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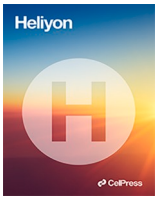

Review article

Stability, challenges, and prospects of chitosan for the delivery of anticancer drugs and tissue regenerative growth factors

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ABSTRACT

Chitosan, a biopolymer derived from chitin, offers significant potential for regulated anticancer drug administration and tissue regeneration growth factors, owing to its biocompatibility, low toxicity, biodegradability, and little immunogenicity. Moreover, its structure can be extensively modified, for example, to create scaffolds, hydrogels, nanoparticles, and membranes, allowing it to be engineered precisely to achieve specific outcomes However, the therapeutic utilisation of chitosan is impeded by significant challenges, such as its inadequate hemocompatibility, durability, and uniformity in commercial manufacturing. Additionally, there is insufficient research offering a thorough examination of the capabilities, limitations, and challenges related to chitosan as carriers for anticancer drugs and growth factors. This article examines the stability, challenges, and advanced application of chitosan as a drug carrier in anti-cancer therapy and growth factor delivery. The problems of unregulated chitosan degradation arising from unsuitable storage conditions are considered and potential solutions, and areas for future research, are proposed to deal with such problems. Consequently, this review is expected to be highly valuable for aspiring scientists studying chitosan-related systems for delivery of anti-cancer drugs and growth factors.

1. Introduction

Chitosan is a naturally-occurring linear polysaccharide, made up of glucosamine and N-acetylglucosamine units, connected by β-(1,4) glycosidic bonds. Chitosan is produced by de-acetylating chitin, under alkaline conditions, in its solid state, or by using chitin deacetylase to enzymatically hydrolyse chitin [1,2]. After cellulose, Chitin is the second most-plentiful natural polysaccharide on Earth. Chitin is predominantly found in the shells of crustaceans, in the cell walls of fungi, mollusks, arthropods, and in certain types of seaweed [3]. The functional properties of chitosan are related to its molecular weight and degree of deacetylation (DDA), which impacts its physico-chemical (e.g., tensile strength, solubility, surface area, viscosity, conductivity, porosity, and flexibility) and biological properties (e.g. biodegradability, antioxidant, bioavailability, and biocompatibility) [4–7]. Additionally, as illustrated in Fig. 1, chitosan is highly amenable to chemical modification via one of its three reactive functional groups: the amino group, and both primary and secondary hydroxyl groups, on its backbone.

The biopolymer chitosan has gained significant interest from researchers and practitioners in the fields of science, applied research, and industrial biotechnology. Chitosan's exceptional physical, biological, and chemical properties, molecular structure, bioactivity and versatility, which are not found in synthetic polymers [8,9] have been at the root of this interest. Chitosan was found to be effective

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in drug delivery some 20 years ago and its use in the biomedical industry has been developed since then. Chitosan has been used in the formulation of biomaterials and in extensive investigation into drug delivery systems. Natural polymers like chitosan are anti-carcinogenic, bio-compatible, hemo-static, bacterio-static, anti-cholesteremic, and fungi-static. In drug delivery systems, chitosan and its derivatives are regarded as safe and efficacious, due to these properties. The biodegradability of chitosan facilitates oral and intravenous medication delivery [10–12].

The Figures illustrate how chitosan is used in drug delivery systems. Fig. 2(a–b) shows how chitosan (in its different forms) is conjugated with drugs and disintegrates within the body distributing medicine, in a targeted manner, in the process [13]. Fig. 3 illustrates how chitosan is used in several specific drug delivery applications [14].

Chitosan-based drug delivery systems have demonstrated considerable promise in the transport of therapeutic proteins, nucleic acids, vaccines, and others [12,15]. Recently, cancer treatment and the introduction of numerous vital growth factors into the human body have been important *foci* in biomedicine and an extensive literature now exists on these topics [10]. Fig. 2(b) illustrates the use of chitosan-based porous matrices, including foams, hydrogels, and sponges, as a means of delivering anti-cancer medications and tissue-regeneration growth factors [16].

For tissue regeneration, chitosan aids in the adhesion, proliferation, and specialisation of numerous cell types, in the transport of several growth factors, due to its hydrophilic properties. Sutankulov et al. [17] noted that chitosan may bind negatively-charged enzymes, proteins, and DNA in slightly acidic conditions, due to its positively charged composition. This property makes it a viable carrier for delivering numerous growth factors. Additionally, chitosan exhibits a diverse array of applications in combating melanoma, bladder, lung, breast, colon, pancreatic, and metastatic cancer [18]. Chitosan can be used in conjunction with anti-cancer medications to create a novel drug delivery system that has several advantages. These advantages include a longer half-life, less adverse effects, less-frequent dosing, targeted drug delivery to the affected area, and improved patient tolerance [14]. The cationic and electrostatic interaction of chitosan with nucleic acids enhance its effectiveness as a carrier for cancer medicines and as a potent immunological adjuvant for cancer vaccinations [18]. Despite the considerable promise that chitosan holds, as a growth factor or as a part of a delivery system for anticancer drugs, significant barriers hamper the clinical implementation of chitosan. These include inadequate hemo-compatibility, durability, and commercial production inconsistency. Its inadequate long-term stability poses a significant obstacle to the expansion of its drug delivery applications. The determination of an adequate shelf life for chitosan formulations unveils an enormous challenge. Chitosan experiences a progressive chain degradation and subsequent functional group extermination during storage, resulting in an irreversible deterioration of its physicochemical properties [14,19].

There is an extensive literature investigating the potential and challenges of chitosan as a delivery system for anti-cancer drugs and growth factors. For instance, there are potential medical and pharmacological applications of CS-based nanocarriers, including nanoparticles (NPs), nanofibers (NFs), nanogels (NGs), and chitosan-coated liposomes (LPs) [20]. Kurczewska [21] focused on nanoparticles made of chitosan that were optimised for the delivery of a certain anti-cancer drug. Sadough et al. [22], reported the potential role of chitosan-based nanoparticles in drug delivery systems for pancreatic cancer. The application of chitosan as a vehicle for the transfer of growth factors, to facilitate tissue regeneration, was reported by Gohil et al., [23]. Improved and enhanced tissue regeneration has been documented by Sivashankari and Prabaharan [24], using chitosan-based scaffolds for growth-factor delivery. Yet very little is known about the material's strengths, weaknesses, opportunities, and threats in growth-factor and anti-cancer drug delivery, as no collaborative research has been published in this area.

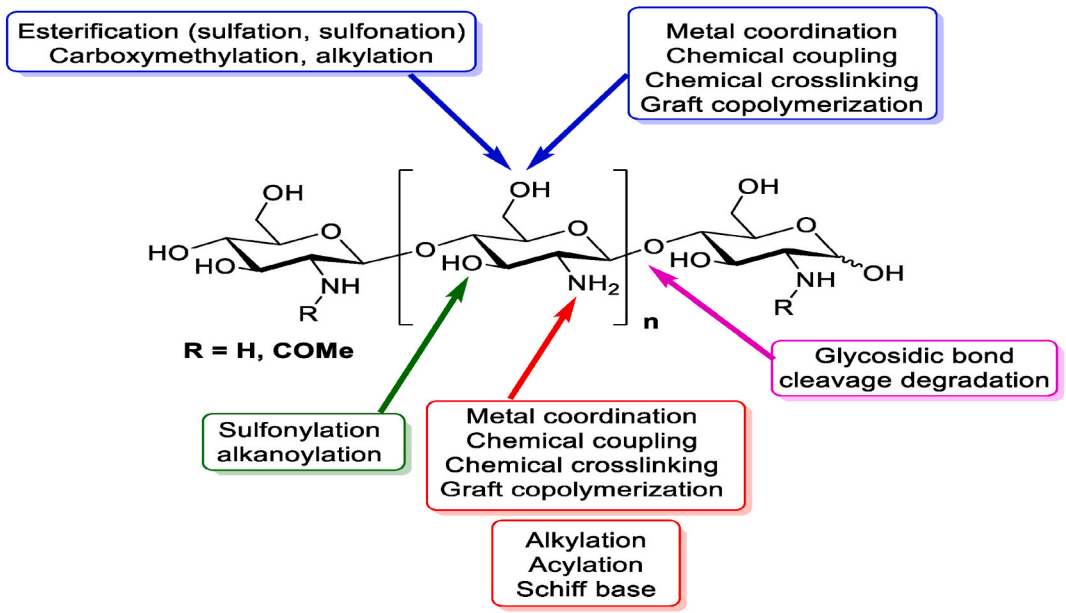

Fig. 1. Functional group-mediated chemical modification of chitosan [4].

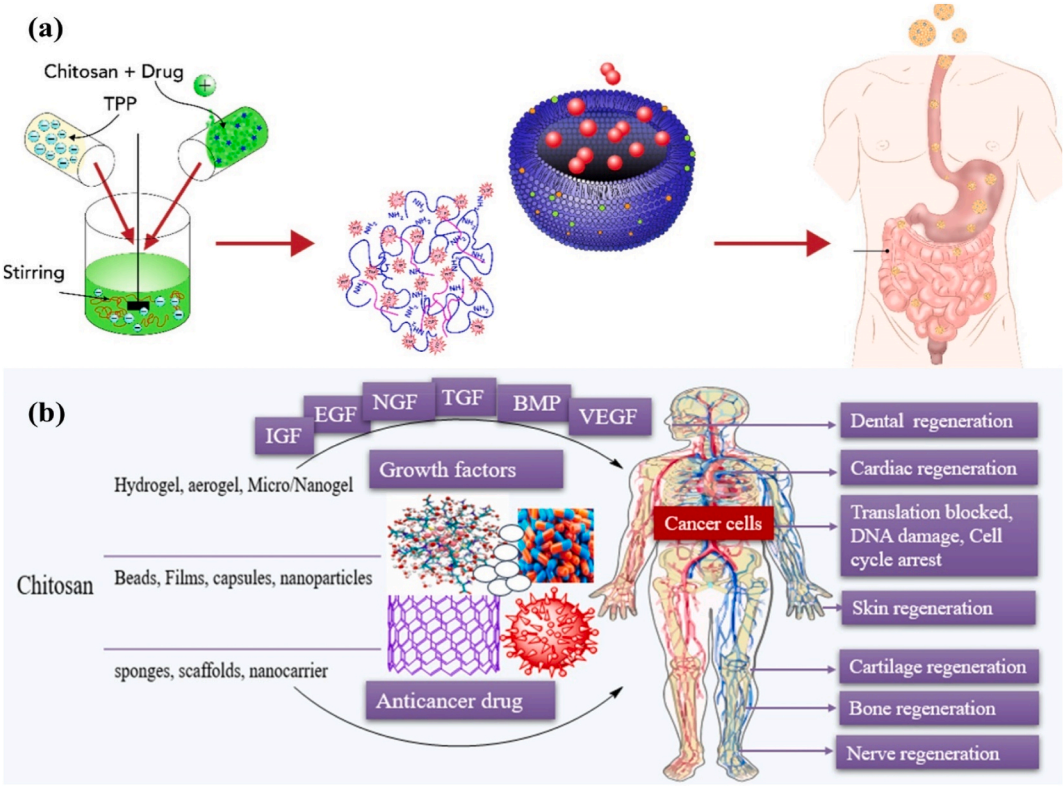

Fig. 2. (a) Chitosan-drug conjugate system for effective drug delivery [13], and (b) Utilising chitosan in its diverse forms for drug delivery.

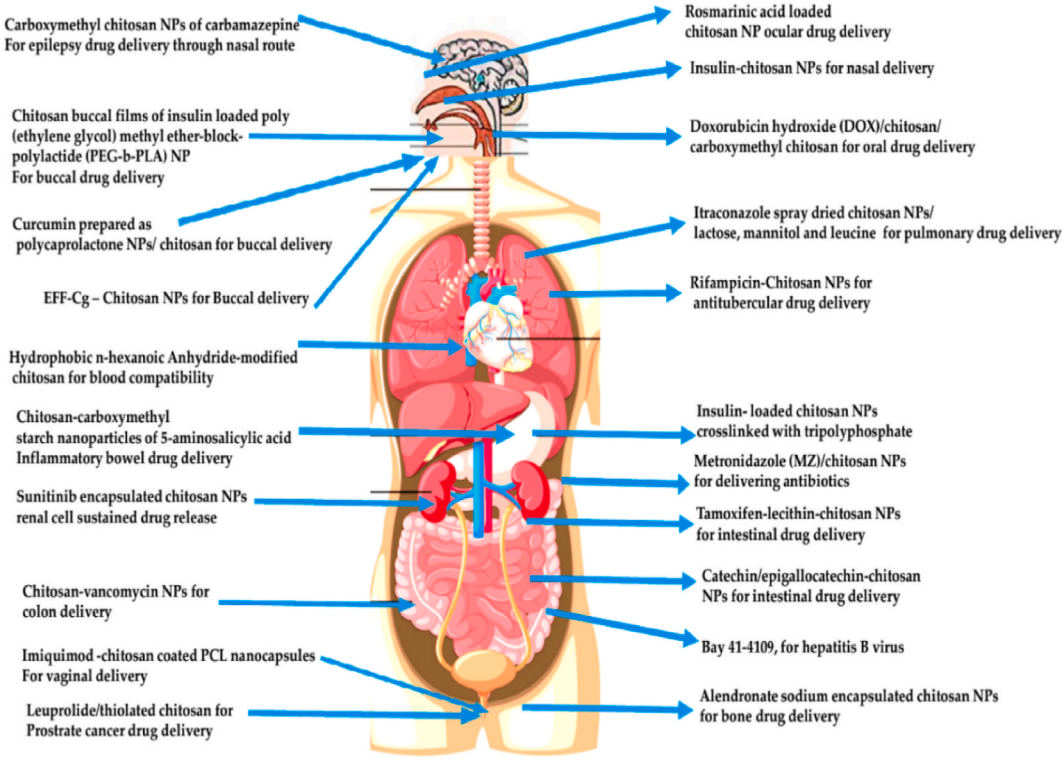

Fig. 3. Synopsis of chitosan's drug delivery applications [14].

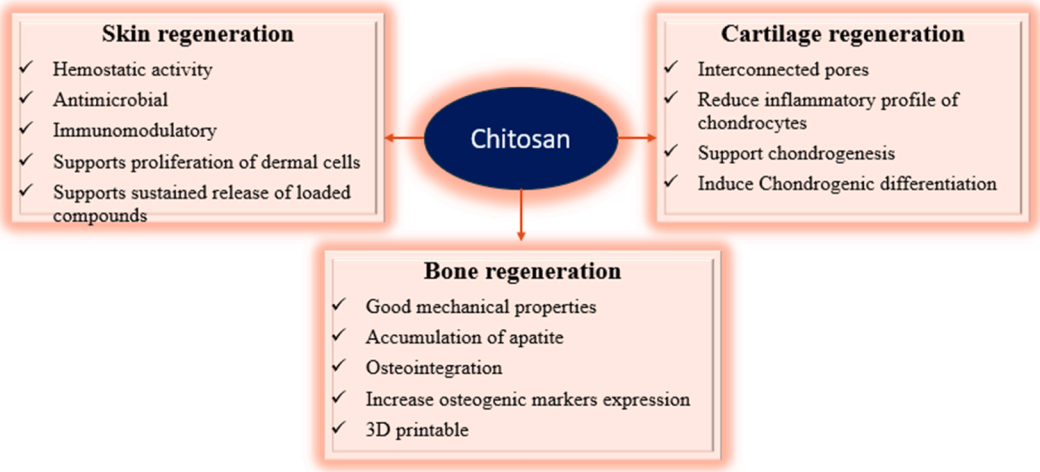

Fig. 4. Advantages of using chitosan for tissue regeneration [33].

Therefore, this review seeks to summarise recent findings in chitosan research to allow us to understand its stability, obstacles and fundamental uses as a drug carrier, in tissue regeneration and in anti-cancer therapy. In the process, we can see the views of many researchers on chitosan's suitability for such applications. Assessments of technical, environmental, and internal aspects, influencing the stability of chitosan-based systems, are also summarised in this paper.

2. Delivery of growth factors for tissue regeneration

In biomedical applications, growth factor delivery has emerged as a critical technique for reaching desired clinical outcomes. As originally described, a growth factor is a secreted, physiologically-active chemical, such as a vitamin or hormone, that can influence the growth in living cells. Growth factors are found in a variety of creatures, including insects, amphibians, humans, and plants, but were initially isolated from the tissues of mice and cattle [23]. Growth factors impact cellular activities like viability, migration, proliferation, and differentiation. They interact with cell surface receptors, transmit growth signals, and alter gene expression. Their impact on cells can be varied, as there are different growth factors, their spatial distribution affects their impact, as does cell number, receptor type and exposure time [25]. For instance, the growth of epithelial cells is stimulated by epidermal growth factor (EGF); muscle and connective tissue cells are stimulated by platelet-derived growth factor (PDGF); neural growth factor (NGF) stimulates the growth of neuronal cells; and insulin-like growth factors (IGF) stimulate growth by mediating the pituitary gland's secretion of growth

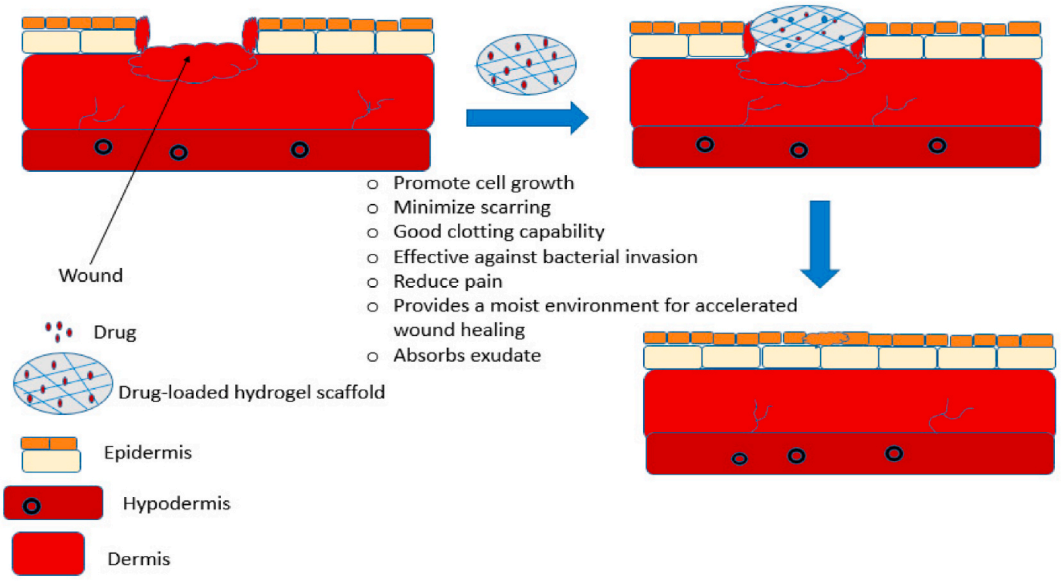

Fig. 5. The mechanisms of chitosan-based hydrogels to promote wound healing [38].

Table 1
Chitosan-based materials for delivery of various growth factors in skin regeneration and wound management.

Function	Materials composition	Growth factors Name	Effects	References
Tissue regeneration	Chitosan hydrogel	Transforming growth factor beta-1 (TGF-β1)	Clinical articular cartilage repair	[44]
	Heparin crosslinked chitosan microspheres	Fibroblast growth factor-2 (FGF-2)	Central nervous system (CNS) repair	[45]
	Nanochitosan loaded Gellan xanthan hydrogel	Basic fibroblast growth factor (BFGF), and bone morphogenetic protein 7 (BMP7)	Bone regeneration	[46]
	Heparin/chitosan nanoparticle-immobilised decellularized bovine jugular vein scaffold	Vascular endothelial growth factor (VEGF)	Accelerated regeneration of tissue	[47]
	Heparin-functionalized chitosan (CS)/poly (γ-glutamic acid) (γ-PGA) nanoparticles (HP-CS/γ-PGA nanoparticles)	Fibroblast growth factor (bfgf) and heparin	Ischemic tissue regeneration and preventing blood vessel rethrombosis.	[48]
	Novel chitosan/collagen scaffold	Human transforming growth factor-β1 (TGF-β1)	Periodontal tissue engineering.	[49]
	Chitosan-gelatin complex as three-dimensional scaffold	Transforming growth factor-β1 (TGF-β1)	Cartilage defects regeneration.	[50]
	Porous nano-hydroxyapatite/collagen/poly(L-lactic acid)/chitosan microspheres (nhac/PLLA/cms) composite scaffolds	Bone morphogenetic protein-2, BMP-2-derived synthetic peptide	Bone regeneration	[51]
	Chitosan/coral composite scaffold	Platelet-derived growth factor B (PDGFB)	Periodontal tissue regeneration	[52]
	Chitosan sponge	Platelet-derived growth factor-BB (PDGF-BB)	Periodonta bone regeneration	[53]
	Porous chondroitin-4-sulfate (CS)–chitosan sponge	Platelet-derived growth factor-BB (PDGF-BB)	Bone regeneration	[54]
	Covalently bonded biodegradable chitosan membrane	Recombinant human bone morphogenetic protein-2 (rhbmp-2)	Guided tissue regeneration (GTR) & new bone formation	[55]
	Calcium phosphate cement (CPC) –chitosan composite scaffold	Recombinant human bone morphogenic protein-2 (rhbmp-2)	Bone repair, osteoblastic induction, and bone regeneration	[56]
Wound management	Polyethylene glycol (PEG) cross-linked cotton-like chitosan scaffold (CS-PEG-H)	Fibroblast growth factor (bfgf) and vascular endothelial growth factor (VEGF)	Enhanced wound healing	[57]
	Dextran hydrogel loaded with chitosan microparticles	Epidermal and vascular endothelial growth factors/ epidermal growth factor (EGF), basic fibroblast GF	Wound healing	[58]
	Chitosan film	Basic fibroblast growth factor (BFGF)	Accelerated wound healing.	[59]
	Chitosan gel	Epidermal growth factor (EGF)	Increase the healing period in burns	[60]
	Light-cured glycol chitosan (GC) hydrogel	Vascular endothelial growth factor (VEGF) and platelet-derived growth factor-BB (PDGF-BB)	Enhanced wound healing, showed outstanding granulation effects	[61]
	Collagen-chitosan composite film modified with graphene oxide (GO) and 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC)	Basic fibroblast growth factor (Bfgf)	Showed outstanding performance in wound remodeling	[62]
	Chitosan:gelatin nanopillars (nano C:G films)	Epidermal growth factor (EGF)	Provide desirable healing characteristics and cause improved melanogenic outputs.	[1]
	Chitosan microneedle array (CSMNA) patch	Ascular endothelial growth factor (VEGF)	Promote inflammatory inhibition, collagen deposition, angiogenesis, and tissue regeneration during the wound closure	[63]
	Semi-interpenetrating network (semi-IPN) hydrogel based on polyacrylamide (paam) and chitosan (CS)	Epidermal growth factor (EGF)	Highest mitochondrial activities and enhanced wound-healing	[64]
	Bio-multifunctional benzaldehyde-terminated 4-arm PEG (4-arm-PEG-CHO)/carboxymethyl chitosan (CMCS)/basic fibroblast growth factor (bfgf) hydrogels (BP/CS-bfgf)	Basic fibroblast growth factor (BFGF)	Having strong wet-tissue adhesion, self-mending, and antibacterial property, excellent biocompatibility and fast hemostasis capacity, display great potential for diabetic chronic wound management	[65]
	Curcumin-loaded chitosan nanoparticles	Epidermal growth factor (EGF)	Promising treatment for dermal wounds	[66]
	Hydrogel composed of a mixture of PVA, gelatin and chitosan	Basic fibroblast growth factor (bfgf).	Contribute to accelerated wound healing	[67]

(*continued on next page*)

Table 1 (*continued*)

Function	Materials composition	Growth factors Name	Effects	References
	Poly (lactic-*co*-glycolic acid) (PLGA), chitosan Tylotoin nanoparticles (CPT nps)	Tylotoin (skin repair peptide)	Promotes the migration and proliferation of keratinocytes, fibroblasts, and vascular endothelial cells; release of TGF-1 and IL-6; macrophage recruitment; and fibroblast to myofibroblast differentiation, increasing drug bioavailability.	[68]
	Chitosan-crosslinked collagen sponge (CCCS)	Recombinant human acidic fibroblast growth factor (FGF)	Improve the recovery of healing-impaired wound such as diabetic skin wound	[69]
	Chitosan film containing basic fibroblast growth factor	Basic fibroblast growth factor (BFGF)	Proliferation of fibroblasts, facilitates wound repair	[70]
	Novel silver and nanoparticle-encapsulated growth factor co-loaded chitosan composite hydrogel	Epidermal growth factor (EGF)	Diabetic foot ulcer, Exhibited thorough re-epithelization, sufficient collagen deposition, and accelerated collagen maturation, highly advantageous for use in the clinical diabetic/ chronic wound treatment.	[71]
	Film-forming spray of water-soluble chitosan (FFSWSC) containing hegf-liposomes	Human epidermal growth factor (hegf)	Accelerated wound closure significantly	[72]
	Rhegf-Loaded Carboxymethyl Chitosan Nanoparticles	Recombinant human epidermal growth factors (rhegfs)	Showed good cytocompatibility. Accelerated the wound-closure rate in full thickness, can be used as a topical wound-healing drug carrier.	[73]

hormone. Erythropoietin, which promotes the production of red blood cells, is used to treat anemia brought on by chemotherapy for cancer, zidovudine (AZT) therapy in AIDS patients, and anemia related to chronic kidney failure. Patients with cancer are given granulocyte colony-stimulating factor (G-CSF; filgrastim) or granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim) to increase the production of white blood cells [26–28]. Furthermore, in regenerative engineering, bone morphogenetic protein (BMP), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and transforming growth factor- (TGF-) are commonly employed [27,29,30].

However, the controlled delivery of growth factors is an extremely difficult process, as the development of an optimal system requires the resolution of a number of different obstacles. A diverse array of methodologies has been utilised to regulate the release of growth factors. Extensive research has been conducted on polymeric carriers in the context of growth factor delivery.

Among an extensive array of natural polymers, chitosan is widely recognised as a highly-promising vehicle for the delivery of growth factors [23,31]. It has been shown that this biomaterial encourages bone, cartilage, tooth, skin, heart, and nerve tissue regeneration and repair, owing to its exceptional biological characteristics [31,32]. The major benefits of CS in tissue regeneration [33] are illustrated in Fig. 4.

Extensive research has been conducted on chitosan-based porous matrices, including sponges, scaffolds, nanoparticles, foams, and hydrogels, for the purpose of delivering growth factors that promote tissue regeneration. For instance, Modaresifar et al. [34], reported that a Gelatin methacryloyl (gelMA)/chitosan nanoparticle composite hydrogel delivered angiogenic growth factor (bFGF), proving itself biocompatible and having a capacity for sustained release. The hydrogel scaffold, capable of releasing over 75 % of bFGF within four days, was ideal for angiogenesis applications. For cartilage tissue engineering, Faikrua et al. [35] documented the utilisation of thermo-sensitive hydrogels, composed of chitosan-starch-β-glycerophosphate, to co-deliver chondrocytes and TGF-β1. The encapsulated growth factor maintained its biological activity throughout the 14-day sustained release *in vitro* from these hydrogels. To achieve higher levels of tissue engineering efficacy, Rajam et al. [36] investigated the feasibility of incorporation of combinative dual growth factors and their controlled release for tissue engineering and drug delivery application. They found high loading efficiency (90 %) in chitosan nanoparticles with EGF/FGF, resulting in sustained growth factor release (50 % was released by day 12) and prolonged release (a constant release up to 35 days), influenced by diffusion and matrix erosion mechanisms. In another study, Azizian et al. [31] introduced chitosan nanoparticles (average size 266 nm), incorporating chitosan-gelatin scaffolding, for the delivery of fibroblast growth factor (FGF) and bovine serum albumin (BSA), in tissue engineering. The introduction of nanoparticles, loaded with BSA-FGF, into chitosan-gelatin scaffolds, significantly improved their biological properties, enhancing their physical properties and promoting fibroblast cell proliferation.

For tissue support and regeneration, chitosan may be easily shaped into scaffolds. Scaffolds with growth factors on them encourage quicker tissue repair and regeneration than those without it [24]. Furthermore, recent research has focused on the application of various chitosan biomaterial forms for skin injury treatment, highlighting their potential to enhance wound healing, reduce fibrosis, and promote anti-inflammatory, antibacterial, and cell proliferative effects [34]. Chitosan aids wound healing by facilitating hemostasis, promoting antibacterial protection, and promoting tissue proliferation.

However, chitosan's mechanical properties limit its usefulness for skin regeneration. To improve strength and elasticity, synthetic polymers, or inorganic substances, can be added to chitosan-based drug delivery systems. Loading with antibacterial, hemostatic, and immune-modulatory drugs can further enhance their effectiveness [32,37].

There are several reports of chitosan-based hydrogels being used successfully for the management of wounds, with good healing

outcomes. Through surface erosion, bulk erosion, and polymeric degradation, among other methods, chitosan, loaded with various drugs, is transported to the site of injury. Subsequently, the drug molecules initiate the healing process within the impaired region. Fig. 5 illustrates the mechanisms by which chitosan-based hydrogels facilitate the process of wound healing [38].

Chitosan displays positive effects at each step of the wound-healing process. In the hemostasis phase, chitosan promotes surface-induced thrombosis and blood coagulation. It also accelerates coagulation *in vivo* by influencing the activation of platelets [39,40]. In the inflammatory phase, CS can regulate the activity of inflammatory cells and the release of pro-inflammatory factors, providing a micro-environment favourable for healing. In the proliferative process, CSprovides a non-protein matrix support for tissue growth. Moreover, CS will gradually depolymerise, to release N-acetyl-β-D-glucosamine. This polymer will stimulate fibroblast proliferation, angiogenesis and ordered collagen deposition at the wound site. Such events will enhance the wound healing process and prevent scar formation in the remodeling process [41,42]. CS is also able to avoid the occurrence of skin infections, which are considered one of the major complications associated with the wound-healing process. Ong et al. [43] reported a new chitosan-based composite dressing, with potent hemostatic and antimicrobial properties, incorporating a procoagulant (polyphosphate) and an antimicrobial (silver) with the chitosan.

The antibacterial effect results from the interaction of CS' positively-charged amine groups with the negatively charged peptidoglycans of the bacterial cell wall. This interaction can lead to internal osmotic imbalances in the microorganisms which inhibit their growth [39,41,43]. Furthermore, CS can bind to the DNA of the microorganisms and thereby inhibit mRNA synthesis. Such bonding can interfere with the expression of proteins that are essential for microorganisms' growth [38]. Table 1 presents a comprehensive overview of chitosan-based materials, their compositions and their role in skin regeneration and wound management systems.

3. Delivery of anti-cancer drugs

Despite advancements in medical technology, cancer treatment remains inadequate due to its high mortality rate, side effects, inefficiency, and high costs [74]. Nano drug delivery systems are rapidly developing in cancer treatment, due to their ability to control drug release and improve bioavailability.

Nanocarriers improve drug delivery in oncology, enabling cancer treatment and diagnosis. These systems, which can be easily cleared in systemic circulation, reduce cytotoxicity, and increase the therapeutic index. They are particularly suitable for use with chitosan, among several materials utilised as nanocarriers.

Chitosan is a biopolymer that is easily modified, readily available, and non-toxic, making it a perfect carrier for the delivery of anti-cancer drugs (Fig. 6) [75,76]. Research indicates that combining anti-cancer drugs with chitosan can enhance drug release periods, minimise side effects, reduce dosing frequency, accurately deliver drugs to diseased areas, and increase patient tolerance [77].

A variety of cancer treatments have made use of chitosan polymers to transport drugs in the form of hydrogels, nanoparticles, and nanofibers. Various features can be achieved by altering the surface moieties, for instance, by introducing a peptide that enters the cell membrane, monoclonal antibodies, or receptors that target particular cancer cells [78–80]. Ailincai et al. [81] reported about drug delivery systems using chitosan hydrogelation with citral and 5-fluorouracil. These systems have micro-porous morphology, uniform encapsulation, enzymatic degradability, and sustained drug release, making them suitable for intraperitoneal chemotherapy. This approach enhances the transportation of drugs to the intended location and minimises the impact on unintended areas.

Fig. 7 shows chitosan nanocarrier's anti-cancer drug carrier activity. The illustration demonstrates how the ligand of chitosan nanocarriers interacts with the overexpressed receptor of cancer cells. Following this binding, receptor-mediated endocytosis occurs, resulting in the creation of an endosome and the subsequent controlled release of the drug. Following the release of the drug, the cell undergoes apoptosis, resulting in DNA damage, translation blockage, and cell cycle arrest [82].

Trapani et al. [84] described the use of methotrexate- (MTX) loaded chitosan or glycol chitosan (GCS) nanoparticles (NPs) for the treatment of brain tumors, both with and without a Tween 80 coating layer. It was demonstrated that the particles could cross the

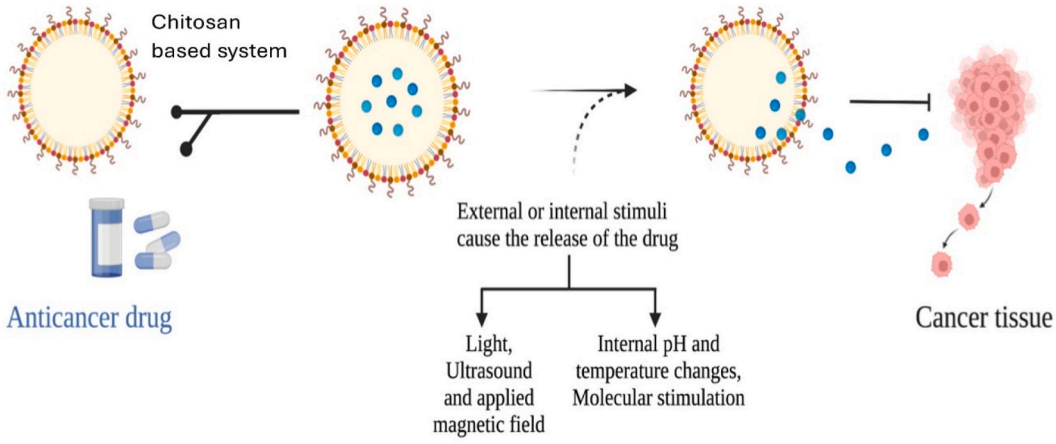

Fig. 6. Applications of chitosan-based system in tumor-targeted drug delivery [78].

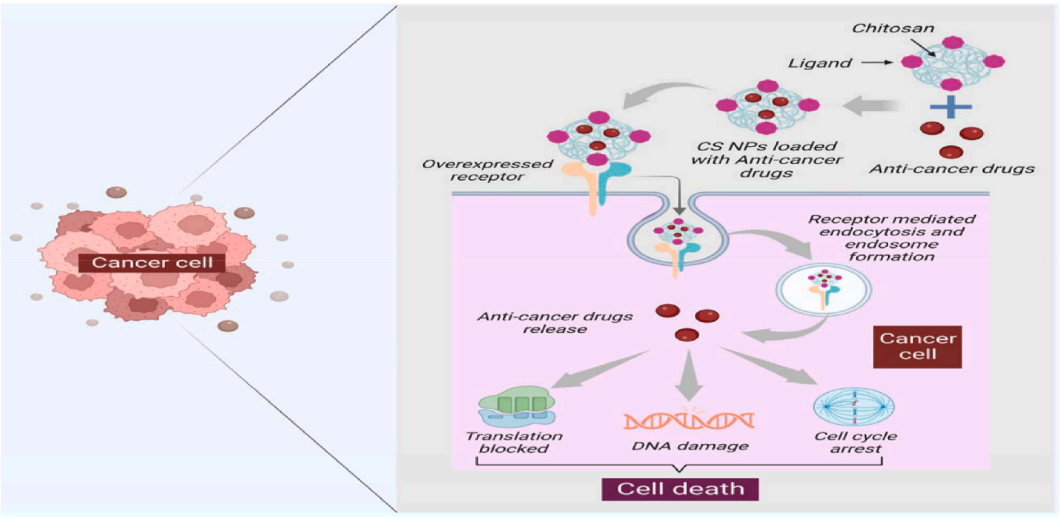

Fig. 7. The activity of chitosan as a carrier for anticancer drug delivery [83].

MDCKII-MDR1 cell barrier and were cytotoxic to the C6 cell line. The most cytotoxic NPs were those based on GCS. The findings imply that Tween 80, even at low concentrations, is adequate to improve the transport of MTX from the NPs across MDCKII-MDR1 cells. Ruman et al. [85] found that Sorafenib (SF)-loaded chitosan (SF-CS) and its folate-coated nanoparticles (SF-CS-FA) enhanced drug delivery to human Hepatocellular Carcinoma and Colorectal Adenocarcinoma cell lines. The nanoparticles showed excellent release under pH 4.8 in PBS solution, better anti-cancer action than free sorafenib, and negligible toxicity to normal cells.

An efficient and safe anti-cancer drug delivery system, using chitosan-based nanoparticles, was immobilised in sodium alginate beads. The anti-cancer drug, doxorubicin, hydrochloride (DOX), was efficiently absorbed by the small intestine of Sprague Dawley (SD) rats, with higher concentrations found in major organs after oral administration of porous beads [86]. A thermos-sensitive, cross-linked, injectable chitosan hydrogel, with good biocompatibility and quick gel formation at body temperature, was reported as excellent at efficient delivery of disulfiram to cancer cells [87]. Moreover, novel folate redox-responsive chitosan (FTC) nanoparticles was examined for intracellular MTX delivery, targeting folate receptors, and providing tumour specificity and controlled drug release [88]. When compared to non-target chitosan-based NPs, these nanoparticles efficiently reduced HeLa cancer cell multiplication.

Many investigations of natural, biologically-active chemicals are being undertaken, in order to create novel chemotherapeutic drugs and cancer treatments. Propolis contains a high concentration of physiologically-active chemicals, which influence multiple signaling pathways that regulate critical cellular processes involved in anti-cancer activity. Elbaz et al. [89] investigated a method for improving propolis oral administration, solubility, bioavailability, and anticancer efficacy. They increased the solubility of propolis and regulated its release with nanoparticles and chitosan microparticles. Propolis-loaded nano-in-microparticles demonstrated improved solubility and controlled release, cytotoxicity, and apoptosis in human liver cancer (HepG2) and human colorectal cancer (HCT 116) cells with considerable reduction in their number. Gupta et al. [90] formulated a paclitaxel-loaded chitosan nanoparticle formulation (PTX-CS-NP-10), which showed improved anti-cancer activity *in vitro* and *in vivo*. *In vitro* release showed a persistent pattern, with over 60% of the drug released within 24 h. The nanoparticulate formulation was biocompatible, safe, and reduced hemolytic toxicity. It also enhanced late cell apoptosis, indicating that the nanoparticulate formulation not only reduced overall toxicity but also improved the anti-cancer efficacy of paclitaxel. A novel approach was introduced by Abruzzo et al. [91] to encapsulate lipophilic molecules into chitosan nanoparticles and deliver them to cancer cells. The nanoparticles were positively-charged, stable in water, and reduced cell proliferation without causing reactive oxygen species (ROS) generation. In human breast cancer cell lines, HeLa cervical cancer cells, and fibroblast cells, a chitosan/polyethylene oxide (CH/PEO/BBR) nanofibers scaffold containing Berberine inhibited cell proliferation [92]. The nano-scaffolds also reduced cell viability in a time-bound way. Wu et al. [93] reported a new class of chitosan-based hybrid nanogels, immobilised with Cadmium-Selenium (CdSe) quantum dots (QDs) in chitosan-poly (methacrylic acid) networks. These nanogels exhibited excellent stability, reversible physical properties, and low cytotoxicity, enabling the illumination of B16F10 cells and regulation of anti-cancer drug release.

Chitosan/multi-walled carbon nanotube (Cs/MWCNT) nanocomposite, for drug carriers, including 5-fluorouracil, curcumin, and water-soluble curcumin derivative, showed higher cytotoxicity against MCF-7 cancer cells and better controlled release capabilities than chitosan. This indicates a strong drug-CNT association [94].

In order to facilitate the targeted delivery of anti-cancer medications to cancer cells, a chain transfer agent was added to pH- and redox-responsive Chitosan Nanogels (Ngs). Several advantages arise from the fact that this method distributes anti-cancer treatments to tumour tissue centrally and does not involve intrusive medication administration [95]. The combination of ultrasound and chemotherapy is proposed for improved anti-cancer therapeutic efficacy. Bifunctional nanodroplets, PFH @chitosan/alginate, show excellent anti-tumour efficacy and tumour-targeting ability when pH changes and ultrasound exposure is applied [96]. They found that

chitosan-based plumbagin microspheres showed significant anti-tumour efficacy and reduced systemic toxicity, with a 22.2-fold increase in elimination half-life ($t_{1/2}$) of plumbagin from chitosan microspheres, as compared to free plumbagin. This finding suggests that chitosan-based microspheres have great promise as a means of anti-cancer drug delivery. Table 2 presents an overview of chitosan-based drug delivery systems against cancer, including their compositions and effects in cancer treatment.

4. Stability of chitosan

Despite the outstanding performance of chitosan in drug delivery and other applications depicted in Table 2 above, chitosan degrades naturally into its basic, non-toxic components eventually. Its ability to help in destroying tumour and other cancer cells never gets turned against the normal cells of the human body Numerous enzymes degrade chitosan *in vivo*, with lysozyme, a non-specific protease present in all mammalian tissues, being the most important. This enzyme converts chitosan into non-toxic oligosaccharides, which can be excreted or incorporated into glycosaminoglycans and glycoproteins [116,117]. Chitosan, with four possible glycosidic linkages such as-D-D-, -A-A-, -A-D- and -D-A- (where A and D denote N-acetylglucosamine and glucosamine monomers, respectively), can be degraded through acid hydrolysis, oxidative–reductive depolymerisation, ultrasonic degradation, or enzymatic degradation, using specific enzymes [7,118], among other means. The potential pathways for chitosan's structural breakdown are depicted in Fig. 8. The mechanism and rate of chitosan degradation are largely dependent on the molecular weight, polydispersity,

Table 2
Chitosan-based anticancer Drug Delivery Systems.

Function	Materials composition	Anticancer drug name	Effects	References
Cancer Treatment	Chitosan nanoparticles (CSNPs), crosslinked with sodium tripolyphosphate (TPP)	Cisplatin (CP) and 5-fluorouracil (FA)	Targeted drug delivery to tumour cells, promoting anti-bacterial and anti-cancer activities	[96]
	Chitosan-coated magnetic nanoparticles (CCMNPs)	Black pomegranate peel extract (BPPE) as a novel anti-cancer drug	Targeted drug delivery to treat breast cancer	[97]
	Chitosan nanoparticles	Doxorubicin (DOX)	Doxorubicin and Doxorubicin-loaded chitosan nanoparticles deliver anti-cancer drug with lower toxicity and less-negative impact on heart	[98]
	Chitosan-modified Fe_3O_4 magnetic nanoparticles	Imatinib	Targeted anti-breast-cancer drug delivery	[99]
	Tripolyphosphate-crosslinked chitosan (TPPCS) nanoparticles	lenalidomide (LND)	Enhanced efficiency for anti-cancer drug delivery	[100]
	Chitosan/polyacrylic acid/Fe_3O_4 magnetic nanocomposite hydrogel	5-Fluorouracil	Enhanced stability of drug dose for a longer time due to controlled release of drug in the colrectal area	[101]
	Chitosan/3-methoxy-4-hydroxybenzaldehyde (vanillin) nanoparticles	5-fluorouracil	Constant and controlled release of 5-FU anticancer drugs to colon.	[102]
	Chitosan (CS), magnetite (Fe_3O_4), graphene Oxide (GO) nanoparticles	Carboplatin (CARB)	Better nano-carrier of the anti-cancer drug carboplatin.	[103]
	Chitosan or glycol chitosan (GCS) nanoparticles (NPs)	Methotrexate (MTX)	Enhancing the transport of MTX from the NPs across MDCKII-MDR1 cells, administration of MTX to brain tumors	[104]
	Polycaprolactone/chitosan blend nanofibers	5-fluorouracil	Anti-cancer drug delivery system for colorectal cancer and improved release efficiency	[105]
	Chitosan nanoparticles	Cytarabine	Possibly better therapeutic efficiency against solid tumors.	[106]
	Chitosan nanoparticles	Paclitaxel	Enhanced anti-cancer effect	[107]
	Chitosan (Cs)/Multi-walled carbon nanotube (MWCNT) (Cs/MWCNT) nanocomposite	5-fluorouracil, curcumin, and water-soluble curcumin derivative	Better slow and controlled release of anti-cancer drug	[108]
	(i) Hydrophobically-modified chitosan nanoparticles (Palmitoyl Chitosan Nanoparticles (pCNP))	Silibinin (SLB)	Controlled-release delivery of SLB for cancer therapy	[109]
	Chitosan nanoparticles	Pravastatin (PRV)	Promising carrier for cancer medication due to sustained drug release	[110]
	chitosan nanocarrier	5-fluorouracil	Functionalisation of chitosan nanoparticles with drugs: solvation and binding energy provides stability and controlled release of the drug	[111]
	Chitosan/palladium nanocomposite	Curcumin (CUR) and 5-Fluorouracil (5-FU)	Prolonged release of the drug, successfully inhibits the growth of cancer cells	[112]
	Polyoxalates cross-linked with chitosan (CS) nanocomposites	Cisplatin (CDDP)	Promising drug carrier for the delivery of CDDP, tumour growth inhibitionist	[113]
	Chitosan (CH) nanoparticles	Tamoxifen	Increases intracellular concentration of Tamoxifen and enhances its anticancer efficiency by inducing apoptosis in a caspase-dependent manner.	[114]
	Chitosan hollow nanospheres (CHN) & polystyrene nanospheres (PS) as templates	Paclitaxel (PTX),	Inhibited proliferation of lung cancer A549 cells and increased their apoptosis	[115]

degree of deacetylation, purity, and moisture content. Chitosan's extreme sensitivity to outside influences and processing parameters (such heating or freezing) can put stress on the material's structure and lead to degradation [19,118]. As DD lowers, degradation increases [117]. Degradation kinetics appear to be inversely related to the degree of crystallinity [119]. Furthermore, the length of the chains (Mw) affects the degradation rate as well [120] (as one example among many).

Chitosan is highly-vulnerable to changes in its environment. Hardness and mechanical strength were reduced, for example, when exposed to high temperatures (40 °C) because the overheated chitosan powder was dehydrated. Additionally, the rate of chitosan degradation, especially in semi-solid and liquid items, may be affected by air temperature. The rate of hydrolysis was found to follow first-order kinetics when chitosan solutions were stored at ambient or elevated temperatures, leading to quicker degradation of chitosan chains [116,121]. In a chitosan solution held at 5 °C, no appreciable chain hydrolysis was observed. As a result, it is recommended that chitosan be stored in closed containers at low temperatures (2–8 °C). High humidity conditions (RH > 60 %) cause water molecules to penetrate chitosan chains more intensively, leading to swelling, reduced physico-chemical properties, and increased hydrolytic degradation [122]. Kurek et al. [123] reported that high humidity increased chitosan film's swelling, releasing active compounds faster, and weakening muco-adhesive properties, due to dilution of functional groups for mucin interactions.

The limited stability and susceptibility to biodegradation of chitosan-based systems limit their practical use in biomedical applications. As a result, establishing a suitable shelf life for chitosan formulations has become a great challenge [116]. Several methods have been developed to preserve the original characteristics of chitosan by preventing polymer chain degradation. Controlling environmental parameters, altering manufacturing conditions (e.g., temperature, relative humidity, light), introducing an appropriate stabilising component, producing chitosan blends with another polymer, or modifying the chitosan structure, using chemical or ionic agents, can all improve stability [19,118,124,125]. Nevertheless, for numerous drug delivery applications, involving release of mini- and macro-drug molecules, comprehending and controlling the degradation rate of chitosan-based devices is essential.

5. Side effects of chitosan in drug delivery: Allergenicity & cytotoxicity

Chitosan is widely respected, across the world, as a non-toxic, biologically-compatible polymer [126]. Chitosan is approved for dietary applications in Japan, Italy and Finland and America's FDA has approved chitosan for use in wound dressings [127].

However, research has shown that chitosan can induce an immunological response (allergy) in certain individuals, thereby causing allergic reactions. So, concern about chitosan allergy may counterindicate use of medications with chitosan components in some patients [128]. It is an issue on which we need more research and on which we should educate medical professionals.

Moreover, alterations of chitosan may result in varying degrees of toxicity. Chitosan formulations induce cytotoxicity into processes including cellular uptake, drug release, augmentation of drug efflux, evasion of drug-induced apoptosis, and activation of DNA repair

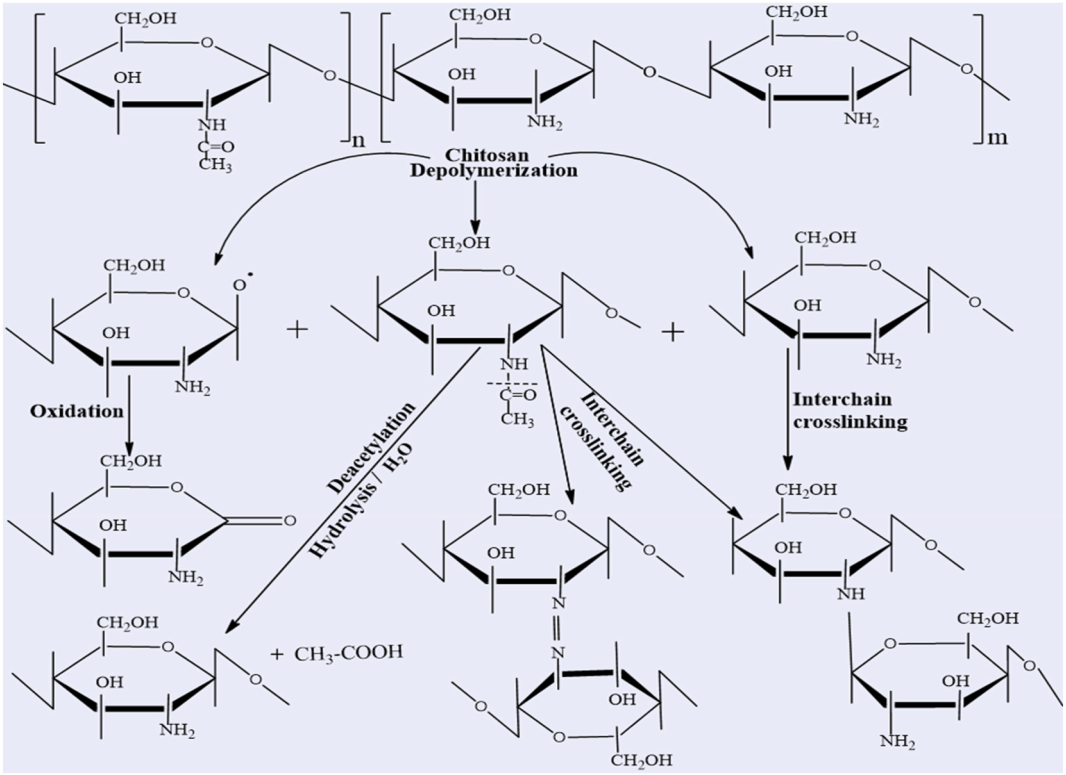

Fig. 8. Possible steps in chitosan's compositional breakdown [19].

pathways. Additionally, chitosan may induce toxicity through cell membrane injury [128]. It is important to bear in mind that the integration of chitosan into drugs may alter the pharmacokinetic and biodistribution profiles of the new, integrated substance, which may be significantly different than those of the component substances. Moreover, the charge interaction may cause alterations in the kinetics of cellular absorption, as is the case with DNA complexes. The reduction or harmonising of the positive charges on the chitosan molecule influences its interactions with cells and the micro-environment, frequently resulting in reduced toxicity and uptake. When a covalent drug conjugate is present, the chitosan undergoes modifications to its physico-chemical properties (eg. hydrophilicity) and conformation (eg. micelle formation). Such modification may thus subsequently impact distribution of chitosan and its assimilation by cells. Additionally, the toxicity profile is influenced by the route of administration, which. in turn, also determines the uptake, concentration, contact period, and cell types affected, of the administration [127,128]. Scientists are attempting to resolve the issue of chitosan's minimal adverse effects, which must be viewed in their proper perspective and not overemphasised. However, until these scientists succeed in eliminating potential problems in chitosan's use, these issues must be borne in mind by those planning to use chitosan-based drug delivery systems.

6. Challenges of chitosan for growth factor and anticancer drug delivery

Though there is a lot of published research on chitosan for growth factor and anti-cancer drug delivery systems, the US FDA has only approved chitosan for a limited number of uses at this time. Since the FDA has not yet approved this material for all biomedical purposes, very few biotech businesses are utilising it, fearing litigation if there are any unplanned impacts on patients. Despite being biocompatible, there are certain challenges in using chitosan nanoparticles as drug carriers [129,130]. The lack of hemocompatibility and poor stability of chitosan nanoparticles are two of the biggest barriers to their therapeutic utilisation. Many scholars have shown the hemostatic properties of chitosan. While chitosan-based nanoparticles have been shown in animal experiments to be safe for intravenous injections, the production of fatal embolisms is a concern. Clinical translational problems could also be caused by the off-target dispersion of chitosan nanocarriers loaded with chemotherapeutic drugs. These carriers are readily phagocytosed by the mononuclear phagocytic system, which is present at key sites throughout the human body [131,132] During apoptosis, chitosan's pharmacological cargo may be distributed to several organs. Chitosan has been licensed by the FDA for use in oral medication delivery and wound healing. Beyond that, medicinal compositions containing chitosan may be hazardous *in vivo* [130,133]. Therefore, it is essential to conduct safety analyses while creating chitosan-based drug carriers and to examine the nano-theranostic platforms they use [134].

Notwithstanding these challenges, chitosan holds great promise for the delivery of growth factors and the treatment of cancer. As new technologies develop and our knowledge of the mechanism of action of chitosan-based drug delivery carriers advances, the limits in place will be lifted.

7. Future perspectives

Chitosan can be used in growth factor and anti-cancer drug delivery because of its excellent pharmacological properties. Many potential applications exist for chitosan and its derivatives. Another strong indicator of their significance is the abundance of scholarly literature on chitosan and its derivatives, based on nanomaterials. The commercial exploitation of chitosan, however, is hindered by the challenges associated with producing uniformly-reproducible chitosan in large quantities from the many marine creatures found worldwide. Chitosan derivativisation raises the total cost of production and raises the possibility of character-uniformity variances. These constraints may be solved by research and technological breakthroughs, which will be aided by the increasing application of and demand for chitosan and its derivatives. Among numerous biomolecules, however, chitosan has proven to be an ecofriendly, non-toxic, and sustainable polymer. As a result, chitosan-based formulations, as growth factor and anti-cancer drug delivery carriers, will be most-promising materials for application in the biomedical field for some time to come.

8. Conclusion

Drug delivery systems utilising chitosan, a naturally-occurring polysaccharide, have demonstrated promising results, particularly for delivery of growth factor and anticancer drugs. Despite the wide variety of chitosan derivatives that have proven useful in biomedical applications, very few have achieved the status of well-established specified compounds. Therefore, there is an enormous demand for additional research to let us utilise chitosan and its derivatives for medicinal products delivery and develop them to their full potential. This paper has summarised the *status quo* on chitosan and its derivatives. Aspiring scientists should read this paper, to understand where we are on chitosan now, and then do the necessary work to show us the ways forward to develop our understanding and use of chitosan fully.

CRediT authorship contribution statement

Md Hasinur Rahman: Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Md Ibrahim H. Mondal:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Conceptualization.

Data availability

The authors declare that no data associated with our study has been deposited into a publicly available repository since no data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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