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Chitosan based nanocarriers as a promising tool in treatment and management of inflammatory diseases

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ABSTRACT

Therapeutic tools in the biomedical field are increasingly utilizing nanoparticles (NPs) with a small size and large surface area. Chitosan (CS), a biotic polymeric carbohydrate found in shellfish, is a promising carrier for these diagnostic systems due to its biocompatibility, low toxic effects, and diverse shapes. CS-NPs are therapeutic transporters with properties such as bionomical, pH, and heat sensitivity, increased homogeneity, and potential to pass through the brain. These nanomaterials can detect and cure pathological conditions using curative instruments. CS-NPs slow down the movement and growth of anti-inflammatory colonies while encouraging the growth of cells causing inflammation. They could provide active substances for treating various medical conditions, such as auto-immune deformities, hyperglycemia, hypersensitivity, and cancer. Scientific resources are dedicated to improving the efficacy of CS-NP active agent compositions. Recent discoveries highlight the medicinal implications of CS-NPs preparations for drug delivery in managing severe inflammatory aberrations.

1. Introduction

In the coming 30 years, the occurrence of severe inflammatory disorders is predicted to rise gradually in the United States (US). According to Rand Corporation's study, approximately 60% of Americans had at least one persistent ailment in 2014, 42% had more than one, and 12% had five or more serious ailments (Tsai et al., 2019). In 2015, approximately 1.3% of individuals in the US were identified with inflammatory bowel disease (IBD). During 2013 and 2015, 22.7% of individuals in the US were afflicted with rheumatoid arthritis (RA), lupus, gout, or fibromyalgia. RA has a widespread frequency of roughly 1%, with females having a 2-3 times higher prevalence than males. According to the WHO, three out of every five individuals suffer from severe inflammatory disorders such as heart attacks, chronic pulmonary diseases, cardiovascular illness, overweight, and hyperglycemia (Medzhitov, 2008). Inflammation is a heterogeneous, stereotyped response to injured neurons, systems, and perfused structures. It can be classified as (a) protective or (b) damaging. According to the causal agent and the amount of destruction, the inflammatory treatment may be fast or convoluted, including numerous cell categories (Malone, 2016). It is additionally influenced by endothelium and peripheral cellular vasodilatory messengers, icosanoids, reactive oxygen species (ROS), metabolites of multienzyme complexes of plasma proteins, different cytokines, neurotransmitters, and neuromodulators. Erythema, temperature, inflammation, discomfort, and malfunction of the damaged area are all symptoms of inflammation. Edema development, fibrin accumulation, and the activation of neutrophils in the damaged region are the key, essential aspects of injury. The neutrophil level might drop depending on the severity of the infarct or the amount of the lesion, contributing to the emergence of an especially persistent reaction in the tissues,

Abbreviations: CS-NPs, Chitosan Nanoparticles; IBD, Inflammatory bowel disease; ROS, Reactive oxygen species; SLNs, Solid lipid nanoparticles; NLCs, Nanostructured lipid carriers; MMP-2, Matrix Metalo Proteases-2; PEC, Polyelectrolyte complex; DM, Diabetes mellitus; GDM, Gestational DM; STZ, Streptozocin; TG, Triacylglycerol; HCV, Hepatitis C virus; NAFLD, Non-alcoholic fatty liver disease; HCC, Hepatocellular cancer; NASH, Non-alcoholic steatohepatitis; HSCs, Hepatic stellate cells; PAMP, Pathogen-activated molecular pattern.

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accompanied by an elevated frequency of macrophages, lymphocytes, plasma cells, and eosinophils. At this phase, some possibilities can occur, which include: (i) the microorganism can be completely eradicated and the wounded skin can be rectified to restore regular framework and purpose; (ii) the bacterium cannot be excluded, it persists at the damaged site, and concurrent stimulation of immunologic modalities tends to lead to the configuration of granulomatous or destructive swelling; or (iii) the skin wound is irrevocable, likely to result in scarification and failure of initial purpose (Ley, 2018; Serhan & Ward, 2010). Nanostructures in medication administration have the potential to enhance the cellular absorption of less-soluble medicines. They also improve pharmaceutical absorption of complicated therapeutic dosages. The morphology of NPs has the potential to alter the pace of drug content and distribution, and the equilibrium among surface area and geometrical symmetry are crucial to the effectiveness of medication administration. Furthermore, medications encased in NPs have a longer circulatory duration, which improves bioavailability and pharmacology (Ghaffarian et al., 2016). CS, a charged polymer with metabolic properties, has indeed been identified as a viable material with numerous clinical uses. CS is a ubiquitous biomaterial formed from organic chitin found in the exoskeletons of arthropods, crab shells, insects, and fungal cell walls (Senel & McClure, 2004). Non-toxicity, biocompatibility, degradability, bioavailability, and adhesiveness are some of its distinguishing characteristics (Kean & Thanou, 2010). CS has great bioavailability as well as low cytotoxicity, immunogenicity, and degradability, implying that it could be used as an efficient pharmaceutical distribution medium. CS is a naturally occurring, continuous amino-polysaccharide made up of glucosamine and N-acetylglucosamine units. Due to its free amine groups, CS has the ability to be quickly adapted to NPs via bridging or by taking advantage of its proclivity for spontaneous self-assembly (Zhao et al., 2018). CS has the composition of 2-amino-2-deoxy-d-glucan linked together with glycosidic bonds. Because of the unique characteristics of the primary amine moieties, CS is highly valuable for pharmacological purposes (Agnihotri et al., 2004). CS is positively charged and mucoadhesive when contrasted to several other biopolymers. As a result, it is widely used in medication distribution technologies. CS has been extensively used in biological and pharmacological procedures such as drug, gene, vaccine transfer, genetic engineering, tissue repair, and cosmetics manufacturing (Xiang et al., 2023). Because of its water stability, it has numerous uses in the cosmetic and pharmaceutical industries as solutions, gels, coatings, strands, and screens. At pH 7 and ambient temperatures, CS can be persistent in solutions. Heating to 40°C to generate gel structure, which exhibits a continuous sol-gel conversion based on trial circumstances (Yang, 2011). Delivering biomolecules to the site of inflammation or to particular cells is the goal of pharmacological intervention for inflammatory diseases. But inflammation increases, which causes vascular and cellular penetration, the basic difficulty in anti-inflammatory medication administration from the inflamed cells to the circulatory sites. Both of these elements will result in a reduction in therapeutic effectiveness and negative treatment significance. Treatment of inflammatory illnesses is complicated by variances in bioavailability, the use of various medications, and drug-related complexes (JessyS, 2013). By enclosing the drugs in an appropriate transport mechanism that possesses the ability to keep them in the region, CS-NPs-based formulations can enhance the medication's persistence at the site of inflammation. Following that, researchers also looked into solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), solid-in-oil (S/O) nanocarriers, nanogels, hydrogels, micro-emulsions, deformable liposomes, micro-emulsion-based gels, etc. (Amal et al., 2015). The organic biocomposite CS, which belongs to the chitin family, has some immunologic properties, such as the ability to reduce the formation of type III collagen and cytokines, which promote inflammation. CS has unique properties that are used as potential stimuli, like anti-microbial, anti--inflammatory, and wound-healing. More stability and greater skin permeation, encasing with thermosensitive polymeric materials, thermoresponsive medication discharge, drug at an acidic pH, enhanced bioadhesion, more retention, and less drug elimination are the important benefits of CS-NPs exposed to bioactive compounds in the inflammatory process (Benettayeb et al., 2022). CS stops the release of IL-8 and TNF-a from melanocytes during rapid hypersensitivity reactions. It also stops Matrix Metalo Proteases-2 (MMP-2) and long-lasting inflammation in human dermal fibroblasts. This may be because CS binds to Zn^{2+}, which is a co-factor of MMP-2 (Oliveira et al., 2012). Therapies for inflamed skin abberations have numerous useful applications of nanomaterials that might enhance delivery, absorption, and localization. Improved transdermal administration, increased tolerability and effectiveness, increased pharmaceutical selectivity, decreased cytotoxicity, and decreased effective component disintegration are all possible with a nanonovel drug delivery system (Nitha & Ramya, 2014). In order to discover substances with improved dispersion, sorption potential, physical properties, and the strength to create films, fibers, and cross-linked configurations and combinations depending on the monomers that are being developed (Jha & Mayanovic, 2022; Lv, 2016), CS exists as one of the most prevalent organic polymers, and its requirements in manufacturing applications are being widely researched due to its fundamental properties. It is seen as a good alternative to synthetic materials for environmentally friendly production methods because it breaks down naturally, works well with living things, is safe, attracts water, is cheap, and can be used in physiological ways. As a result, the biological potential of CSs is a primary aid for enzyme immobilization. However, its importance is limited, and to circumvent this limitation, different pre-treatments, such as chemical and physical alterations to its framework, allow it to be used for a broader range of purposes. Because of its unusual socioeconomic and ecological significance, CS has emerged as a biopolymer that is particularly appealing for a variety of applications (Jha & Mayanovic, 2022) Chitin undergoes alkaline deacetylation to produce CS, which is a common component of the external skeletons of aquatic creatures, arthropods, and microbial cellular membranes. In contrast to chitin, which is insoluble in many organic solvents, CS is solvable in weak acid concentrations under pH 6.0 (Hahn et al., 2020; Rouhani Shirvan et al., 2019; Santos et al., 2020). Because of CS-NPs' biochemical and bioadhesive qualities, nanomaterials can enhance transmucosal penetrability, facilitate diffusion via the extracellular channel, and even stimulate the conformational rearrangement of tight junction-associated molecules (Peppas & Huang, 2004). The implementation of CS-NPs in biomedical fields such as bioimaging, drug and gene delivery methods, tissue engineering, and pharmaceutical methodologies (Rahimian et al., 2015) in addition to the removal of hazardous contaminants (Shoueir et al., 2018) has greatly expanded. It has been widely used in medical treatments because it fights free radicals, allergies, inflammation, blood clotting, microbes, HIV, high blood pressure, Alzheimer's, diabetes, obesity, and cancer - all of which are very good for health (Nejati et al., 2018; Zhang, Sun, & Jiang, 2018).

2. CS-NPs production/synthesis

- *Ionotropic gelation*

The electrochemical contact involving the amine group of CS, as well as a negative charge unit of polyanion, such as tripolyphosphate, is used. In the absence or presence of supporting chemicals such as poloxamer, CS are hydrolyzed in acetic acid. After that, polyanion is introduced, and nanostructures are synthesized at room temperature while being mechanically stirred. By varying the CS-to-stabilizer ratio, particulate size and surface charge can be altered. When the content and polymeric-to-polyanion proportion were increased, there was a significant rise in particle homogeneity and size (Jonassen et al., 2012). They also revealed that nanomaterials distributed in saline solutions are more durable owing to the lower particle size discovered due to the influence of sodium chloride. Also, it can be due to adding a monovalent salt to the

solvent, such as sodium chloride, which filters out the electrostatic resistance amongst the positively charged amine groups on the CS strand. So, it increases the elasticity of polymer chains in solutions and, consequently, their resilience (Ilium, 1998). CS also has the ability to generate hydrogels in the presence of particular polyanions when the amine functional group is highly protonated. This phenomenon results from anionic molecules mediating intermolecular and intramolecular cross-linkages (Janes et al., 2001; Terbojevich & Muzzarelli, 2009). Ionic gelation or polyelectrolyte complexation have recently been used to create CS-based nanomaterials. It is emphasized that gelation is the preferred terminology when CS gelation is produced by micro-ionic compounds like phosphate, citrate, and sulfate, whereas polyelectrolyte complexation occurs when ionic macromolecules are utilized rather than small biomolecules (Bhattarai et al., 2010). The latter method is also known as complex coacervation or interfacial coacervation (Kissel et al., 2006; Poncelet, 2005). This process depends on the electrostatic interaction of negatively charged ions with the positively charged amino groups of chitosan. Chitosan with the crosslinking agent—typically sodium sulfate or tripolyphosphate (TPP)—form a gel that causes the creation of nanoparticles.

- *Microemulsion method*

A surface active agent was dispersed in N-hexane and CS in acetic solution, and glutaraldehyde was introduced to the emulsifier-hexane combination while continuously agitating at room temperature. In the presence of a surfactant, nanostructures were generated. To accomplish the connecting mechanism between the free amine groups of CS and glutaraldehyde, the mixture was agitated continuously. In this approach, glutaraldehyde acts as a crosslinking agent (Fang et al., 2009). The chemical solution is then extracted by low-pressure vaporization, and excessive surfactants are retrieved by precipitating with CaCl2, which is subsequently eliminated by centrifugation. The inclusion of the antigenic agent glutaraldehyde is the main downside of this approach. Furthermore, covalent coupling may cause protein or peptide integration into nanomaterials to fail. Production of chitosan-based nanoparticles using different methods, as shown in Fig. 1.

- *Emulsification solvent diffusion method*

An emulsion is formed by mechanically stirring an organic solvent into a CS solution comprising a buffering ingredient such as poloxamer, accompanied by high-pressure homogenization. The emulsion is then heavily dissolved in water. Polymer deposition happens when organic solvents are diffused into water, resulting in the formation of nanomers. The two key techniques have their drawbacks, which include the usage of organic solvents and the strong shear pressures employed during NP formation. The emulsion solvent dispersion approach of CS-NPs preparation is a derivative of the initial technique designed to generate poly (lactic-co-glycolic) acid-based NPs (Niwa et al., 1993), creating limits on the miscibility of an organic solvent with water. The methodology for generating CS-NPs comprises stirring an organic phase and providing the hydrophobic substance into an aquaeous mixture including CS and stabilizers like poloxamer and lecithin (El-Shabouri, 2002). This results in the creation of an oil-in-water emulsion, which is then homogenized under high pressure. At this point, acetone disperses into the aqueous phase, lowering the absorption of CS and, hence, the formation of nanomaterials during polymeric deposition. To allow for thorough acetone dispersion, an excess proportion of water is frequently supplied. Subsequently, centrifugation separates the NPs. This approach shows remarkable encapsulating effectiveness while encapsulating hydrophobic medicines such as cyclosporin-A. Characteristics like CS atomic weight, homogenization velocity, and duration time are likely to influence the processability of the carriers. Acetones are also claimed to be vital because their quick dispersion upsets the organic stage boundary, causing them to autonomously generate a wider area and, as a result, contribute to the development of much finer particles. Particles generated without acetone have diameters that are larger than 1.2 micrometer. Regardless of this technique's potential to manufacture successful vehicles, it is critical to emphasize the necessity for rigorous preparatory parameters, like organic solvents and high shear forces, which are lacking in various approaches. The method of prepapration shown in Fig. 2.

3. Other methodologies

3.1. Polyelectrolyte complex (PEC)

Polyelectrolyte interactions were synthesized initially due to the self-structure of cationic-charged polymers and plasmid DNA as a consequence of cationic polymer and DNA charge neutralization. CS-NPs can be made naturally by mixing DNA solution with chitosan that is soaked in acetic acid solution and stirring it by hand at room temperature (Erbacher et al., 1998).

3.2. Reverse micellar technique

The reverse micellar technique was documented by Brunel et al. (2008). This approach can also produce ultrafine NPs with confined size ranges. An aqueous phase of CS is added to an organic medium

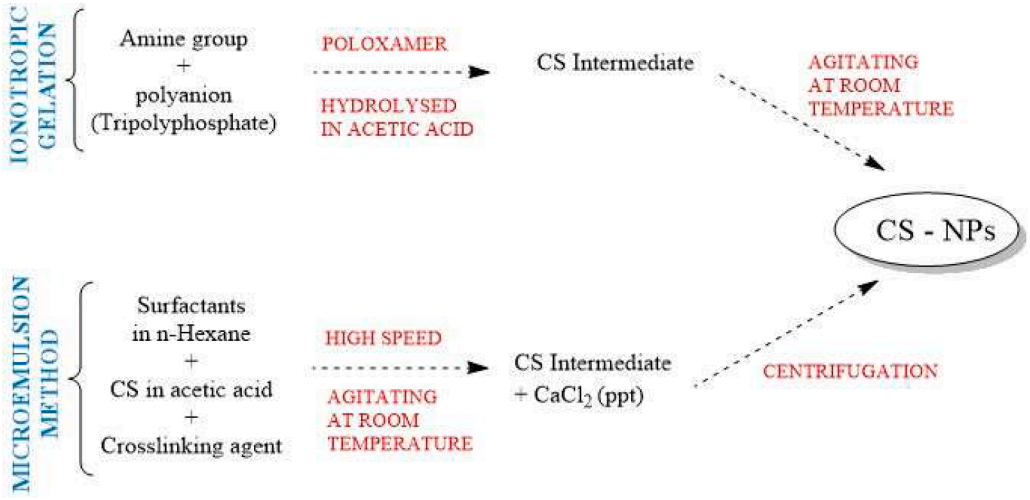

Fig. 1. Production of Chitosan based Nanoparticles using ionotropic and microemusion methods.

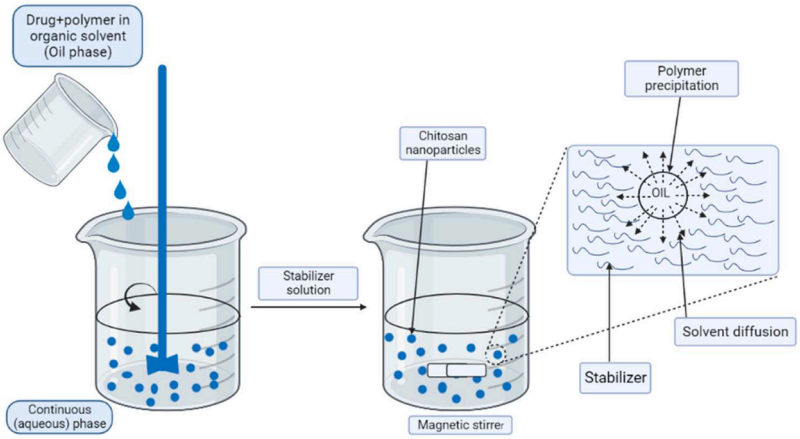

Fig. 2. Emlusification solvent diffusion method for the production of chitosan based nanoparticles.

containing surfactant while it is being stirred all the time to make reversible micelles (Zhao et al., 2011). Numerous approaches for producing CS-NPs are being explored since they have proven to possess enticing characteristics for drug delivery. But, in contrast, the technique of preparation and the properties of nanostructures are affected by a number of relevant factors, such as secondary components in the configuration and time. The treatments require a long duration, and, at times, invasive processes restrict their applicability. The preponderance of investigators operating in the field prefer approaches that involve merely a hydrophilic condition (mostly polyelectrolyte complexation and ionic gelation).

3.3. Coacervation

When chitosan interacts with counterions and polymers such as gelatin or alginate, phase separation occurs. Chitosan nanoparticles are formed as a result. Advantages include the ability to encapsulate a wide range of materials and the opportunity for controlled release. Disadvantages include complex particle size management and the potential usage of organic solvents.

4. Modifications for enhancing CS properties

CSs effectiveness is found to be determined by characteristics such as cationic nature and solubility. It has numerous drawbacks, including high hydrophilicity, low ductility, swelling, and being substantially less durable. Poor absorption is a critical hindrance to its application. Because CS is insoluble at physiological pH 7.4 and is inefficient as an absorption promoter, it cannot be used in biomedicine. Enhancing the solubility of CS is critical for its efficacious usage for numerous purposes. These chemical compounds of CS can get around the problems that come with unaltered CS. They have been getting more and more attention over the last ten years because they are better than unaltered CS in many ways, including their ability to dissolve, gel, form hydrophobic derivatives with amphiphilic properties, and self-structure nanocrystals and chemical conjugates with a wide range of biologically active and healing substances. Other notable advantages involve greater biocompatibility and characteristics for complexing biomolecules (e.g., DNA, RNA) (Fig. 3) (Jiang et al., 2023; Khalaf et al., 2023).

- *Hydrophobic chitosan derivatives*

It is derived using CS reductive analysis. The hydrophobicity of alkylated CS increases with chain extension from C6 to C12. The degree of substitution (DS) is an important factor in the development of hydrophobic regions through alkyl linkages (Negm et al., 2020).

- *Amphiphilic chitosan derivatives*

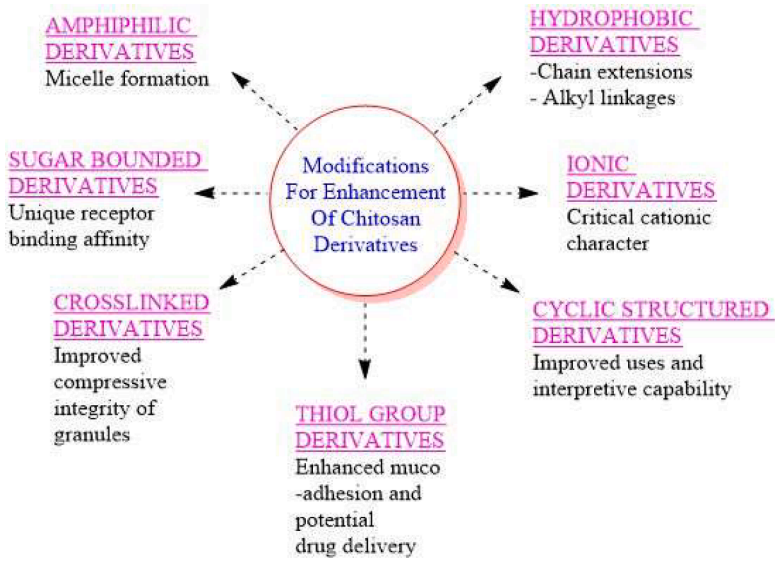

Fig. 3. Schematic Representation showing derivatives for enhancing CS properties.

consist of hydrophilic moieties and a hydrophobic nucleus that enables them to form micelles in water because of their amphiphilicity (Mateescu et al., 2015).

- *Ionic chitosan derivatives*

The cation character of the CS is critical for a variety of purposes, including permeation improvement, bioadhesion, transfected efficacy, and bioactivities (Li et al., 2020; Negm et al., 2020).

- *Sugar-bound chitosan derivatives*

It possesses unique receptor-binding affinity characteristics (Wang et al., 2018).

- *Chitosan derivatives with cyclic structures*

It has been designed for better uses such as medication delivery, cosmetology, and quantitative science, and it has the interpretive capability to be used as a polymer-based structure in controlled drug delivery (Bakshi et al., 2020).

- *Chitosan derivatives with thiol groups*

Mucoadhesion has been greatly enhanced, especially improving the ocular bioavailability, and they are potential drug carriers and efficacious as nanomedicine. It has outstanding cohesive characteristics for the sustained release of implanted medicinal substances over a long duration (Guaresti et al., 2020).

- *Crosslinked chitosan derivatives*

The compressive integrity of the granules improves as the CS is crosslinked. Heavily crosslinked molecules reduce swelling, reduce interior fluid absorption, and reduce medication absorption from the exterior. Crosslinkers have the impact of reducing medication delivery and blocking release rates (Khalaf et al., 2023).

- Diabetes mellitus

Treatments for diabetes that depend on CS serve two purposes: they may be employed alone, as an anti-diabetic medication, or as a pharmaceutical solvent. Because of its powerful pharmacologic properties, the treatment of several clinical anomalies is associated with hyperglycemia. It has a positive effect on reducing beta cell apoptosis in the pancreas. Additionally, CS-based vehicles have the ability to distribute drugs in a targeted and sensitive manner. CS networks are also improved single-step techniques for stem cells that differ from cumulative insulin-secreting cells with high glucose tolerances. CS's anti-diabetic efficacy has been established in a wide range of studies, although there are significant limitations to its usage in diabetes care. Diabetes has had an increasing commercial and medical influence in recent decades. When adopting hereditary hazard mitigation measures, diabetes mellitus (DM) needs continual surveillance and specialized support (Care, 2019). "The basic approach for diabetes treatment is to control the constant plasma glucose levels; nevertheless, hyperglycemia deficits can result in a range of life-threatening consequences, involving cardiovascular disease, nephropathy, neuropathic diseases, and retinopathy" (Menini et al., 2020). The primary therapies for type 2 diabetes include physical activity and the use of anti-diabetic medicines. Because of its favorable physicochemical features, CS is an intriguing carbohydrate biopolymer for biomedical applications (Najafi et al., 2022). Numerous studies have shown that CS has a favorable role in pancreatic cell resilience and proliferation, lowering hyperglycemia, and preventing DM linked to poor lipid regulation. Furthermore, CS has been employed in several nanomedicines to carry diverse anti-drugs in order to lower glucose levels. Type 1 DM (T1DM) and Type 2 DM (T2DM) are the two most common kinds of diabetes, either of which is caused by inadequate insulin production. T1DM impacts infants and teenagers, but T2DM strikes middle-aged and elderly individuals who have had diabetes for an extended period of time owing to poor lifestyles and nutritional preferences (Najafi et al., 2022). Multiple studies have found that inflammation and immunology have a role in the development of T1DM, T2DM, and gestational DM (GDM). Long-term immune system activation, culminating in chronic irritation, causes pathology rather than healing, ultimately leading to the progression of T2DM. Fascinatingly, it shows that low-grade inflammation is linked to an increased chance of acquiring T2DM. Furthermore, subclinical inflammation causes insulin sensitivity, which is connected to metabolic spectrum symptoms such as hyperglycemia (Banerjee et al., 2020). Innate immunity and inflammatory cytokines are important in the improvement of T1DM. Cur-CS-NPs reduced macrophage activation consecutively in the development of fresh blood vessels, hastening the wound recovery phase. So, Cur-CS-NPs might be a possible way to speed up the healing of diabetic tissues in a rat model of diabetes by reducing inflammation. Among the most serious and persistent diabetic consequences, diabetic wound healing delays place an enormous financial burden on individuals (Ariyanti et al., 2019; Han et al., 2019; Liu et al., 2019). Nevertheless, no standard solution is now available due to the intricate pathophysiology, which includes significant bacterial infection, slow angiogenesis, and chronic inflammation (Chammas et al., 2016; Miller et al., 2014; Ricco et al., 2013). Wound healing is generally divided into four stages: hematoma, inflammation, proliferative, and remodeling (Chen et al., 2015; Koh & Dipietro, 2011; Mahdavian et al., 2011). Dysfunction of these steps in the diabetic wound healing mechanism frequently leads to delayed and ineffective wound restoration. It is well recognized that macrophages (M) perform a crucial role in wound healing inflammatory reactions, like clearing dead cells and cell debris from the wound (Ben & Wu, 2014; Ning et al., 2016; Singer & Clark, 1999). A sulfated chitosan (SCS)-doped collagen type I (Col I/SCS) hydrogel as a potential for diabetic wound therapies is investigated, and its effectiveness is evaluated using a streptozocin (STZ)-induced diabetes lesion paradigm. The results showed that the Col I/SCS hydrogel made wound closure much more common and improved collagen deposition and revascularization in diabetic lesions. Flow cytometry and immunofluorescent labeling studies showed that the Col I/SCS hydrogel sped up the removal of severe activation in diabetic wounds that wouldn't heal by lowering the polarization of M1-like cells. Furthermore, ELISA research demonstrated that the Col I/SCS hydrogel lowered pro-inflammatory interleukin (IL)-6 synthesis while increasing anti-inflammatory cytokines such as IL-4 and transforming factor beta 1 (TGF-1) synthesis during wound healing. Chitosan and its compounds have hypocholesterolemic and hypolipidemic properties, lowering plasma and liver triacylglycerol (TG) and total cholesterol (TC).

- *Inflammatory liver disease*

Inflammation and tumorigenesis are tightly linked pathways impacting cancer development. Inflammasomes are key signaling platforms that detect pathogenic microorganisms, including hepatitis C virus (HCV) infection, and sterile stressors (oxidative stress, insulin resistance, lipotoxicity) able to activate pro-inflammatory cytokines interleukin-1β and IL-18. Different inflammatory diseases associated with the liver are shown in Fig. 4.

Inflammation and carcinogenesis are two closely related mechanisms that influence cancer development. Inflammasomes are critical signaling platforms that detect pathogenic pathogens, such as HCV infection, as well as sterile stresses (oxidative stress, insulin resistance, lipotoxicity) capable of activating pro-inflammatory cytokines interleukin-1 and IL-18.

Hepatic inflammation is a common trigger of liver disease and is considered the main driver of hepatic tissue damage (Younossi et al.,

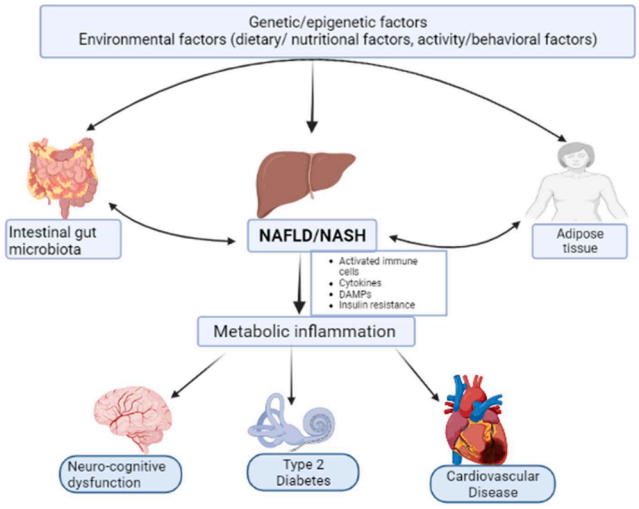

Fig. 4. Different inflammatory diseases associated with liver.

2017), triggering the progression from non-alcoholic fatty liver disease (NAFLD) to severe fibrogenesis and, finally, hepatocellular carcinoma (HCC). Liver diseases, whose etiology can be diverse, are becoming one of the most serious public health problems.

Hepatic inflammation is a prevalent cause of liver illness and is thought to be the primary cause of hepatic tissue destruction, causing the development of NAFLD, severe fibrogenesis, and, eventually, hepatocellular cancer (HCC). Liver illnesses, which can have a variety of etiologies, are quickly becoming one of the most important public health issues.

The diseases usually occur in response to chronic hepatocellular injury caused mainly by the abuse of alcoholic intake, chronic infections such as those caused by the hepatitis C virus (HCV), bile duct damage, NAFLD, or non-alcoholic steatohepatitis (NASH) (Younossi et al., 2017). NAFLD was defined for the first time in 1980 (Ludwig et al., 1980) as an accumulation of fat (> 5%) in liver cells in the absence of excessive alcohol intake (Chalasani et al., 2012). NAFLD has become a major global health problem, which leads to an increased risk of obesity, diabetes mellitus, and cardiovascular disease (Marchesini et al., 2003).

Chronic hepatocellular injury caused mostly by alcoholic misuse, chronic infections such as those produced by the hepatitis C virus (HCV), bile duct damage, NAFLD, or non-alcoholic steatohepatitis (NASH), are the most common causes of the disorders (Younossi et al., 2017). NAFLD was initially identified in 1980 (Ludwig et al., 1980) as an accumulation of fat (> 5%) in liver cells in the absence of heavy alcohol use (Chalasani et al., 2012). NAFLD has become a serious worldwide health issue, increasing the risk of obesity, diabetes, and cardiovascular disease (Marchesini et al., 2003).

Unfortunately, no recognized pharmacologic medications have indeed been developed yet (Musso et al., 2016), making it critical to find efficient medicines for the management and therapy of NAFLD. Dietary organic substances have lately gained a lot of interest as viable methods for improving NAFLD (Fan & Cao, 2013; Kazankov et al., 2019). The inflammatory reaction in NAFLD is defined by elevations in pro-inflammatory mediators in the hepatic system, which can be triggered by different stimuli such as TC, cholesterol, free fatty acids, and gut-derived endotoxins (Carter-Kent et al., 2008). On the other hand, inflammation and pro-inflammatory proteins may make hepatocytes react badly, which leads to too much lipid in the liver and has a big effect on how NAFLD starts (Buzzetti et al., 2016). Many variables that can trigger the NLRP3 inflammasome have been discovered. Improper NLRP3 stimulation can promote the beginning and development of a variety of illnesses, especially those associated with aging. It's widely recognized that hepatitis C virus infections have an important influence on the progression of liver inflammation and illness by promoting IL-1 release and NLRP3 stimulation. The increase in functionality of the NLRP3 inflammasome exasperates liver disease, leading to serious liver fibrosis and, more recently, hepatocellular cancer. TNF and reactive oxygen species (ROS) are released by inflammatory cells and the hepatocytes themselves as a consequence of liver injury and inflammation. These agents can induce peroxidation of plasma and mitochondrial membranes, which results in necrosis or apoptosis of cells (Begriche et al., 2013). All of this makes liver endothelial cells work harder, which makes more cytokines and eventually makes hepatic stellate cells (HSCs) work harder. This causes a change in their phenotype that is linked to the growth of pro-fibrogenic and pro-inflammatory functions (Diehl et al., 2005). Many compounds serve as DAMPs and pathogen-activated molecular patterns (PAMPs) during the lipid buildup process, causing inflammation. This includes fatty acids, adenosine triphosphate (ATP), uric acid, and peptides originating from the cell membrane. Furthermore, a new study reveals that cholesterol particles are prevalent within hepatocytes in the hepatocytes of humans and mice with steatohepatitis and can behave as DAMPs. Hepatic inflammation starts and stays active thanks to immune neurons like Kupffer cells, monocytes, neutrophils, dendritic cells (DCs), natural killer cells (NK), and NK-T cells (NKT). These neurons produce cytokines and chemokines, especially TNF and interleukin (IL)-1, as well as ROS (Tilg & Diehl, 2000). In liver illness, fatty acid accumulation causes irritation in the hepatocytes, which enhances caspase-1 activity and IL-1 production. This causes the liver to generate more DAMPs, resulting in a response loop that intensifies the inflammatory reaction. Cytokines that can activate functional activities in immune cells influence inflammatory signals in the liver.

- Autoimmune diseases: Alzheimer's and Parkinson's diseases, rheumatoid arthritis, inflammatory bowel disease

4.1. *Alzheimer's and Parkinson's diseases*

Cognitive abilities and dementia get worse over time in people with Alzheimer's disease (AD). This happens because neurons die, neurotransmission pathways get messed up, and a lot of different substances build up in the central nervous system (Soria Lopez et al., 2019). The main pathophysiological sign is the buildup of amyloid plaques and neurofibrillary tangles in the brain. Other signs include dystrophic neurites, astrogliosis, neuropil threads, and microglial stimulation (Lane et al., 2018). Parkinson's disease (PD) is marked by a progressive degradation of voluntary motor coordination caused by the aggregation of alpha-synuclein-containing Lewy bodies in the substantia nigra pars compacta of the brains and the death of dopaminergic neurons, resulting in a decrease in dopamine levels (Lotankar et al., 2017). Muscular tightness, tremor, bradykinesia, and decreased posture impulses are the chief diagnostic signs of Parkinson's condition, and they continue to deteriorate as the infection progresses (Diaz & Waters, 2009). CS-NPs appear as disintegrating yet durable carriers for CNS drug administration. Additionally, because of their mucoadhesive nature and inherent biocompatibility, CS-NPs may not only improve medication absorption into the brain via the nasal pathway but also operate as anti-AD and anti-PD therapies. It works better than traditional preparations at combining neurotoxic drugs and relieving symptoms when administered through CS-NPs. Furthermore, it was discovered that administering substances in conjunction with CS nanomaterials can add value to a variety of progressions, including elevated antioxidants, better suppression of cholinesterases, an expanded half-life (Hanafy et al., 2015) lower effective dosage, lower toxicological effects (Nagpal et al., 2013) and disguised pungency of actives during nasal spray dosages. Whereas these advancements show that CS-NPs have a high possibility for treating AD's diagnostic manifestations, in an attempt to create validated clinical CS-NP-based AD's therapies, the connection between NP constituents, physiochemical attributes, and medicinal effectiveness must be regarded more thoroughly. CS is not only a promising

transporter for microencapsulation and blood-brain barrier (BBB) administration, but it may also be used as a standalone treatment modality to avoid and alleviate the manifestations of degenerative disorders (Nagpal et al., 2013). CS compounds like quaternized chitosan could be used to make injectable formulas that work, like hydrogels, for giving drugs to specific areas in PD (Elnaggar et al., 2015). In the therapy of PD, CS nanovectors can be perfect transporter supply vehicles for DA across BBB. The ability of CS to recognize and differentiate alpha-synuclein monomers and fibrils, which are believed to assemble, is a core part of the etiology of PD (Khatri et al., 2018; Ren et al., 2017).

4.2. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a persistent autoimmune illness that induces arthritis. It is seen in various nations and is more common in females than in males. Eugenol acknowledges CS-NPs as a natural antioxidant that can be used as the initial medicinal ingredient to combat the RA alternative of methotrexate. CS-NPs are endogenous biopolymers with degradability, biodegradability, low cytotoxicity, and the potential to easily manufacture efficient drug formulation products (Yaghoubi et al., 2015). Also, CS is a cationic polysaccharide that comes from the basic chitin acetylation process of parasite cells and the crustal outer shell. It plays a big role in wound healing, cell polymorphism stimulation, fibroblast starting, cytokine production, and other things (Liu et al., 2017). Monocyte Chemoattractant Protein (MCP1)-1/CCL2 is a cytokine that increases monocyte movement and stimulation and is found in synovial cells as well as RA-infiltrated monocytes. As a result, MCP-1 suppression may modulate inflammation by inhibiting monocyte concentration in the joints (Gong et al., 1997). As a result, the current research was carried out to explore the impacts of encased Eugenol with nanocarriers on neonatal Collagen-Induced Arthritis (CIA) RA in order to identify a potential therapeutic substance as well as reduce the need for medications. Eugenol is a naturally occurring phenolic compound found in many herbs, such as cinnamon and clove. It can reduce inflammation, damage nerves, lower body temperature, fight free radicals, kill fungi, and help nerves (Barboza et al., 2018). Nano-Eugenol also reduced the indications of RA-related joint inflammation, synovial hyperplasia, and cartilage degradation.

4.3. Inflammatory bowel disease

Organic polysaccharides like pectin, alginate, and CS were created as hydrophobic drug delivery systems that can be taken by mouth to treat inflammatory colon disease. These devices are non-toxic, simple to make, and approved. These polysaccharide-based formulations guard against premature medication release and preferentially deliver IBD medicines into the small intestine, colon, and stomach (Khare et al., 2020). Positively charged CS-NPs with increased aiming effectiveness in the normal inflammatory intestinal mucosa (Lautenschläger et al., 2013) have been reported. CS offers enormous promise for the development of nanostructures for the delivery of drugs in the management of IBD. The polymer is inexpensive to produce and has the potential to increase paracellular and transcellular transportation in the mucosal epithelium. Furthermore, it is impervious to upper gastrointestinal proteolytic disintegration, possesses pH-sensitive features, and its positively charged NPs can open tight intestinal mucosal connections, making the monomer a possible therapeutic carrier, especially for the inflammatory colon. So, CS is not degraded in the intestinal tract (Benabid & Zouai, 2016; Wu et al., 2014).

- *Hypersensitivity reactions*

External chitin triggers macrophages and other innate immune responses and regulates the adaptive type-2 allergic response, according to Shibata et al. (2000). Nevertheless, it has been recognized that chitin and CS decrease allergies, as well as the immunologic consequences of chitin and CS. Alpha-chitin is often extracted from the carapace of a marine crustacean, whereas beta-chitin is typically extracted from squid pens, which are accessible as a residue of food manufacturing. Because alpha-chitin is the most prevalent polymorphic form, it has received more attention than beta-chitin. Because of the parallel structure of the major chains, beta-chitin is moist and hydrophilic due to poor intermolecular hydrogen bonding (Aranaz et al., 1998). Antihistamines stop the effects of histamine by blocking H1 receptors. They can be used to diagnose a lot of different conditions, such as allergic reactions, idiopathic chronic urticaria, motion sickness, vertigo, and insomnia (Katselou et al., 2017; Sanchez-Borges et al., 2013). On the other hand, aspirin, the most commonly utilized medication worldwide, has some drastic consequences, such as extending bleeding time, increasing gastric irritability, prioritizing ulceration, and provoking oversensitivity in some areas of study. Moreover, penicillin and its analogues, such as amoxicillin or ampicillin, can elicit acute or subacute allergies that are triggered by immunoglobulins E and G (Dumitriu Buzia et al., 2016; Tamura et al., 2013). Microencapsulation of bioactive compounds is very important in the sustained delivery range (Dumitriu Buzia & Dima, 2016; Dumitriu Buzia et al., 2015). This is because the technique can be used over and over again and the nanoparticles are very small. A plethora of experiments have illustrated the significance of natural polymers over the years, including their nontoxicity and suitability with medication materials, nontoxic, preventative, anti-oxidant, and degradable characteristics, as well as their ability to create controlled release processes of active ingredients (Dragostin et al., 2017). Using physically altered CS via cetirizine as a polymer matrix, this work aimed to produce microparticles containing aspirin and penicillin, both of which are recognized to be extremely allergic. Mast cell stimulation by immunoglobulin E-mediated stimulation is regarded as a critical occurrence in allergic reactions (Dragostin et al., 2017).

- *Cancer-related inflammation*

Because their core molecules are so sensitive, CS and/or its variants can be easily changed or derivatized. This makes it possible to package anti-cancer drugs, especially drugs that don't like water. Hydrophobically altered CS oligosaccharides can self-assemble into NPs, which are potentially useful transporters for tumor-targeted drug and gene distribution (Termsarasab et al., 2013). Therapeutic implications for CS-NPs for tumor diagnostics and treatment have been addressed due to their low systemic cytotoxicity in vitro and in some in vivo models, as well as their high toxicity towards tumor cells and malignancies (Mohammed et al., 2017). CS-NPs may preserve biological compounds against high pH and/or metabolic breakdown, hence extending medication lifetime (Din et al., 2017). So, nanosized transporters could greatly control pharmacokinetics, making medicines work better while lowering their safety, and they could also deliver psychoactive molecules in a controlled and, in some cases, site-specific way. Due to their potential to circulate in the bloodstream for relatively long durations of time and to accumulate in tumor areas, nanocomponents are suitable substances for targeted tumor therapy. (Mukhopadhyay et al., 2021). CS-NP dose-dependent tumor reduction was linked to tumor angiogenesis prevention. CS-NPs can also be employed to transfer siRNA to important tumor metabolic pathways. CS-NPs and analogues have the potential to be a unique class of anti-cancer medicine due to their low or non-toxicity (Xu et al., 2009). Because CS nanostructures can hold a lot of drugs and keep their properties for a long time, they are a good choice for delivering naturally occurring chemicals that fight tumors in cancer treatment (Yee Kuen et al., 2020). CS-NPs can improve the bioavailability and half-life of synthesized anti-tumor drugs, allowing for more efficient cancer treatments (Zavareh et al., 2020). The size of CS nanomaterials influences their anti-tumor effectiveness, as smaller aggregates have a higher sensitivity to cancerous cells. Surprisingly, CS-based nanotechnology distribution systems have high durability at the target organ, which is normally marked by a mildly acidic pH, making them a

beneficial characteristic for anti-cancer medication administration. More crucially, compounds such as arginylglycylaspartic acid (RGD) can be used to modify CS nanomaterials to increase their focused distribution (Yadav et al., 2020). CS-NPs can be used for theranostics in conjunction with medication administration. Because CS nanomaterials have an 8-day stability and significant cellular absorption in cancerous cells, they can be employed as a guideline for tumor resection (On et al., 2020). Because of the negative charges of DNA, the positive charge of CS enables its usage for enclosing genomic information, sparking interest in employing CS-NPs for targeted delivery in the treatment of cancer (Mohammadzadeh et al., 2021). Inflammatory-related diseases and characteristics are shown in Table 1. The mechanisms of cancer-related diseases are shown in Fig. 5.

Table 1
Inflammatory related diseases and characteristics.

	Diseases	Characteristics	Reference
Inflammatory Related	Diabetes mellitus	- two purposes- as anti-diabetic medication, and as a pharmaceutical solvent - therapies for type 2 diabetes include physical activity and the use of anti-diabetic medicines.	51, 53
	Inflammatory liver diseases	- Inflammasomes are key signalling platforms that detect pathogenic microorganisms - Hepatic inflammation triggering the progression from non-alcoholic fatty liver disease (NAFLD) to severe fibrogenesis and, finally, hepatocellular carcinoma (HCC)	67
	Autoimmune diseases	Alzheimer's disease - accumulation of amyloid plaques and neurofibrillary tangles in the brain along with dystrophic neurites, astrogliosis, neuropil threads, and microglial stimulation Parkinson's diseases- chief diagnostic signs are Muscular tightness, tremor, bradykinesia, and decreased posture impulses Rheumatoid arthritis - Eugenol acknowledges CS-NPs as a natural antioxidant that can be used as the initial medicinal ingredient to combat RA alternative Inflammatory bowel disease- formulations guard against premature medication release and deliver drugs into the small intestine, colon, and stomach	80,82,88, 92
	Hypersensitivity reactions	Mast cell stimulation by immunoglobulin E-mediated stimulation is regarded as a critical occurrence	104
	Cancer-related inflammation	encapsulation of anti-cancer drugs, hydrophobic pharmaceuticals. (self-assemble into NPs, which are useful transporters for tumor-targeted drug/gene distribution)	105

5. Therapy for target inflammatory diseases

Inflammatory and allergy illnesses are among the most common infections worldwide. Inflammation is a fundamental component of host reactivity to a variety of triggers, such as physical trauma, microbiological infestation, UV irradiation, and immunological mechanisms. Severe or persistent soreness can exacerbate a variety of disorders, including cancer, psoriasis, multiple sclerosis, RA, and chronic asthma. Allergy is an immune system illness caused by excessive reactivity. There are particular tissue components in the initial phases. However, as the disease progresses, vascular endothelial cells and connective tissue cells such as fibroblasts are involved. Regular defensive units such as macrophages, neutrophils, monocytes, and T-lymphocytes are also implicated. The majority of such stimulated cells produce a plethora of proinflammatory proteins such as prostaglandins, leukotrienes, cytokines such as tumor necrosis factor (TNF), interleukins, and others (Lowenstein & Castro, 2003). CS is a good RNA distribution carrier. You can change how complexes form between CS and RNA by choosing CS with the right chemical weight and levels of acetylation (Lee et al., 2012). CS sticks to DNA and prevents nucleases from destroying it, extending DNA's time in the gastrointestinal tract (GIT). CS may have auxiliary qualities such as promoting endocytosis and increasing immunological responsiveness (Bolhassani et al., 2013; Illum et al., 2001). An extensive coagulation technique is used to create plasmid DNA that is encased in NPs, and the outcomes indicated that the plasmid DNA was efficiently enveloped in CS-NPs and transcribed in vivo (Guliyeva et al., 2006). GIT processes digest protein-based medications quickly. These drugs, however, are not typically destroyed by GIT enzymes when they are encapsulated in CS-NPs. Furthermore, CS-NPs considerably improve medication accessibility (Sinha et al., 2004). CS-NPs control how drugs are distributed, help proteins break down, and make it easier for hydrophilic materials to be absorbed through the epithelial layer. They are for the administration of medications that react in the GIT. CS-NPs demonstrated great drug capture efficacy, good stability, low breakout, and consistent insulin-like medication delivery (Wang et al., 2006).

6. Biological effects of CS-NPs

Herbal remedies are organically formed as a blend of biological compounds from plant ingredients that can be acquired from raw or refined herb sections and are used for therapy. In comparison to current pharmaceuticals, the benefits of herbal remedies include higher efficacy, lower cost, and favorable features such as reduced adverse effects. Around the world, medicinal herbs are employed to treat a variety of chronic and acute ailments, including cardiovascular issues, urogenital difficulties, sleeplessness, inflammation, and immunodeficiency. Herbs are utilized in traditional health methods all over the world for the treatment of several diseases, mostly DM, but also cancer and various inflammation-related disorders, owing to the availability of many beneficial chemicals, some of which have significant bioactivities. *Momordica charantia* (MC) diet-rich foods have been intensively examined to address a variety of disorders, including T2DM, dyslipidemia, obesity, and cancer, demonstrating that MC preparations have hypoglycemic and lipid-lowering characteristics (Alam et al., 2015). Persistent systemic inflammation leads to increased blood glucose concentrations in individuals with diabetes and serves as a danger variable for cardiovascular events and overweight. Prolonged inflammation plays a role in the etiology of many disorders, including neurological ailments, obesity, metabolic disorders, cardiovascular illness, type 2 diabetes, and malignancy (Minihane et al., 2015). Prolonged systemic inflammation correlates to increased blood glucose concentrations in individuals with diabetes and is a potential variable for acquiring cardiovascular disease and obesity. MC samples have now been studied primarily for one's prospective use, such as in chemo-preventive agencies. Numerous research findings have assessed the effectiveness

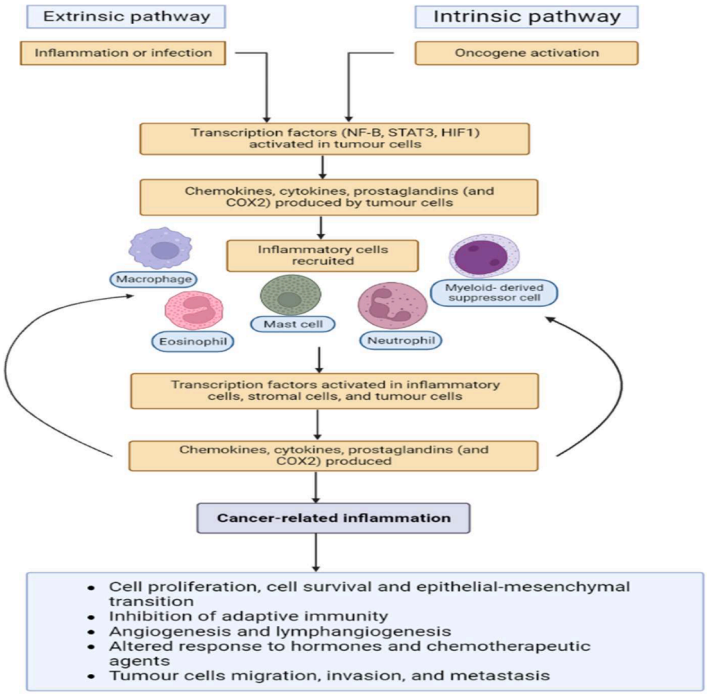

Fig. 5. Mechanism of cancer related inflammatory diseases.

of MC derivatives or purification elements against various malignant cells, implying that consuming MC as part of a healthy diet may help reduce the threat of many tumors. The preponderance of research demonstrated anti-proliferative and immunomodulatory impacts (Nerurkar & Ray, 2010). Organic biocomposite CS and its derived products have a wide range of substantiated therapeutic potential, including anti-oxidant, wound-cure, immunostimulant, hypocholesterolemic, anti-bacterial, obesity therapies, anti-inflammatory, anti-cancer, bone tissue engineering, fungicidal, tissue regeneration, anti-diabetic, and mucosal adjuvants. CS, when contrasted to other polysaccharides, has amazing mucoadhesive properties, is less viscous, conveniently amended into chemical and biological molecules, and has mucilaginous properties, which allow substances to remain in the respiratory system for an extended duration of time, delivering a better pharmacological response. CS-NPs would be most effective when utilized to transfer poorly water-soluble medications, biomolecules such as proteins, and enzymes via the airways in the body. Crystallized CS was effectively synthesized from linked chitin particles in the crab tendons. The calcium phosphate that makes up the inorganic part of the crab tendon was broken down very quickly to 0.5 wt% after being treated with a 50 wt% NaOH solution. This happened because N-acetyl amide groups on the hydroxyapatite crystals that were attaching to calcium ions were taken away. The resultant tendon, CS, had outstanding dynamic characteristics because proteins and calcium phosphate could be eliminated without destroying the ordered microstructure.

7. Applications of chitosan formulations

CS possesses the characteristics requisite for sustainable usage as a medicinal excipient. This has sped up studies on CS-NPs as medication delivery carriers around the world. These approaches are extremely useful in the sustained delivery and target investigations of nearly all classes of active compounds. CS's adaptability is deemed multidimensional (Merzendorfer & Cohen, 2019), with a large spectrum of alternatives in various fields such as nutrition, biotech, biomaterials, therapeutics (Islam et al., 2019; Quiñones et al., 2018), healthcare, agribusiness (Choudhary et al., 2019), ecological preservation, etc. (Morin-Crini et al., 2019). Applications of Various Chitosan Formulations, as shown in Fig. 6.

8. Colon targeted drug delivery

CS is an established and prospective copolymer for drug discovery in the colon because it is biodegradable by the bacteria found in the intestines (Lorenzo-Lamosa et al., 1998). It was found that there was a pH-sensitive multiprocessor nanoparticulate technology with CS microcores inside enteric acrylic spheres. In vitro released studies demonstrated no chemical production in stomach pH for 3 hr, followed by a rapid flow in basic pH for 8–12 hr (Lorenzo-Lamosa et al., 1998).

9. Mucosal delivery

Such interfaces are utilized to administer the medicine over time at a predetermined level using a bioadhesive component. Because CS has mucoadhesive qualities, it can be used to create biocompatible dosing schedules that can be administered via different routes, such as ocular, nasal, buccal, gastro-enteric, and vaginal-uterine. Nasal mucosa has permeabilities that allow drugs better access to the absorption sites. Particle distribution to the oral mucosal route is readily absorbed by Peyer's patches of gut-associated lymphoid cells (Genta et al., 1998). Because of the existence of unbound amino groups in an acidic medium, CS is protonated, and the resulting soluble polysaccharide is positively charged, allowing it to adhere firmly to negatively charged sites such as specific substrates and the mucosal spectrum. As an outcome, CS composition may considerably enhance the resident period of medication on cell and tissue surfaces and demonstrate controlled delivery of pharmaceuticals there, improving bioactivity and reducing pharmaceutical administration frequency. CS has been shown to improve drug penetration via mucosa without harming the physiology (Artursson et al., 1994; Van Der Lubben et al., 2003). The effective method of CS has been proposed to be a mix of mucoadhesive and a transitory expansion of epithelial cells with rigid synapses.

10. Ocular delivery

Because of its strong layer-producing characteristics, chitosan is

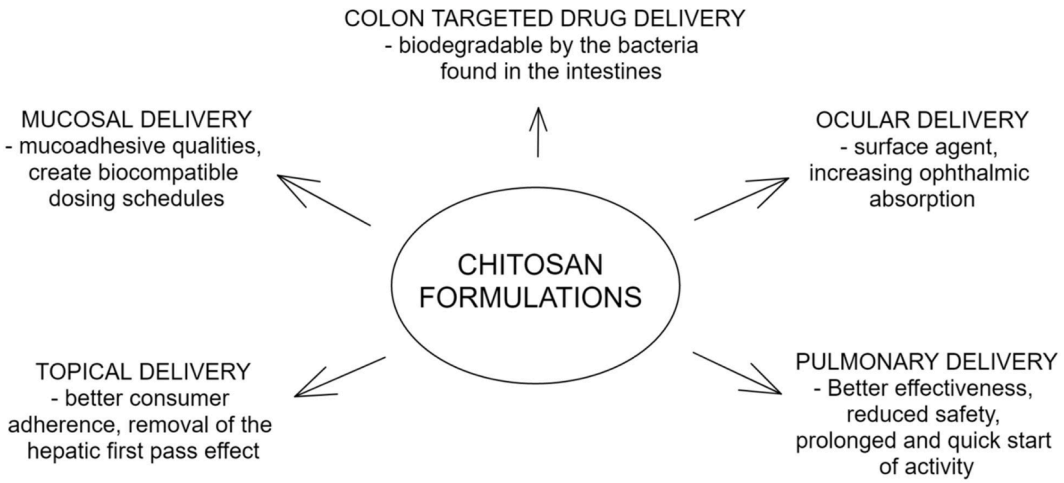

Fig. 6. Applications of various chitosan formulations.

employed as a surface agent in medication delivery techniques. Antibiotic medicines were reported to have a longer retinal retention time than CS alternatives (Felt et al., 1999); however, CS-coated nanocrystals were more effective at increasing ophthalmic absorption. CS-NPs can interface with and keep attached to the ocular mucosa for lengthy durations of time, making them attractive transporters for increasing and regulating medication distribution to the ocular surface. For at least 24 hours, these colloid drug transporters remain connected to the cornea and conjunctiva. CS-coated microspheres have various improvements over untreated NPs, including improved drug payloads, mucoadhesive characteristics, and longer drug delivery (De Campos et al., 2001).

11. Topical delivery

Many external formulations have already been created over the past three decades because external distribution of medications has benefits over traditional dosing such as ease, better consumer adherence, and removal of the hepatic first pass effect. CS has been used in dermal drug carriers due to its good mucoadhesive properties and capacity to maintain the passage of bioactive components. Resulting in a rise in repulsions between LC and CS cations, raising the concentrations and MW of CS increased both the frequency and range of drugs (Varshosaz et al., 2006).

12. Pulmonary delivery

Better effectiveness, reduced safety, and a prolonged and quick start of activity are all advantages of pulmonary medication delivery. The lung's large epithelial surface area, high organ vascularization, incredibly thin absorbent alveolar epithelial outer layer, enormous ability for solute interaction, and great blood flow are all significant variables that make it an optimal drug route for the therapies of both local and systemic ailments. CS undertakes enzymatic depolymerization in the appearance of lysozyme, which is either the greatest essential antimicrobial enzyme found in respiratory tract fluids or has been intensively investigated for providing multiple antibacterial agencies into the airways based on the biochemical weight, degree of deacetylation (DD), and hydrolysis time (Islam & Ferro, 2016).

13. Toxicity

Problems with stability and/or penetration frequently prevent the use of polymers in therapeutics. The biopharmaceutical sector has solved these restrictions by developing acceptable non-injectable nanocarriers. Nanotechnology also allows encased compounds to sustain their metabolic potency from the manufacturing process to their ultimate delivery. CS has risen to prominence as a vehicle substance due to the several approaches that may be used to create nanomaterials leveraging those additives. These entail either hydrophilic or lipophilic surroundings, which lead to relatively mild or vigorous and tedious procedures.

CS has piqued the interest of experts owing to its great death ratio over microorganisms, notably gram-positive and gram-negative bacteria, as well as its minimal sensitivity for mammalian cells (Kong et al., 2010). Several studies on the toxicology of CS and its substitutes reveal that, irrespective of molecular weight, the lethality of CS increases with an increasing level of acetylation. Another finding is that cytotoxicity is proportionate to molecular mass (Wiegand et al., 2010). CS has been more popular as a scaffold for drug discovery and tissue engineering purposes due to its well-known favorable characteristics (Saber-Samandari & Saber-Samandari, 2017). Although the potential for employing CS as a pharmaceutical additive is not recent, this polysaccharide does not seem to be included in any drugs currently in the marketplace. Components play an important role in medication distribution, but inventing new compounds is a time-consuming procedure due to financial and administrative issues, as well as establishing that these compounds are acceptable for usage (Baldrick, 2010; Kean & Thanou, 2010). CSs' cytotoxicity is affected by its MW, DD, polymer concentration, and a few other non-specific parameters. Studies on chitosan's toxicity have shown that it rises as the degree of acetylation rises, regardless of molecular weight. However, it has also been said that chitosan sensitivity is closely linked to molecular mass (Younes et al., 2016). The knowledge on the cytotoxicology of CS variants varies greatly, and this could be attributed to the reality that polysaccharide analogs are quite different, as are the cell lines used in the experiments. Ahmed (Ahmed et al., 2014) proposes that reduced molecular weight chitosan compounds with higher acetylation degrees are more effectively decomposed. To assure the integrity of CS, scientists must remove any protein, metal, or other pollutants that might produce hazardous consequences. There are catalysts that exhibit action against CS, at least in vitro; however, it may be more challenging to extrapolate or extend the data when it pertains to compounds, as they can give undigested compounds. These types of chemicals must be short enough to be therapeutically relevant and renally eliminated.

14. Future perspective

Several factors, such as differences in preparation, cultivar and flora diversity, harvest stage, parts of plants used, and other factors, can lead to different conclusions in different publications. This makes it hard to find the best therapeutic dose in terms of both effectiveness and safety. This work discusses the appealing features and diverse possibilities of

CS-based microparticles, as well as their varied qualities, various manufacturing processes, and pharmacological and biological purposes. These qualities, together with its low toxicological characteristics, make chitosan an intriguing and prospective excipient for the medicinal sector, both now and in the future,.

15. Conclusion

CS is a great addition for supporting enzyme immobilization because it has many functional groups built into its structure. This means that it can be easily changed to improve its physiological properties while still being able to work as a support without the need for a crosslinking agent. The use of such chemicals, on the other hand, can improve the ultimate qualities of these bioprocesses. To make these biochemical changes, the best method and chemical reagents must be picked based on what changes need to be made, such as how well the enzymes dissolve in water, how reliable they are, how well they react to changes in pH, and how strong the connections between enzymes need to be made stronger, among other things. Physiological changes might be possible by mixing chitosan with other organic or inorganic parts to make a composite complex. When the unique properties of each part are mixed, they form a hybridization that has intermediary functions.

Declaration of competing interest

Authors declare that there is no conflict of interest financial or other.

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