15].

2.2. Biodegradability

CS nanoparticles could be depolymerized into beneficial biological molecules by the function of enzymes in the human body. The glucosamine-N-acetyl-glucosamine, glucosamine-glucosamine, and N-acetyl-glucosamine-N acetylglucosamine units are the moieties of CS degradation under enzymatic function [16]. Probably, lysozymes of serum, interstitial tissue fluid, and saliva are involved in this degradation. Moreover, the bacterial enzymes of the colon are other possible candidates for the degradation of CS. Besides, proteases and porcine pancreatic enzymes may hydrolyze CS in living organisms [17]. Therefore, the intermediate units of CS degradation could be used in different biochemical cycles in the human body without any immunogenicity.

2.3. Mucoadhesivity

CS nanoparticles have the capability of adhering to the surfaces of cells and biological molecules. The presence of surface functional groups, including amine (NH_3) and hydroxyl (OH), plays a pivotal role in this aspect of CS nanoparticles [18]. This unique feature is also involved in the adsorption of cargoes at the site of action without affinity to mucus. CS nanoparticles could easily pass through interstitial fluid pathways, open the tight junction in the epithelial border, interact with the membrane of target cells, and transfer into the cells based on the enhanced permeability and retention (EPR) effect [19].

2.4. Biocompatibility

CS nanoparticles have been introduced as excellent biocompatible and hemo-compatible biopolymers. This nanoparticle may be present in the liquids of the human body without remarkable interference with the performance of various cells, especially the cells in the circulatory system [20]. The performance of these nanoparticles in blockage of bleeding and coagulation. Additionally, CS nanoparticles have demonstrated several biomedical abilities, such as inducing the granulation capacity of tissue, chemoattraction inside the serum and tissues, hemostasis, stimulation of activity of macrophages and neutrophils, and preventing scar formation [21].

2.5. Nontoxicity

CS nanoparticles have no inflammatory and immunogenic properties in living organisms. The toxicity assays approved the non-toxicity of these nanoparticles. The items involved in the possible toxicity of CS nanoparticles include molecular weights, concentrations, and degrees of deacetylation [22].

2.6. Antioxidant activity

CS nanoparticles eliminate the reactive oxygen species (ROS) in the targeted cancerous tissues and repair damaged tissues under the negative effect of ROS in both in vitro and in vivo circumstances. CS may mimic the vitamin C antioxidant function and reduce the free fatty acid and malondialdehyde concentrations in the circulatory systems [23]. Furthermore, this biomaterial declines the lipid peroxidation in the human body. CS is the cofactor of superoxide dismutase, catalase, and glutathione peroxidase, which are involved in removing ROS. The antioxidant mechanisms of action of CS nanoparticles include the donation of a proton or transferring an electron from surface amine groups

of CS, donation of a proton from hydroxyl groups at C2, C3, and C6 positions of CS, and chelation of ferrous ions [24].

2.7. Immunomodulatory

CS nanoparticles have chemotactic properties and could respond to various internal and external chemical stimuli, such as in a chemotactic manner correlated with neutrophils and macrophages. CS biopolymers are involved in tissue granulation, chemoattraction, and hemostasis, which, in turn, stimulate the function of immune system cells (macrophages and neutrophils), and consequently block the scar formation [25]. CS nanoparticles may induce the inflammatory mediators (like interleukin-1 and nitric oxide) and activate macrophages against tumors [26].

2.8. Hemostatic and blood clotting

CS nanomaterials exhibit remarkable hemostatic and blood clotting performances. Hemostasis is the major process of the early stages in wound injury, which controls bleeding and adjusts wound closure in the damaged tissues [27]. CS possesses the coagulation function owing to its hemostatic feature and can be administered as an anticoagulant after harsh tissue damage. The presence of available surface amino groups is involved in wound healing by attachment to platelets and induction of tissue regeneration. A high rate of deacetylation of CS biopolymer is mentioned to have excellent anticoagulant function. Moreover, CS nanoparticles reduce the generation of antithrombin after bleeding and play a vital role in the coagulation process [28].

2.9. Macrophage activation

CS biomaterials have a stimulatory effect on the activation of macrophages, which is mainly attributable to the presence of N-acetylglucosamine units in their structure [29]. CS nanoparticles may stimulate the polarization of anti-inflammatory macrophages and initiate the induction of pro-inflammatory dendritic cells at the site of action. In addition, CS activates the macrophages through stimulating the secretion of MCP-1, MIP-1, IL-8, and RANTES in them [30].

3. CS in passive and active drug delivery to cancer cells

The development of novel DDSs against cancerous tissues is one of the most significant achievements in the suppression and even eradication of cancer. CS nanoparticles, owing to their physicochemical and biomedical properties, are contemplated as potential candidates for the delivery of therapeutic/bioactive agents to cancerous tissues. CS-based DDSs have several FDA-approved products in the market. There are two major types of DDSs, which are classified based on the mechanism of drug delivery to the site of action: passive DDS and active DDS [31, 32].

Passive DDS refers to the accumulation of the drug carrier in the cancerous tissues based on the pathophysiological and physicochemical characteristics of the tissue and nanocarrier, respectively. As a matter of

fact, this type of DDS works through the EPR effect [21, 33]. On the other hand, the ligand-based internalization of DDS into the target tissues which takes place by receptor-mediated uptake is another type DDS, called active DDS (Fig. 2). Two major issues may effectively affect the passive DDS: 1) the leaky microvasculature of tumor which is accompanied by DDS fenestration and 2) the EPR effect that leads to the assembling of drug-loaded nanocarrier to the target site [34]. The passive drug delivery to cancerous tissues takes place owing to the sort of issues associated with the EPR effect. The high proliferation rate of endothelial cells, rate of blood flow to the site of action, inappropriate formation of the basement membrane, deficiency in the formation of smooth-muscle layer (pericyte deficiency), stage of cancer, and abnormal formation of blood [35]. The diameter and surface charge of CS-based nanocarrier should range from 10 nm to 200 nm and above/below ±45 mV, respectively, to have an efficient drug/therapeutic delivery to cancer sites. This size and surface charge not only guarantee the penetration of DDS into the site of action but also affect the treatment efficiency and clearance of DDS. The EPR effect may enhance the accumulation of necessary growth elements and nutrients in the cancerous tissues by over 10-fold compared with normal tissue in the human body [36].

On the other hand, the ligand-receptor interaction mediates the efficient internalization of CS-based DDS into the cancerous cells in active DDS (Fig. 2). This strategy has drastically lower adverse effects than passive DDS since the carrier could escape from the clearance mechanism of the kidney and liver after administration, provide higher drug dosage in the cancerous cells, get away from the immune system cells, and ignore the repetition of drug administration [37, 38]. There is a wide spectrum of receptor-targeting ligands to decorate the surface of DDS in an active mechanism. These ligands have specificity for the receptors of specific cancers on the cell membrane [39]. These ligands include folic acid, hyaluronic acid, transferrin, DNA/RNA aptamers, antibodies, etc. Homogeneous overexpression of these unique receptors on the surface of target cells and high binding affinity between the ligand and receptor are key issues in the CS-based active DDSs [2].

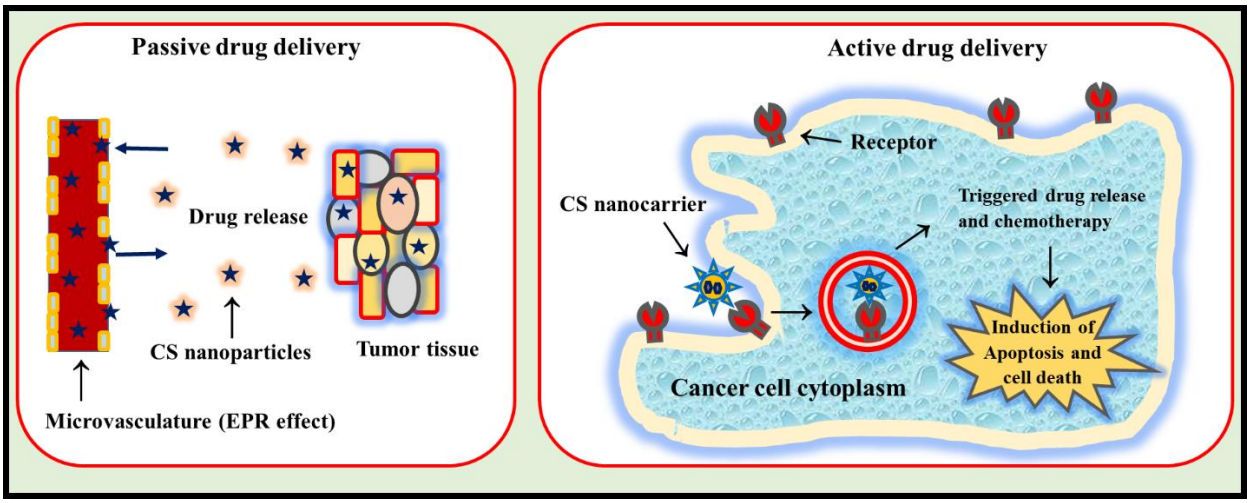

Fig. 2. Passive and active DDSs based on CS nanoparticles for cancer therapy.

4. Conclusion

Cancer has a high rate of prevalence and mortality across the world. Although there are various conventional modalities for the treatment of cancer (such as surgery, chemotherapy, and radiotherapy), the presence of high drawbacks makes them inefficient. The CS-based nanotechnology is a kind of cutting-edge tool in cancer therapy, which would serve as an appropriate alternative to conventional methods. CS nanoparticles have excellent physicochemical features, like high stability in the serum, which may effectively affect the function in the human body after administration. This nanomaterial has the approval of the FDA for some biomedical applications. The biomedical properties of CS nanoparticles are introduced them as great candidates for the fabrication of novel DDSs. These nanoparticles have been developed for passive and active DDSs to improve the efficiency of cancer treatment. Totally, CS-based DDSs would be potential candidates for cancer therapy in the near future, and may be replaced with conventional chemotherapy.

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