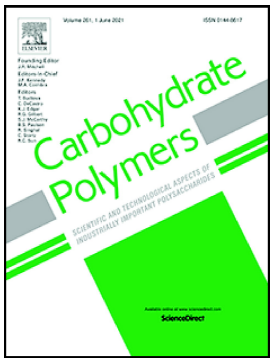

Biomedical applications of polysaccharide nanoparticles for chronic inflammatory disorders: Focus on rheumatoid arthritis, diabetes and organ fibrosis

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Title: Biomedical applications of polysaccharide nanoparticles for chronic inflammatory disorders: Focus on rheumatoid arthritis, diabetes and organ fibrosis

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Abstract

Polysaccharides are biopolymers distinguished by their complex secondary structures executing various roles in microorganisms, plants, and animals. They are made up of long monomers of similar type or combination of other monomeric chains. Polysaccharides are considered superior as compared to other polymers due to their diversity in charge and size, biodegradability, abundance, bio-compatibility, and less toxicity. These natural polymers are widely used in designing of nanoparticles (NPs) which possess wide applications in therapeutics, diagnostics, delivery and protection of bioactive compounds or drugs. The side chain reactive groups of polysaccharides are advantageous for functionalization with a nanoparticle-based conjugate or therapeutic agent such as small molecules, proteins, peptide and nucleic acid. Polysaccharide NPs show excellent pharmacokinetic and drug delivery properties, facilitate improved oral absorption, control the release of drugs, increases *in vivo* retention capability, targeted delivery, and exert synergistic effects. This review updates the usage of polysaccharides NPs particularly cellulose, chitosan, hyaluronic acid, alginate, dextran, starch, cyclodextrins, pullulan, and their combinations with promising applications in diabetes, fibrosis and arthritis.

Key words: Polysaccharides; Nanoparticles; Drug delivery; Inflammation; Arthritis.

1. Introduction

One of the significant complications in achieving efficient drug delivery is their incapability to cross the cellular membrane. Plasma membrane acts as a border between the cell and its surroundings to exertcellular response which is fundamental for cell function [1]. This membrane can limit or block the entry of particular therapeutic agents inside the cellular organelle. The lysosomal or endosomal degradative compartments are not the absolute therapeutic objective and hence, a hunt for competent strategies with the ability to deliver or transport the therapeutic agents that thwart the biological membranes followed by subsequent protection against the vicious hydrolytic surrounding conditions of lysosomes is indispensable. This can be accomplished by means of novel drug delivery systems (NDDS) having enhanced encapsulation potential for target specific delivery of genes, drugs, diagnostic and theranostic agents to the particular cells or to specific intracellular organelles and releasing their contents in a controlled manner over a specific duration of time [2]. In this context, various nano-based polymeric nanoparticles (NPs) have emerged as novel candidates in the area of biological research and its application. Growing evidence from pre-clinical to translation to clinical settings has highlighted its tremendous potential in the area of biological sciences [3-6]. The size of polymeric NPs ranges between 1-1000 nm, exhibiting the typical characteristics of ultrafine colloidal particles. Source materials, in their nanoforms show different properties as compared to their original form like enhanced binding efficiency, increased reactivity and improved therapeutic outcome [7, 8]. For the synthesis of polymeric nanoparticles, the use of polymers is not limited to synthetic origin such as polyethylenimine, polycaprolactones, polyacrylates and poly(lactic-co-glycolide) but also natural polymers like polysaccharides, and proteins [9]. In general, transportation of macromolecules across the cell membrane and from there to lysosomal vesicles happens via endocytosis. Following the uptake of NPs, they are competent to increase the drug concentration and serve as an intracellular reservoir of drug for an extended release [10, 11]. Therefore, natural polymer based nano-formulations appears to be superior because of their presence in most of living organisms and their use in the biological settings does not provoke or produce any toxic effects in the organism pertaining to their biodegradability and biocompatibility. Amongst different natural polymers, polysaccharides have the tendency to attach to cells with swift internalization and degradation and thus, enable the release of drugs or conjugates at the intracellular space [12]. Increased reports on the use of polysaccharide based NDDS have

substantially increased in the past few years [13]. In this review, we have made an attempt to summarize the therapeutic potential of polysaccharide NPs against chronic inflammatory disorders including rheumatoid arthritis (RA), diabetes and organ fibrosis. This review highlights the recent advancements in polysaccharide NPs for these chronic diseases and their unique advantages over the conventional polymers.

2. Limitations of current treatment options of chronic inflammatory diseases

In the treatment of chronic inflammatory diseases, the major focus is to alleviate the inflammation and then the cause behind it. In some autoimmune chronic inflammatory diseases such as RA, principal therapeutic approach is on disease altered anti-rheumatic drugs (DMARD) namely sulfasalazine, methotrexate, and hydroxychloroquine that works by suppressing the immune system which may lead to secondary infections in long term use [14, 15]. Moreover, supplementary medications are also required due to delay in the effectiveness of these drugs. Non-steroidal anti-inflammatory drugs (NSAIDs) are popularly utilized as ad interim drugs in chronic inflammatory diseases, inhibiting cyclooxygenase-1 (COX-1) and COX-2 but have significant side effects like cardiovascular and gastrointestinal toxicity along with renovascular effects [16].

In addition, there are multiple pathways responsible in this cascade, so focusing over a few targets is not sufficient. It can cut-turn into another compensatory response if the incorrect target is suppressed. Additionally, some proteins such as antibodies are also utilized in treating inflammatory diseases that focus on the suppression of TNF-α and anti-B cell agents that are administered via injection, which is a non-patient tractable approach. These are alternative therapies for those patients who have miscarried the traditional strategy for the treatment, which also have some side effects such as hyperemia, itchiness, shortness of breath and variety of mycobacterial infections. Major impediment of current treatment options is that none of the therapies are solely competent enough and multiple supplementary drugs needs to be administered to the patient [17, 18].

3. Advantages of nanomedicine

With the advent of nanotechnology, the domain of drug delivery has gone through extensive modifications, as a result, various nanomaterials have been approved for clinical use. It has given

us many clinically approved nanoformulations, which are being used for the accurate diagnosis and treatment of several diseases [19, 20]. These could be utilized to encapsulate free molecules as well as protein based drugs to increase their time in blood circulation with controlled release. Drugs delivered through these nanomaterials have been shown to encompass lesser side effects and toxicity along with better results [21-23]. As in case of RA, drug delivery to the target site is of major concern that could be effectively achieved with the help of nanotechnology. It has benefitted with the pharmacokinetic solutions for multiple drug administration in autoimmune and inflammatory disorders [24].

In contrast to the traditional treatment options, NPs aid in the amelioration of delivery of various insoluble drugs and maximized their bioavailability with controlled release. Nanotechnology facilitates the transport of drugs across biological barriers. They can increase efficiency of treatment and reduce the development of tolerance [25]. Furthermore, experimental findings have indicated that these nanomaterials exhibit efficient tissue penetration hence, aid in more targeted action of the drug. Consequently, benefits of nanotechnology in treating chronic inflammatory diseases offers various innovative methods to enhance the efficiency of presently available immunosuppressive therapies and helps to compensate side effects related to classical treatment options [26].

4. Advantages of polysaccharide nanoparticles over other types of nanoparticles.

Polysaccharides are being conventionally used in nanotechnology due to different chemical composition, size, molecular weight and the charge present over them. They are used for personalized treatments that helps to reduce drug dose and alleviate side effects [27]. They can be amended into any shape and size to carry the drug and to deliver at the target site that prevents adverse effects caused to healthy tissues. Another beneficial use of polysaccharides as nanocarriers is their abundance in nature and they are highly accessible material which makes their processing very cheap as compared to the other synthetic nanomaterials [28]. The most commonly wielded polysaccharides and their derivatives as nanoparticles are chitosan, hyaluronic acid, alginates, pectin, carrageenan, chondroitin, guar gum, fucoidans, cyclodextrin, cellulose etc. They possess hydrophilic groups attached to their structure that are responsible for their high solubility in water and the genesis of non-covalent bonds with biological membranes which enhances their bioavailability in blood stream hence provide sustained action [29].

Chitosan acts as an ideal carrier for various drugs because of its nontoxic nature, high biocompatibility, low immunosuppressive, and bio-degenerative nature. By virtue of its capability to create a protective polymeric network, it enhances the stability of drug inside gastrointestinal environment against enzymatic degradation [30]. With the intention to elevate drug's half-life in the body, chitosan has been predominantly incorporated into nanocarriers that non-covalently interact with biological tissues and act as a bio-adhesive. Polysaccharide nanoparticles not only act as a system to encapsulate the drug but because of their good availability, non-toxicity, biodegradability, lesser side effects and more availability in nature, they are widely utilized in treating chronic inflammatory diseases [31, 32].

5. Diabetes

5.1 Overview of pathophysiology of diabetes

Diabetes is a heterogeneous disorder correlated with disturbed metabolism and inappropriate hyperglycemia. The pathophysiology of diabetes is an intricate process that encompasses several hormones into cogitation. It is characterized by progressive beta-cell dysfunction and insulin resistance. Genetics plays a major role in type2 diabetes (T2DM) in comparison to type-1diabetes (T1D) [33, 34]. Three primary cytokines comprehended in inflammatory response in T1D are tumor necrosis factor-alpha (TNF-α), interferon gamma (IFN-γ), and interleukin-1 beta (IL-1β). Patients suffering from diabetes have substantially inflamed beta cell pancreatic islet due to the pancreatic islet's apoptosis, known as insulitis. It may trigger due to the synergic response of these cytokines which further promote the synthesis of nitric oxide. In case of obese individuals, bioactive substances such as adiponectin, chemokines, TNF-α, and interleukins facilitate inflammatory response. Due to augmented infiltration by B cells and T cells (immune cells) and macrophages into the adipose tissues, a low-grade islet inflammation gets triggered. This inflamed pancreatic islet is not able to produce adequate amount of insulin for the body which results in hyperglycemia. Consequently, metabolic stress is produced due to pernicious influence of inflammatory and autoimmune mediated pancreatic islet [35].

5.2 Polysaccharide nanoparticles for the treatment of diabetes and associated complications

Diabetes mellitus (DM) is a chronic metabolic disorder which adversely affects the quality of life of patients. Worldwide more than 4 million deaths were reported in the year 2020 and the risk

factors include stress, sedentary lifestyle, lack of physical activity, obesity, genetics and age [36]. Diabetic patients exhibit impaired insulin production, action and resistance is classified into type 1 diabetes mellitus T1DM (also called as insulin-dependent DM and T2DM called as insulin-independent diabetes mellitus) T2DM, respectively. T1DM involves autoimmune damage of pancreatic β-cells resulting in complete insulin deficiency whereas T2DM is due to insulin resistance [37, 38]. DM leads to the development of other secondary complications including macrovascular and microvascular disorders. In both types of diabetes, the target of therapy is to reduce hyperglycemia and its associated complications [39]. Currently available oral therapies are based on glycemic control. In case of T1DM and severe conditions of T2DM, insulin administration is preferred [40].

Marketed anti-diabetic drugs are available in the form of conventional dosage forms such as capsules or tablets and this poses many disadvantages including reduced bioavailability, short half-life and duration of action, frequent dosing, risk of hypoglycemia, irritation in the digestive system and low water solubility [41]. Further, widely, used therapy for T1DM is insulin administration through the subcutaneous route. However, this presents several limitations such as poor patient compliance, tissue necrosis at the site of injection, nerve damage, chances of developing an infection, self-administration leads to dosing error causing hypoglycemic shock and death [42]. Hence, developing a more appropriate, safe and non-invasive approach to surpass the disadvantages of conventional therapy includes the loading of insulin and other oral hypoglycemic drugs into polysaccharide nanoparticles is an emerging strategy to treat DM.

In drug delivery, nanosystems are a widely used approach to increase drug bioavailability, producing more sustained or prolonged release of drugs with improved drug stability so that drug can be easily delivered to the target site inside the body. NPs exhibit distinctive features that affect the physical, chemical, and biological behavior. Modified NPs can be smoothly taken up by cells and used a successful delivery tools for the currently available bioactive drugs [43].

Encapsulation of drugs into nanoparticles inside the polymeric matrix or attached to the surface, favors the release of the drug near the absorption site, increased circulation time, improved average residence time with less clearance [44]. Drug loaded NPs are chiefly used for specified as well as controlled drug delivery into the body with better physicochemical features of the drug. Drug containing nanoparticles present several advantages such as enhanced stability, high

carrier capacity, and drugs targeting a specific site, compatible with hydrophilic and hydrophobic substances, wide therapeutic window, reduce the drug side effects, and reduce the dosing frequency with better patient compliance. NPs could be administered via variable routes such as injection and oral administration [45].

Polysaccharide based NPs are an emerging tool for the management and treatment of DM and associated complication. Polysaccharides can be categorized into two categories such as polyelectrolytes and non-polyelectrolytes. In addition, polysaccharides are classified based onan intrinsic charge such as cationic charge carrying chitosan, anionic charge carrying are alginate, hyaluronic acid, pectin, heparin, and neutrally charged polysaccharides like dextran. They have excellent properties to prolong the release of drugs. Besides, they have an affinity with mucosal covering of the pulmonary, nasal, and gastrointestinal tract. It also helps to improve the proteins and peptides permeability and bioavailability at the absorption site [46]. Polysaccharide nanoparticles with their potential roles in treating diabetes is shown in **Table 1.**

Table 1: Polysaccharide based nanoparticles used for the treatment of diabetes

S. No.	Polysaccharide nanoparticles	Molecular weight (Da)	Source	Applications in diabetes	Ref.
1.	Starch	Amylose: 10^7 -10^8 Amylopectin: 10^6 -10^7	Higher plants	Controlled release of insulin such as trans-nasal insulin delivery, anti-diabetic potential	[47, 48]
2.	Cellulose	10^4 -10^7	Cell wall of green plant, algae and oomycetes	Possess potent diabetic wound healing properties	[49]
3.	Dextran	10^7 -10^8	Bacterial strains	Aids in releasing growth factors in diabetes for wound healing and in insulin delivery	[50]
4.	Cylodextrin	2 x 10^3 -10^7	Starch degradation via enzymes.	Oral insulin delivery	[51]
5.	Pullulan	Thousands to 2000000	Bacterial homopolysaccharide and *Aureobasidium pullulans*	Wound healing, oral insulin delivery	[52]
6.	Guar gum	NA	Extracted from the seeds of *Cyamopsis tetragonoloba*	Anti-diabetic activity, decreases postprandial glucose levels for prolonged time and	[53, 54]

				aids in controlling diabetes	
7.	Chitosan	3800-20000	Cell wall of fungus, shells of shrimp and krill, crab	Effective oral insulin delivery	[55]
8.	Alginate	200000-500000	Cell wall and marine brown algae	Enhanced glucose-triggered insulin delivery or oral insulin delivery, anti- diabetic drug delivery	[56]
9.	Pectin	50000-180000	Cell wall of all plants	Enhance the glucose uptake and anti-diabetic potential in synergy	[57, 58]
10.	Hyaluronic acid	Can reach upto10^7	Vertebrate organism	Wound healing and aids in treatment of type 2 diabetes	[59]

5.3 Polysaccharide nanoparticles for insulin delivery

TIDM patients are solely dependent on the administration of external insulin to control the hyperglycemia and the insulin preparations available in the market are administered through the subcutaneous route.The insulin administration pathway has been shown in **Figure 1**. Further, nowadays insulin therapy is also recommended at the chronic/severe stage of T2DM along with a combination of oral hypoglycemic drugs.To control blood glucose, multiple injections are required, which leads to patient discomfort and poor compliance [60, 61]. Therefore, researchers are developing a nanotechnology based approach for insulin delivery to enhance the period of action, reduces the need for frequent dosing with better patient compliance [62]. Further, high mobility and small size of NPs favors high intracellular uptake [10]. Insulin loaded NPs protect it from enzymatic damage in the gastrointestinal tract with improved pharmacokinetics, bioavailability and therapeutic efficacy of insulin after administration [56].

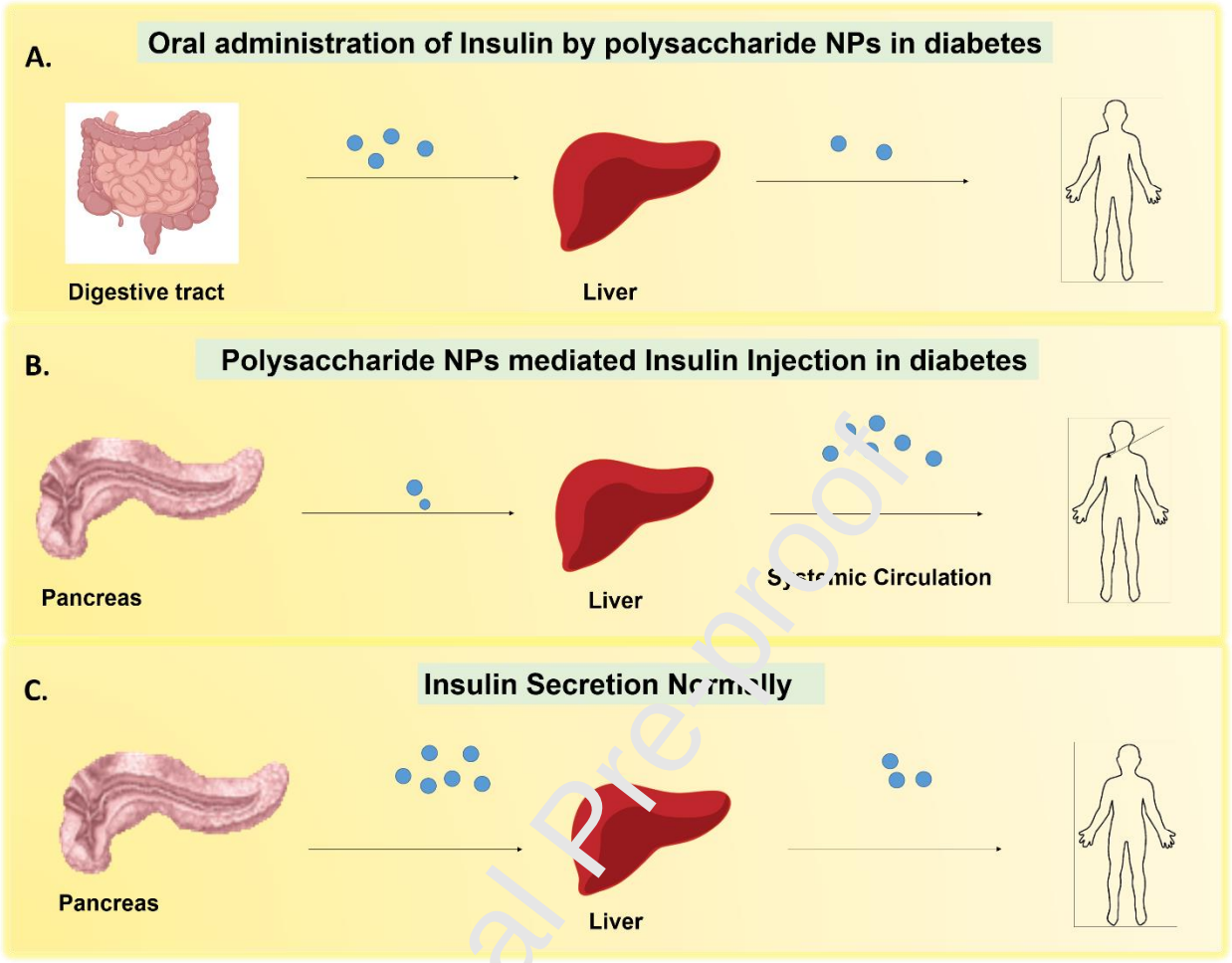

Figure 1: Insulin administration pathways. (A) Oral administration of insulin along with polysaccharide NPs in diabetic patients, (B) Polysaccharide NPs-mediated insulin injection in diabetic patients, (C) Endogenous insulin pathway under physiology.

In addition, there are various other pathways for insulin administration such as buccal, nasal, oral, inhalational and other are still under investigation [63, 64]. From these, the oral insulin delivery system has gained wide attention. However, it is very challenging to develop effective oral insulin which is resistant to gastrointestinal enzymatic degradation with increased gastrointestinal stability [65]. Several oral delivery systems for insulin-loaded NPs were established, like natural polymeric, synthetic polymeric, solid lipid, liposomes, nano-emulsions and inorganic NP.Among these nanoparticles, natural polymeric NPs are more biocompatible, biodegradable with enhanced safety and physiological stability[61 ,60]. It has been reported that polysaccharides such as chitosan, alginate, dextran and glucan are used for designs of NPs-based oral delivery of insulin [66-68].

Mukhopadhyay et al, .showed chitosan-based insulin NPs for the delivery of insulin through the oral route. The size of these self-assembled chitosan-insulin NPs reaches from 200 to 550 nm having an overall spherical/subspherical shape that ensured ~85% of the encapsulation of insulin within the NPs. In addition, *in vitro* experiments revealed that in gastric tissue a good amount of insulin was retained and a considerable amount was delivered in simulated intestinal condition. Further, *in vivo* experiments in mice showed that treatment with oral chitosan-insulin NPs reduces the glucose level with a significant amount of intestinal absorption in alloxan-induced diabetes model [69]. Similarly, Zhao et al., used a response surface methodology to develop and optimize insulin chitosan NPs. They reported that within the first 1 hr, more than 16.8%of the overall drug was delivered and more than 93% was released slowly within 24 hr, presenting prolong drug release with change of morphology of NPs [70]. Insulin is released from NPs possibly due to pH variation and strong ionic concentration in the gastrointestinal tract resulting in weakened electrostatic interactions with the disassembly of matrix network [71] .

In the acidic environment of the stomach, chitosan is highly soluble due to the amine group's protonation that causes dissociation/swelling of the chitosan-NPs resulting in the burst delivery of insulin. On the other hand, in the basic pH of the small intestine, the network of polymers gets weakened resulting in the disruption of NPs due to deprotonation and water insolubility of chitosan-based-NPs. Therefore, to tackle this limitation, chitosan has been modified by chemical cross-linking to produce a more rigid network of polymers [66]. Li et al synthesized carboxymethyl chitosan and phenylboronic acid based NPs for the oral delivery of insulin with improved gastrointestinal tract stability. The loading of insulin was done into the NPs through ionic interactions with carboxymethyl chitosan and the hydrophobic interactions with phenylboronic, a glucose-sensitive unit. Thereafter, an experiment was conducted to study the insulin release form the loaded NPs. The NPs were incubated in the variable pH condition of the phosphate buffer solution having varied glucose concentrations. They reported 16.6% of insulin release from the NPs in simulated gastric fluid (pH 1.2-2.0) condition indicating diminished and sustained release of insulin at low pH conditions because of protonation of carboxy groups of carboxymethyl chitosan thereby reducing the NPs swelling [72].

In addition, Kondiah et al. studied the gastric absorption and immediate release of trimethyl chitosan copolymer-based oral insulin and reported significant enhancement in the levels of glucose within 4h of insulin administration to diabetic New Zealand white rabbit model [73].

Likewise, Elsayed et al. developed insulin-loaded chitosan NPs by polyelectrolyte complexation technique for the oral administration of insulin. They revealed that the formulated NPs are resistant from proteolytic destruction, thereby prolonged the duration of action of insulin over 24h duration [74] .

Contrary to chitosan, the protonation behavior of alginate is different; alginate is insoluble at low pH (gastric) whereas at high/alkaline pH, it exists in soluble form. The NPs based on alginates reported to be released faster in the simulated intestinal fluid condition indicating the rapid dissolution of alginate-based NPs at neutral or basic condition but it behaves opposite in simulated gastric fluid [75]. Therefore, stabilizing the alginate NPs to achieve controlled delivery of insulin in the simulated intestinal fluid can be done using various chemical and physical cross-linkers. But, before using the linkers the safety of chemical and physical cross-linkers should be carefully considered. Further, several studies showed that a divalent ion Ca^{2+}could be utilized as a potential crosslinking agent for the development of alginate-NPs. As the concentration of cross-linker goes on increasing in the range of 0.5–1.1 mM, the delivery of insulin gets declined indicating an improvement in the release kinetics of calcium alginate-based NPs [76].

Also, Bhattacharyya et al.prepared a controlled oral delivery system by encapsulating the insulin with pH-sensitive polyurethane–alginate NP through crosslinking of the sodium alginate with calcium chloride. Further, NPs treatment showed improvement in glucose level in diabetic mice with improved bioavailability of 6.75%. The polyurethane–alginate-based insulin NPs are resistant from the enzymatic degradation and possess a controlled release profile with no sign of kidney and liver damage in mice [77]. In addition, Bhattacharyya et al. designed another experiment and prepared polyurethane-alginate/chitosan core-shell NPs of size 90-110 nm for the administration of insulin via oral route. These NPs reported to be safe in acute toxicity studies and showed sustained swelling and insulin release with improved insulin encapsulation potency (greater than 90%) and bioavailability (10.36%) [78].

Further, Lopes et al.formulated insulin-loaded alginate/dextran sulfate with a double coating of albumin andchitosan. This NPsystem is capable to prevent 70% release of insulin in a simulated gastrointestinal fluid condition, presenting controlled release of insulin following the passage to simulated intestinal fluid conditions. The albumin coating protects the insulin from the degradation by proteases thereby improves the stability of NPs at low pH as well as at basic pH.

This dual coating on NPs showed enhanced association with the intestinal cells as compared to the uncoated-NPs, leading to increased insulin permeability through Caco-2/HT29-MTX/Raji B cell monolayers [79]. Unlike chitosan and alginates, hyaluronic acid is negatively charged, more energetically stable due to its stereochemistry [80] .

Liu et al. prepared calcium carbonate-based NPs coated with hyaluronic acid for the oral delivery of insulin [81]. Likewise, Han et al. developed pH-sensitive insulin-coated with hyaluronic acid nanoparticles of size 182.2 nm for oral insulin delivery using the reverse-emulsion-freeze-drying method NPs are resistant from the degradation in gastric as well as protected from the proteolytic loss and showed 95% entrapment efficiency with strong hypoglycemic action in diabetic animals [82]. It has been studied that CD44 on pro-inflammatory cells in obese adipose tissue is associated with inflammation and develop resistance against insulin T2DM. Rho et al. have shown that HA-NPs gets assembled in adipose tissue of diet-induced obese (DIO) mice because of enhanced expression of CD44, inhibit hyaluronic acid (HA) binding to CD44, and downregulate HA promoted inflammatory cascade by stimulating CD44 clustering, thereby resulting into enhanced insulin sensitivity and glycemic control as shown in **Figure 2** [83].

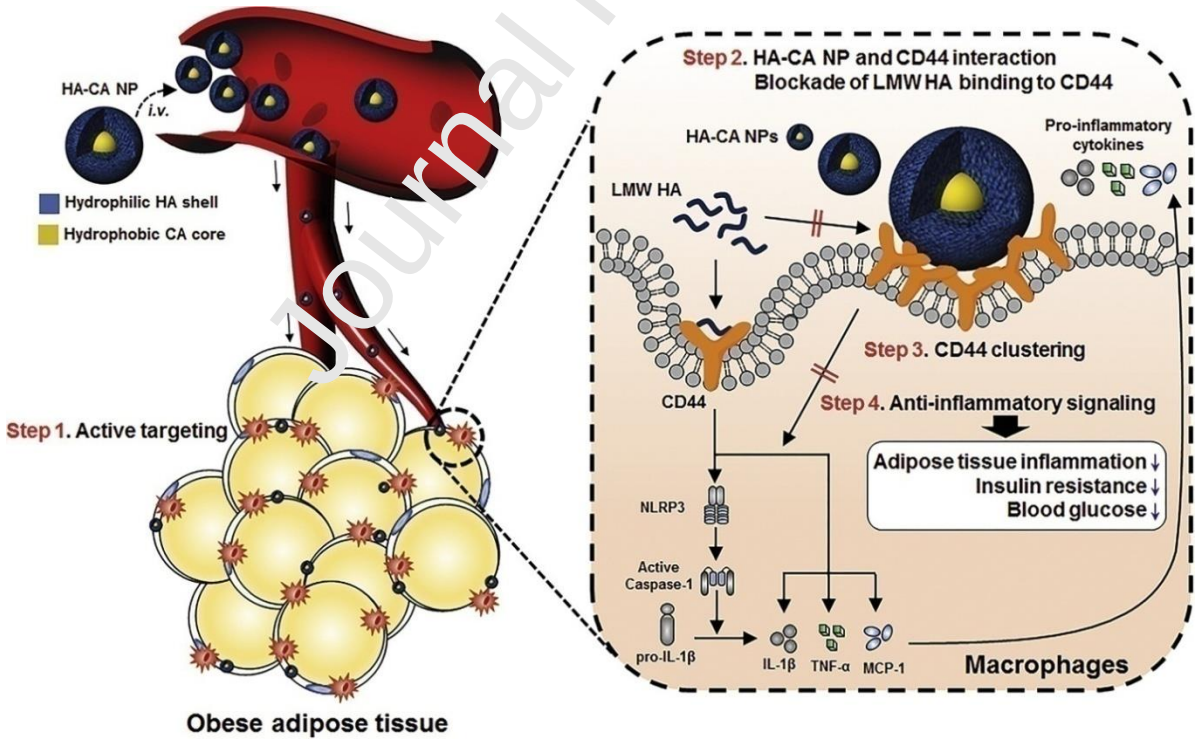

Figure 2: The role of HA-NPs in enhancing insulin sensitivity and glycemic control by promoting CD44 clustering. This figure is adapted with permission from [83].

Furthermore, other polysaccharides such as dextran a water-soluble, complex branched glucan comprised of approximately 95% αD-1-6 (glucopyranose) association 1,3-branching. Dextran is a biocompatible and biodegradable polysaccharide and contains many hydroxyl groups in its structure which allows a variable number of chemical modifications [84]. In the view of this Alibolandi et al. prepared a dextran-poly-lactic-co-glycolic acid NPs for oral delivery of insulin.The author has blended the insulin aqueous solution with dextran–poly-lactic-co-glycolic acid copolymer showed more than 90% encapsulation of insulin with 30% loading capacity at a copolymer to insulin ratio of 10:3 and also exhibited insignificant insulin delivery in simulated gastric fluid and controlled release in simulated intestinal fluid. The *in vitro* permeability of dextran-poly-lactic-co-glycolic acid NPs and bioavailability is reported as greater than the free insulin [85]

Chalasani et al. formulated NPs using dextrans of variable mass and epichlorohydrin as cross-linking agent by an emulsion method. The surface of nanoparticles was altered using succinic anhydride, and linked with amino vitamin B_{12} derived carbamate linkage. *In vitro* studies revealed that conjugated NPs prevent 65-85% of trapped insulin from the gut proteases and also showed insulin release through burst mechanism accompanied by diffusion dependent first-order kinetics with 75-95% delivery within 48 h. Among different dextrans, dextran 70K showed the best results for the oral delivery of insulin [86]. Moreover, glutaraldehyde cross-linked gelatin NPs have been prepared to offer a sustained release pattern of oral insulin through swelling mechanism [87]. Hence, developing insulin encapsulated polysaccharides-based NPs with glucose-responsive property could be very challenging, but it opens novel methods for safer and efficacious delivery of insulin by oral administration.

5.4 Polysaccharide nanoparticles for delivery of synthetic FDA approved anti-diabetes drugs

Drug loading into NPs can improve the stability, prevents enzymatic degradation in the gastrointestinal tract, contact time with gastrointestinal epithelium is increasing with enhanced residence time, pharmacokinetics and bioavailability. Generally, the drugs are entrapped within the matrix of NPs or may attach over the surface so that the drugs reach the absorption site and are released to produce maximal efficacy [44]. NPs based drug delivery gain more attention because of several advantages such as the potential of controlled release of drug, targeting, biocompatibility, safety makes potent utilization of these nanostructures in drug delivery [88].

Pereira et al.used metformin hydrochloride-loaded poly-lactic-co-glycolic acid for the treatment of diabetes-induced periodontitis in rats [89]. Further, Woo et al.prepared the pioglitazone loaded poly)lactide-co-glycolide (nanospheres of the size range 125~170 nm by using the emulsion-evaporation method with more than 85% entrapment efficiency at the loading of 30% of pioglitazone when formulated with 3% (w/v) of polyvinyl alcohol.

Further, *in vitro* study reveals that pioglitazone released at a constant rate for 40 days indicating controlled released of preparation and *in vivo* study reported that the treatment with pioglitazone loaded poly-lactide-co-glycolidenanospheres significantly reduced the glucose level in diabetic rats without any toxicity to vital organs including heart, kidney, liver, spleen and lungs [90]. Borkhataria et al.formulated the pioglitazone hydrochloride-loaded chitosan NPs of size range 250-503 nm by using a variable concentration of ionic gelation of chitosan with tri-polyphosphate anions with zeta potential +30.70 to +40.50 mV.The formulated NPs exhibited 54-77%of encapsulation efficiency by 29-52% of loading capacity. *In vitro* experiment reveals that the pioglitazone hydrochloride-loaded chitosan NPs exhibit sustained release of the drug for 20 h with improved kinetics release profile [91]. Repaglinide loaded ethyl cellulose NPs were prepared and characterized by using the solvent diffusion method exhibited an encapsulation efficiency of 86.4% with 9.61% of drug loading capacity [88].

In addition, Naik et al. used oil in water single emulsion solvent evaporation technique to develop sustained release nateglinide-loaded ethyl cellulose nanoparticles of size 248.37 nm with 91.16%encapsulation efficiency [92]. Moreover, Averineni et al.developed the gliclazide loaded chitosan NPs by salting out of chitosan with sodium citrate having better efficiency of encapsulation and drug loading capacity. The drug was delivered from the formulated NPs initially through the burst mechanism accompanied by a sustained release for a period of 24h. Further, increased polymer content in the NPs lead to decrease the rate and quantity of the drug release. The authors reported the 1:2.5 is the ideal ratio for producing enhanced encapsulation efficacy and sustained drug delivery with high stability for three months [93].

Further, Devarajan et al. formulated the gliclazide-loaded Eudragit L100 & RSNPs as a sustained release carrier having increased efficiency using controlled precipitation method and solvent evaporation method respectively with high encapsulation efficiency. Further, gliclazide-loaded Eudragit NPs exhibited superior efficacy in comparison to drug gliclazide in diabetic rats [94] .

Likewise, Dora et al, used the solvent displacement method to formulated glibenclamide-loaded Eudragit L100 NPs with increased efficacy as compared to simple glibenclamide in the alloxan-induced diabetic rabbit model [95]. Li et al. prepared oral exenatide-loaded NPs using ionotropic gelation method with altered chitosan, that was linked with goblet cell-target peptide, CSKSSDYQC (CSK) peptide. The CSK-chitosan NPs exhibited low toxicity as compared to non-modified chitosan and increased the drug permeation across the Caco-2/HT-29 co-cultured cell monolayer. The bioavailability of the CSK-chitosan NPs was reported to be 1.7-fold higher as compared with the non-modified chitosan, with better hypoglycaemic effect [96] .

5.5 Polysaccharide nanoparticles for delivery of plant delivery molecules for improvement of anti-diabetic activity

Besides insulin replacement therapy and oral hypoglycaemic drugs, herbal drugs also have anti-diabetic activities including increased uptake of glucose in the cells, restoring β-cells functioning, enhancement of insulin synthesis, decrease in insulin resistance and regulation of the carbohydrate and lipid metabolism. Many plant's secondary metabolites exhibit anti-diabetic activity. In general, phytochemicals encapsulated in polysaccharide nanocarriers can exhibit better carrying capacity of drugs, modulated the drug release, reduces the toxicity, and also enhanced the glucose-decreasing potency of the formulations. Poly-lactic-co-glycolic acid complexed with polyvinyl alcohol, poly-ε-caprolactone, poly-lactic-co-glycolic acid, poly-lactic-co-glycolic acid-polyethylene glycol, chitosan, chitosan-gum-arabic, chitosan-alginate and chito-oligosaccharidesare used as nanocarriers to enhance the pharmacokinetic features and anti-diabetic efficiency of naturally derived phytochemicals like luteolin, curcumin, silybin, thymoquinone, fisetin, ferulic acid, and astaxanthin, etc. as compared to their free form [97] .

Preclinically, it has been observed that herbal extract loaded NPs improved the glucose level and Hb1Ac in diabetic animal. The phyto-nanoformulation recommended for wound healing showed a decline in the level of inflammatory mediators TNF-α and IL-6, enhancement in the levels of transforming growth factor-β (TGF-β), which all together leads to granulation tissue formation and less wound healing time [98]. It has been reported that topical phyto-nanoformulation increases the levels of various growth factors include fibroblast growth factors, platelet-derived growth factor, and vascular endothelial growth factor thereby stimulating angiogenesis and epithelialization [99]. These achieved 98-100% wound healing pre-clinically. However, further

clinical investigations are required to study oral and topical delivery of phytochemicals in the management of diabetes-related impaired wound healing.

Curcumin is one of the well-established phytochemical which restores β-cell functioning, but has poor water solubility (8 mg/L), chemical instability, poor absorption rate, high metabolism, fast excretion with an average half-life of 2h [100]. To overcome all these drawbacks, curcumin was encapsulated with chitosan NPs which improves solubility and was also showed enhanced muscle cell glucose uptake potency of curcumin [101]. Curcumin is mainly recommended for wound healing.To improve the biocompatibility and tissue regenerating property, curcumin-PGT (prostaglandin transporter), Dicer substrate small interfering RNA (DsiRNA) chitosan NPs were developed with excellent anti-diabetic activity [102, 103]. Furthermore, resveratrol has poor pharmacokinetic and biopharmaceutical properties. It has good antioxidant activity and has β-cell-protective properties. Encapsulation of resveratrol with casein nanoparticles shows an enhancement in pH stability, higher penetration rate and controlled drug release with 10 times increase in oral bioavailability [104] .

Similarly, naringenin encapsulated in solothin-maltodextrin nanocarrier and naringenin-loaded chitosan NPs coated with alginate shows protection of drugs from gastric pH and allows sustained release with an increase in oral bioavailability [105]. In addition, quercetin-succinylated chitosan-alginate nanocarrier enhances the oral hypoglycaemic effect of quercetin in diabetic rats in comparison to free quercetin [106]. Gymnemic-acid is a well-known anti-diabetic phytochemical and gymnemic-acid-chitosan NPs showed 24hr controlled release of drugs with better efficacy in the control of glucose levels [107]. Similarly, researchers found excellent thermal stability and controlled release for 14 h in *in vitro* studies of Rosmarinic acid-chitosan nanocarriers and rosmarinic acid-loaded solid lipid NPs (Witepsol H15). This nanosystem was used for topical drug delivery with better wound healing property in comparison conventional rosmarinic acid-gel. Moreover, it allows sustained delivery of drug for a period of 14 h. However, very limited clinical reports are available on rosmarinic acid nanoformulation in diabetes management [108] .

Glycyrrhizin is another phytoconstituent with less water solubility, was embedded with chitosan-gum-arabic NPs. The NPs showed improved bioavailability with enhanced sustained-release property [109]. Sibylin provides good stability, mucoadhesion, sustained release, increase in

absorption rate when administered with chitosan nanocarrier [110]. Inhibition of α-glucosidase and α-amylases are properties of catechin, which are enhanced by catechin-grafted inulin and catechin-grafted chitosan NPs [111]. Ferulic acid-chitosan NPs enhanced the decrease blood glucose levels and an increase in plasma insulin levels in diabetic rats in comparison to free ferulic acid [112]. Taken together, phytochemicals when delivered in the form of nanoformulations orally or topically improve its anti-diabetic action by a reduction in their drawbacks like less stability, low water solubility, and higher degradation in gastric and external environment with low skin penetration rate.

6. Overview of the pathology of rheumatoid arthritis

RA is a chronic, debilitating disorder with slackening course. The pathophysiology of RA is not completely understood and the disease can be triggered from any external factor or stochastic event. This may result in an autoimmune reaction leading to dysregulated inflammation of joints, T-cell activation, synovial cell hypertrophy and endothelial cell activation [113]. Various genetic as well as immunologic co-morbidities are associated with the propagation of this disease. Immune activation results into incitement of T-lymphocytes that lead to the synthesis of antibodies in an uncontrolled manner. Lymphocytes and immune cells of synovium produce rheumatoid factor and anti-cyclic citrullinated peptide antibody (anti-CCP) in response to the preformed antibodies [114]. Chronic inflammation triggers the synovial membrane enlargement that grows out over the surface of cartilage and results in the development of a tumor like mass known as 'pannus'. As a result of destruction of subchondral bone, there is a rise in the count of synoviocytes, immune cells and cytokines in the synovial fluid. Due to which immigration of polymorphonuclear leukocytes (immune cells) starts occurring which results in synovitis. This inflamed synovium is hypoxic and as a consequence of increase in fluid volume, the capillary flow of synovial fluid decreases [115]. Lysosomal enzymes secreted by these inflammatory cells lead to destruction of cartilage and cause bone erosion. Similarly, prostaglandins produced in the process result in vasodilation and chronic pain in the joints. Various resident factors of synovium, change their phenotype and aggravate in succession with the disease and result in the induction of various inflammatory mediators. In consequence, it is apparent that RA is not just a single disease but is an orchestrated response to various pathways leading to auto-reactivity of the immune system [116].

6.1. Polysaccharide nanoparticles for the treatment of RA

RA is considered as a multifactorial, poly-articular and chronic autoimmune inflammatory disease that is known for bone and cartilage wrecking in the synovial joints evolving into joint deterioration. It leads to inflammation in the joints, pannus formation, synovial hyperplasia, bones and cartilage deterioration and is frequently linked with stiffness, swelling, continuing arthritic pain and effort infirmity [23, 117,118]. RA affects nearly 1% of adults in the USA and Europe and 0.5% in other parts of the world. The occurrence of RA is higher in women as compared to men in the proportion of around 3:1. Stimulation of different types of inflammatory cells viz. B cells, CD4 helper T cells, dendritic cells, mast cells and macrophages together with the liberation of cytokines namely IL-6, IL-1 and matrix metalloproteinases play crucial role in the progress of RA. Significant angiogenesis and relocation of leukocytes into synovial tissue from the blood cells are also observed. The main objective of treating RA is to reduce inflammation along with maintenance or improvement of joint function. Early diagnosis and treatment prior to permanent joint deterioration is needed to keep normal, active and productive lifestyle [119, 120].

Presently, treatment of RA with glucocorticoids, DMARDs, NSAIDs, and biologic drugs either mask symptomatic ease or joint pain. However, these treatments provide only temporary relief and leads to impaired adverse effects, namely cardiac complications, immunosuppression, ulcers and gastrointestinal injury leading to generation of opportunistic infections. Various biologics such as infliximab (Remicade), Etanercept (Enbrel), and adalimumab (Humira) are utilized for the treatment of RA and other inflammatory conditions. Inspite of clinical advances, still there is an urgent need to evolve RA treatments considering efficacy and safety concerns linked with currently accessible drugs [121, 122]. To surpass these restrictions, generation of novel therapeutic agents or approaches has been suggested.

One of the best illustrations of novel therapeutic strategies includes the use of effective and novel drug delivery agents likewise NPs. Currently, NPs have been determined efficaciously for specified release of drug at the inflammation site. However, NPs allow target specific release of therapeutic agents via loose vasculature in the inflammation affected areas that improve disease treatment by modulating retention effect and enhanced permeation during drug delivery [123]. Therapeutic agents allow encapsulating within the NPs that aid in modifying the drug

pharmacokinetic, biological distribution and site-specific release of the targeted drug [124, 125]. Moreover, some of the cell receptors are involved in the pathogenesis of RA, thus, specific targeting is attainable by attaching to particular ligands on the surface of NPs administered to cell receptors that are over expressed on the targeted diseased cells [126]. Side effects due to non-selective and non-specific activity of current therapeutics for RA could be decreased by encapsulating these therapeutic agents or phytochemical molecules in NPs for the targeted delivery of therapeutic agents.

Drug delivery via NPs avoids high or frequent dosing and aids in achieving appropriate local concentration of drug. Moreover, NPs can be engineered to prevent these therapeutic agents from degradation and in turn enhancing their bioavailability while minimizing the risk of off target effects [127]. The mechanism of action of these NPs can be enhanced by targeting specific receptors for invading and delivery of drug, while the uptaking of NPs by the liver and spleen could also be inhibited by altering their physiochemical properties. Once the NPs reach at the site of action, it is followed by delivery of the therapeutic agent or drugs in a controlled manner based on the temperature, pH, redox conditions and solubility etc. Researchers have successfully generated nano-carriers that can specifically respond to biological or physical stimuli are called as smart or intelligent delivery system [128]. The advancement and development in nanomedicine and nanofabrication have encouraged the utilization and exploration of a variety of nano-carriers and micro-carriers to enhance the permeability, stability and bioavailability of the therapeutic agent while decreasing the immunogenicity.

These nano-carriers can enhance the physical stability of the encapsulated drug and prevent them from enzymatic lysis. Moreover, specific properties like surface charge, shape and size can be altered to enhance the *in vivo* aspects and behavior of drug uptake such as enhanced intracellular uptake, enhanced tissue or organ retention and prolonged blood circulation. As explained earlier, the release of therapeutic agent can also be regulated in an optimum controlled manner like sustained release at the target site maintaining a constant amount within a therapeutic range and allow the burst release as a response reaction against specific signs in the pathological microenvironment [129].

Currently, natural polysaccharides have attained extensive interest considering the generation of nano-carriers and micro-carriers due of their favorable attributes, for instance, biocompatibility, biodegradability, natural abundance and low immunogenicity. Polysaccharides are a significant

ingredient of natural polymers which are generally extracted from plants (guar gum and pectin), algae (alginate), microbial (xanthum gum and dextran) and animal (chondroitin and chitosan) products. These natural polymers are cheap, abundant and easy to modify through reactive sites [130-133]. In this section, the advancement and development of various polysaccharide NPs based approaches for the treatment of RA are discussed and summarized in **Table 2**.

Table 2: Polysaccharide-based nanoparticles used for the treatment of rheumatoid arthritis (RA)

S. No.	Nanoparticles	Drugs	Testing method	Therapeutic effects	References
1.	**Dextran**	MTX	*in vivo*	Anti-rheumatic and arthritic effect	[134, 135]
2.	**Cellulose**	Curcumin	*in vivo*	Anti-inflammatory agent, anti-arthritic in adjuvant induced arthritis in rats	[136]
3.	**Guar gum**	NA	*in vivo*	Improves arthritis induced by Collagen II mice model	[137]
4.	**Starch**	Piroxicam	*in vitro*	Anti-inflammatory activity and anti-oxidant activity.	[138]
5.	**Chitosan**	siRNA-TNF-α	*in vivo*	Improvement in arthritis; decline in TNF-α expression	[139]
		EGFP plasmid	*in vitro*	Excellent transfection efficiency	[140]
		IL-1Ra plasmid	*in vivo*	improved arthritis, decline in PGE2 and decreased IL-1Ra level	[141]
		Kartogenin	*in vivo*	Increases drug retention time in osteoarthritic rats	[142]
		Methotrexate	*in vitro and in vivo*	Significant decline in IL-6 and IL-8.	[143]
		Berberine	*in vitro and in vivo*	Anti- apoptosis shown osteoarthritis	[144]
		Dexamethasone and methotrexate	*in vitro and in vivo*	Stimulate synovial cell line with pro-inflammatory mediator, potent activity against mouse macrophages, increased anti-arthritic and antioxidant activity	[145]
6.	**Hyaluronic Acid**	HA-γ-secretase inhibitor	*in vitro and in vivo*	Ligand-dependent targeting of CD44	[146]
		PEG-HA-TRAIL		Sustained and targeted delivery of TRAIL	[147]
		Prednisolone	*in vitro*	Decrease in bone erosion and joint	[148]

		(PD)	*and in vivo*	swelling, decline concentration of inflammatory cytokines.	
7.	**Alginate**	IL-10/DNA Tuftsin-modified alginate	*in vitro and in vivo*	Macrophages repolarization	[149]
		Glycol-split heparin-d-erythro-sphingosine	*in vitro*	Generate potential suppressive effect	[150]
		Transforming growth factor-β (TGF-β)	*in vivo*	Articular cartilage defects	[151]
		IL-10 plasmid DNA	*in vitro and in vivo*	Considerably decrease in concentration of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) expression and inhibit the expansion of inflammation and joint injury	[152]
		Glucosamine sulfate	*in vitro and in vivo*	Drug delivery and improved osteoarthritis	[153]

Chitosan is a linear, positively charged polysaccharide comprised of 2-acetamido-2-deoxy-d-glucopyranose (N-acetyl-D-glucosamine) and 2-amino-2-deoxy-glucopyranose (D-glucosamine) residues connected via β-(1-4)-linkages. Chitosan is acquired through alkaline deacetylation of naturally produced and amply present chitin, the second most abundantly found polymer after cellulose and is present in exoskeleton of crustaceans. Nearly 60% of chitosan must be built up of glucosamine residues to vary from chitin. Similar to other polysaccharides it is used because of its biocompatibility, mucoadhesive, biodegradability and inexpensive nature. Based upon the level of deacylation, its biodegradability in lysosomes into amino sugars that are non-toxic that are safer and easily absorbed by the body [154, 155]. Moreover, it is flexible for modifications such as covalent bonding to form NPs, ionic crosslinking, films, nano-gels and fibers etc. The mucoadhesive property of chitosan allows better absorption of protein based high molecular weight drug molecules. Chitosan based NPs with size ranges from 300 to 3000 nm generated by addition of precipitant salt were utilized to encapsulate bovine serum albumin (BSA) and ova albumin of varied molecular mass. Chitosan is considered as a weak base i.e., its pK_a is 6.4, hence in acidic conditions it carries cationic charged amino groups which could be used for

polyelectrolyte complexes alongwith metal anions and anionic group containing molecules such as phosphates or citrates. While in neutral or basic environment, chitosan shows lower water solubility due to which supplementary alteration with some hydrophilic molecules like PEG or glycol is needed. Also, water soluble chitosan could be conjugated chemically at its primary amine and hydroxyl groups with hydrophobic groups to stimulate NPs connection [133, 156]. Although chitosan NPs do not show active *in vivo* targeting but could possess targeting side groups conjugated with its backbone to stimulate receptor mediated endocytosis. Hence, chitosan NPs could be utilized as actively or passively in diseased animal models. Considering all these possibilities, it can be utilized for *in vivo* NP based drug delivery or in theranostic nanomedicine. In a study, a nanocomplex of polymerized siRNA targeting Notch1 or TNF-α with chitosan polymers and was utilized for the treatment of RA as shown in **Figure 3** [157, 158]. The results obtained by microcomputed tomography and MMP-2 specific nanoprobe demonstrated that intravenous injection of these chitosan NPs considerably inhibited bone erosion and inflammation in tissues in an RA mice model [159]. For the treatment of RA, chitosan coated calcium phosphate encapsulating bovine lactoferrin was orally administered in an arthritic mice which decreased joint inflammation and inhibition of inflammation-related genes expression via c-Jun N-terminal kinase, nitric oxide, MAPK and IL-1β etc [160]. Moreover, chitosan coated NPs have the capability to remove the calcium pyrophosphate crystals from the joints of mice, showing their therapeutic prospective in the treatment of chronic inflammatory diseases. Also, chitosan-HA nanogels encapsulating anionic photosensitizers were also prepared for specifically targeting synovial macrophages that can attain photodynamic treatment in case of RA [161].

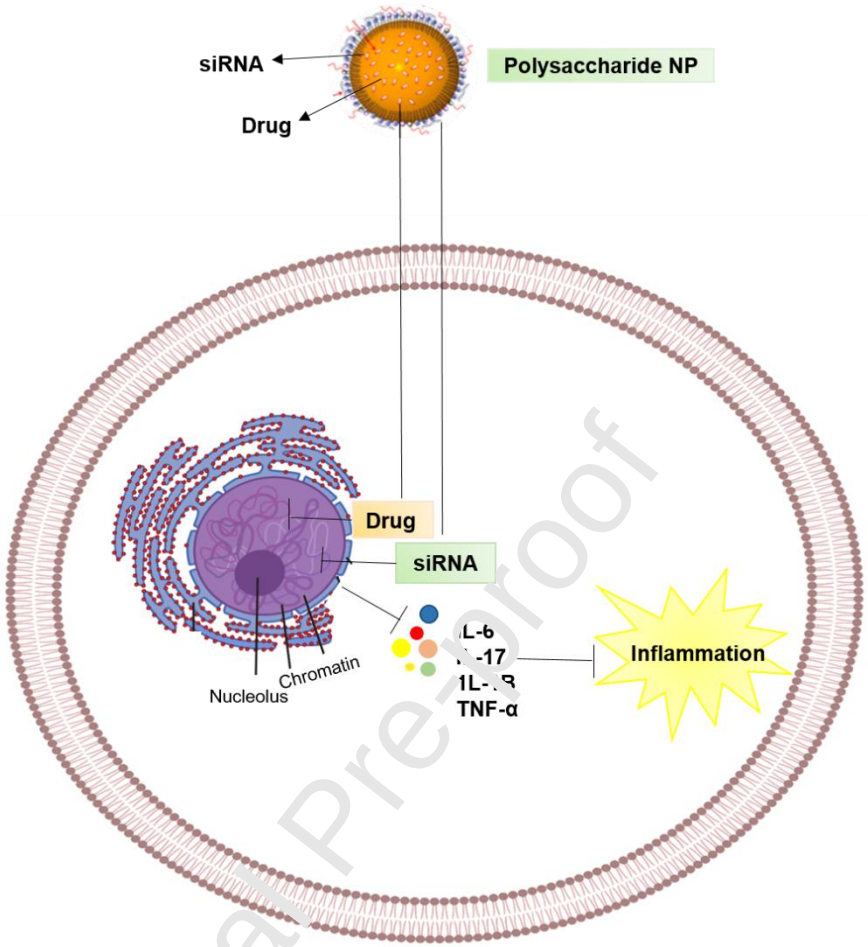

Figure 3. Polysaccharide nanoparticle (NP) approach in rheumatoid arthritis. siRNAs and drugs are delivered by NPs to inhibit the expression of pro-inflammatory cytokines, that prevents RA.

Hyaluronic acid (HA, also called as hyaluronan) is a linear, negatively charged anionic polysaccharide. It is non-sulfated glycosaminoglycan consisted of repeating units of *N*-acetyl-D-glucosamine and D-glucuronic acid disaccharide, bound by alternative glucosidic beta-(1,3) beta-(1,4) linkages. HA is present throughout in the body in connective, neural, epithelial tissue particularly in the skin, synovial fluid and vitreous of the eye. HA plays a crucial part in cell proliferation, cell-cell adhesion and regulated cell motility. It is necessary for inflammation, wound healing and embryonic development. Also, it possesses a requisite structural module as in a 70 kg person there is nearly 15 g of HA present [162, 163]. It can work as a shock absorber and lubricant, and it is FDA approved to treat knee ache in osteoarthritis or RA. Naturally, HA is present in freely circulating, attached to cell surface receptors, glycosaminoglycans or proteins

via covalent binding or electrostatic interactions. HA based NPs are used to keep the bio-adhesive and targeting features and unaltered HA have had successful outcomes in nanomedicines [164]. HA can easily encapsulate protein based therapeutic agents in well hydrated environment, preserving the protein structure. Scientists have found that positively charged proteins such as lysozyme could be successfully loaded on HA via ionic interactions and hold the secondary structure of protein through the building of HA and protein complex coacervates. Therefore, HA can generate complex coacervates with proteins having positive charge via electrostatic interactions that could enhance the physical durability of encapsulated therapeutic protein [165, 166]. HA can function as both targeting ligand and drug carrier. It is reported that inhibitors of γ-secretase can potentially enhance inflammatory arthritis by modulating the notch signaling pathway. Hence, Park et al. generated hyaluronic NPs carrying a γ-secretase inhibitor i.e. dual antiplatelet therapy (DAPT). Moreover, in synovial tissues of RA such as in lymphocytes and macrophages, the overexpression of CD44 is reported, it is studied that HA-NPs can successfully target the inflamed joint of RA by binding to the CD44 expressing inflamed cells. Therefore, Heo et al. prepared HA-NPs encapsulating a γ-secretase inhibitor namely DAPT for targeting the inflamed RA site thereby acts as a therapeutic agent for treating RA as shown in **Figure 4** [146]. The HANPs exhibited therapeutic capacity in a RA mouse model by decreasing neutrophil infiltration, tissue damage and clinical scores [167, 168]. TRAIL i.e., TNF associated apoptosis inducing ligand has been reported as pro-apoptotic on fibroblast-like synoviocytes (FLS) hence, is a potent therapeutic agent for RA.

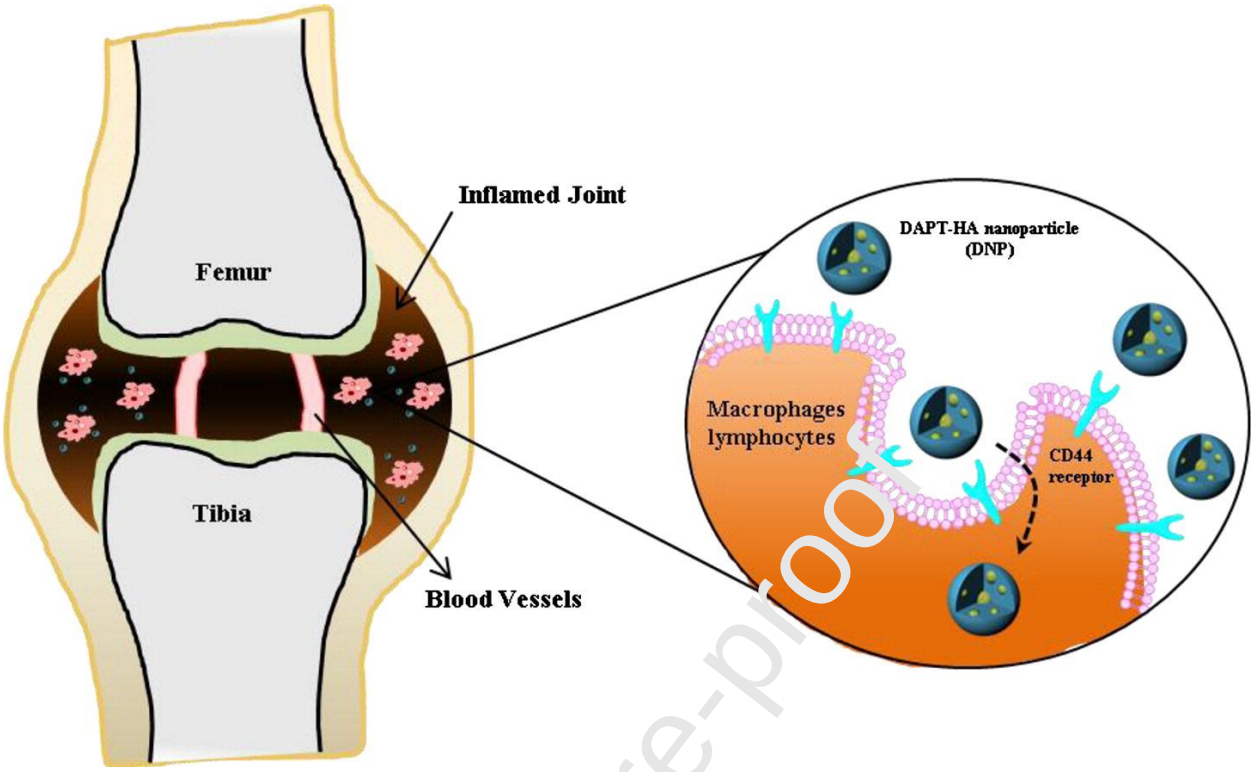

Figure 4: HA-NPs encapsulating a γ-secretase inhibitor (DAPT) for targeting the inflamed RA site acts as a potential therapy in RA. This figure is adapted with permission from [146].

In one of the studies, HA was complexed with PEGylated TRAIL and the resulting NPs showed prolonged lifetimes and sustained release of TRAIL, emerging as a favorable therapeutic consequence[169]. Moreover, Lee et al. prepared a HA-AuNPs-TCZ complex which has the potential to bind to VEGF and IL-6R for treating RA. TCZ is an immunosuppressive drug inhibiting IL-6 and HA is utilized for preventing cartilage and lubrication as shown in **Figure 5** [170].

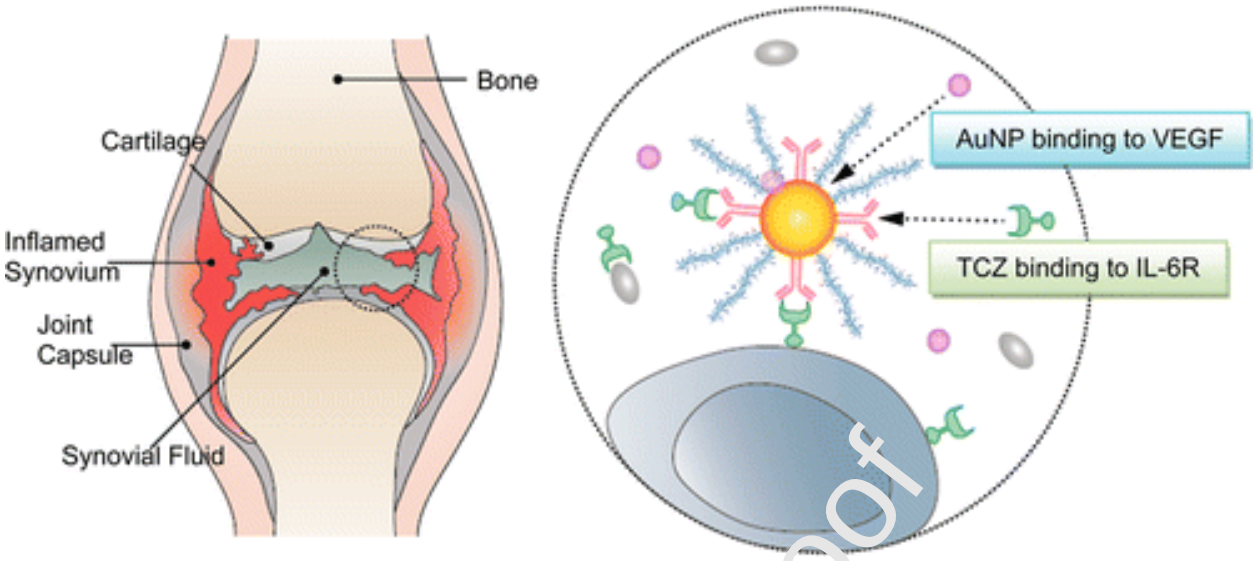

Figure 5: The potential of HA-NPs complex in treating RA as it is involved in protecting cartilage and provide lubrication. This figure is adapted with permission from [170].

Alginate is an anionic linear polysaccharide with magnificent mucoadhesive properties that exhibit biodegradability and biocompatibility. It is an unsymmetrical block copolymer consisting of α-L-guluronic acid and α-L-guluronic acid residues. It is a favorable molecule for targeted delivery of heat sensitive therapeutic agents as it requires very mild temperature in aqueous environment during preparation [171]. Additionally, alginate exhibit the capability to mask fragile therapeutic agents specially proteins and peptides from the acidic condition of the stomach, enabling their safe delivery to the intestine [172]. Alginate is mostly complexed with other different polymers such as chitosan to enhance the efficiency of delivery of therapeutic agents. Alginate NPs modified with tuftsin, packed with IL-10 plasmid DNA can effectively repolarize macrophages to an anti-inflammatory state from a pro-inflammatory state and protect the joint injury linked to adjuvant-induced arthritis and RA [173].

Various other polysaccharides have also been explored in biomedicine as gene delivery or drug carriers. Guar gum, pectin, cyclodextrin, β-glucan, carrageenan, fucoidans, chondroitin, cellulose and others also employed as templates for creating NPs and these nanoformulations have been utilized for drug delivery such as peptide and antibody delivery, delivery of synthetic FDA approved anti-arthritic drugs, for delivery of plant derived molecules for improved anti-arthritic activity and for encapsulation purpose [174].

6.2 Polysaccharide nanoparticles for delivery of synthetic FDA approved anti-arthritic drugs

Polysaccharide NPs have the potential to increase the oral bioavailability of less soluble compounds and enhance the tissue uptake and adherence capability to the capillary wall. Many of the FDA approved drugs are successfully delivered to the target site in RA. Higaki et al. illustrated the encapsulation of betamethasone sodium phosphate in PLGA NPs for targeting inflammation in the joints of rats with antigen-induced arthritis (AIA) and in mice with AbIA (anti-type II collagen antibody induced arthritis) [175, 176]. The rats were allowed to inject intravenously with PLGA NPs after the appearance of initial stages of arthritis. After one week of treatment, there was a significant decline in paw inflammation and inflammatory reaction. Moreover, histological analysis revealed a large decline in the amount of inflammatory cells in the joints. One more study by Hwang et al. investigated the usage of alpha methylprednisolone conjugated with cyclodextrin NPs for the treatment of RA [177, 178]. This conjugate was injected into rats with AIA intravenously and it reduced arthritis score. Also, histological analysis after 28 days revealed reduction in synovitis showing that polysaccharide NPs have the ability to upgrade the efficacy of RA treatment [179].

Thao et al. developed albumin NPs loaded with tacrolimus to enhance the anti-arthritic efficacy and improved targetability. They investigated spherical morphology with a mean diameter of 185 nm having charge +30.5 mV. Due to the encapsulation, the water solubility of these designed NPs is enhanced by 46 times as compared to that of the free form of tacrolimus (TAC). These albumin coated TAC NPs gets discharged steadily from the developed NPs within 24 hours, that gives sufficient time for treatment and targeting by intravenous injection at inflamed arthritic site [180]. *In vitro* studies revealed that anti-proliferative activity of TAC albumin NP upon activated T-cells in comparison to that of non-activated T-cells. As per the clinical score, the TAC NPs showed significantly greater anti-arthritic potential than that of oral suspension of TAC and intravenous injection of TAC solution. Therefore, they concluded that these new albumin coated TAC NPs may be significantly effective for drug delivery and increased solubility with enhanced accumulation of drug in joints for the treatment of RA [180].

Ishihara et al. showed the curative potential of betamethasone disodium 21-phosphate (BP) that are encapsulated in NPs of PEG-block-PLGA copolymers and PLGA homopolymers in mice

with AbIA and in rats with AIA for the treatment of inflammation in joints. The conjugate was delivered intravenously. In rats with AIA, paw inflammation decreased by 35% after the first injection. The degradation of PEG copolymer along with BP during incubation was studied and it was found that BP accumulated in the inflammatory lesion of arthritis rat models and the concentration of BP successively declined. Results revealed that the enhancement of BP in the lesion was because of retention effect and enhancement in permeability. Also, the internalization in inflammatory macrophages was explained because of lost coating polymer i.e., PEG and the delivery of BP with the hydrolysis of PEG in the cells [181].

6.3 Polysaccharide nanoparticles for delivery of plant derived molecules for improved anti-arthritic activity

Currently, the scientists focus of the plant based bioactive compounds, their pharmacological potential and chemical constituents of several plant species for generation of novel active ingredients having lesser side effects than presently available molecules [182]. Since long time, plants are known for huge source of medicinally important natural compounds that can be used for the development of novel and highly efficacious drugs. Presently, many of the nanomedicines make use of these plant-based active ingredients [183]. The release of these active ingredients from NPs improves the bio-distribution and pharmacokinetic profile. Polysaccharide based NPs offer benefits against existing formulations because polysaccharide coated NPs directed towards specific issue show enhanced absorption/uptake by the cells with low toxicity profile. Bioactive ingredients such as berberine, ellagic acid, curcumin, quercetin, resveratrol and some other compounds such as doxorubicin, vancomycin and paclitaxel can be loaded into polysaccharide NPs for the tissue/cell targeted delivery [184].

Polysaccharide NPs loaded with plant based active ingredients exhibit improved activity with sustainable release, reduced toxicity and increased cellular uptake [185]. American College of Rheumatology has indicated that currently available drugs for RA have high toxicity and restricted efficacy [186]. Furthermore, patients are not satisfied with current therapies and around 60-90% of RA patients depend on alternative and complementary medicine or active ingredients extracted from the plant sources [187]. There are various phytoconstituents such as flavonoids, terpenoids, steroids and fatty acids that have been studied for their anti-RA activity. These

compounds have shown efficacy for RA treatment with their specific targeting potential against inflammatory mediators, namely cytokines, nitric oxide, NFκB, chemokines, lipoxygenase (LOXs) adhesion molecules, and arachidonic acid (AA) [182]. These active phytoconstituents can be coated or encapsulated with polysaccharide based NPs for better efficacy, targeted delivery and lower toxicity for the treatment for RA.

Polyphenols, gallic acid, quercetin like active ingredients from *Punica granatum* exhibited considerable efficacy against cartilage destruction. Furthermore, it is non-toxic to chondrocytes in RA rat models. Moreover, it has downregulatory action against NFκB and JNK-MAPK pathways [188]. Another important phytoconstituent is thymoquinone (TQ), a bioflavonoid, and is known to treat inflammatory disorders. Administration of TQ in rats with AIA showed inhibition of serum levels of TNF-α and IL-1β [189]. Resveratrol is polyphenolic phytoconstituent obtained from grapes. Moreover, it inhibits ROS, IL-1, tumour protein p53-induced apoptosis, LTB-4, MPPs and PGE2 in animal models with RA. Hesperidin, a citrus flavonoid showed therapeutic benefits in rats with AIA where it downregulates the formation of TNF-α, IL-6, IL-1 and prevents paw swelling in rats with RA. Also, it significantly suppresses the proliferation of synoviocytes in rats with AIA. Curcumin is mostly utilized for its antioxidant and anti-inflammatory activity [190]. It is documented that curcumin in rats with RA inhibits catabolic mediators like stimulated nitric oxide, IL-β, COX-2, PGE_2, MMP-3, MMP-9, IL-8. Furthermore, it also prevents JAK/STAT, NFκB and JNK pathways in human chondrocytes [191].

Similarly, there are other phytoconstituents for RA therapy that are known to show promising results. Encapsulation of these phytoconstituents in polysaccharide based NPs have been shown to enhance the bioabsorption of such phytoactive compounds [192]. Polysaccharide based NPs release both hydrophilic and hydrophobic drugs in a controlled manner with good stability, high drug dose loading capacity and suitable for topical and systemic drug delivery. Moreover, considering the higher surface area-to-volume ratio, the polysaccharide based NPs give a remarkable advantage in the biodistribution and pharmacokinetic features of these phytotherapeutic agents at the place of action [193, 194].

6.4 Polysaccharide nanoparticles for peptide and antibody delivery

Therapeutic proteins and peptides have grabbed significant attention due to their various vital activities in biological functioning. The release of therapeutic proteins and peptides to targeted site is, nevertheless, challenging because of their internal susceptibility to various environmental conditions [195]. Polysaccharide NPs are utilized as a masking agent to prevent encapsulated therapeutic proteins and peptides and allow their endolysosomal escape and promote cellular penetration. Polysaccharide NPs can provide not only physical prevention from environmental conditions but also target these therapeutic agents to specific site of action [196]. In this regard, various features of polysaccharide NPs such as size, shape, surface and structure need be taken into consideration as these features play a crucial role in NP stability, specificity, therapeutic efficacy and protein release kinetics.

Denosumab is a monoclonal antibody that works against receptor RANKL that plays a crucial role in the activation of osteoclasts causing rheumatoid bone erosions and differentiation of macrophages into osteoclasts. Inhibiting the activity of RANKL with denosumab may be beneficial in inhibiting erosions [197]. Encapsulation of denosumab in HA NPs showed increased efficacy for the treatment of RA. Lee et al. studied hyaluronate gold NP/tocilizumab complex for treating RA. Tocilizumab was used as an immunosuppressive monoclonal antibody that aims to target IL-6 receptor. HA NPs showed lubricant and cartilage protective effect. *In vitro* results demonstrated the therapeutic potential of these HA-Au NPs loaded with tocilizumab monoclonal antibody targeting IL-6R and VEGF for the treatment of RA [198].

7. Overview of pathology at organ fibrosis

Organ fibrosis is a process of pathological scarring due to hardening, overgrowth and excessive deposition of extracellular matrix (ECM) by activated profibrotic fibroblast resulting in dysfunctioning of organs. Several factors such as allergic reactions, tissue injury or any persistent infection that can trigger chronic inflammation in the organs could lead to fibrosis. Due to secretion of soluble mediators such as IL-10 and platelet-derived growth factor (PDGF) by immune cells; fibroblasts underlying the connective tissues could get stimulated[199]. The imbalance between synthesis of ECM and its degradation leads to fibrotic tissue deposition resulting in organ damage. Moreover, TGF-β is considered as one of the cardinal elements initiating the fibrotic response in many organs and causes fibroblast migration as well as its proliferation. It actuates a multifarious reaction orchestrated by various proteins and cofactors

which mediate the resulting transcriptional response in a cell [200]. Myofibroblasts serve as important mediators in the process of fibrosis which gets activated by paracrine as well as autocrine signals and interacts with receptors present on fibroblasts. In conclusion, organ fibrosis is not operated by a single entity rather as a part of an intricate signaling network consisting of multiple signaling pathways resulting in degradation of normal tissue architecture [201].

7.1. Polysaccharide nanoparticles for treatment of lung fibrosis

In the neoteric epoch, arrays of treatment recourses have been developed for the management of pulmonary infections such as lung fibrosis. However, the unpropitious effects arising from traditional methods have always caused concern either for local or systemic application. It encompasses numerous diminutions, including pharmacokinetic instability, drug resistance and low therapeutic index. Inhalational route for systemic drug delivery acts as an effective substitute due to its non-invasive nature, high permeability through pulmonary membrane and rapid onset of action. Pulmonary delivery of NPs along with therapeutic agent has been considered recently for both lung and systemic circulation. However, therapeutic options based upon polysaccharide nanocarriers have been proved to be a favorable candidate to abolish the impediments of conventionally used drug therapy owing to their low pulmonary toxicity, biocompatibility and diverse nature [202].

These NPs can bind non-covalently to the drug or by encapsulation and help in targeted drug delivery. They have also shown to have precise control over composition of particles and sustained drug release activity with more ability to penetrate biological membranes. To prevent any adverse effects such as pulmonary embolism, submicron sized particles are administered through intravenous route [43]. Lungs have high vascularization with larger surface area of alveolar epithelium which acts as promising feature for more drug absorption. Therefore, inhalation route of drug administration seems to be a better alternative to intravenous route in which NPs are generally suspended in a gaseous medium. Polysaccharide NPs have their precedence as they can be contrived according to the patient's stipulation. HA is one of the foremost, naturally occurring extracellular matrix entities which contains negative charge and is comprehensively present in several tissues of the body [203]. Due to its non-immunogenicity, biodegradable nature and versatility in nature, it has been widely studied as a nanocarrier for

various drug delivery options. It acts as a predominant signaling molecule present in alveolar and bronchiolar region which work as regulator of inflammatory response of pulmonary tissue [204]. Hybrid NPs composed of hyaluronic acid along with iron oxide have been instigated where both are conjoined electrostatically and have been proved to be efficient in delivery of peptides. With the advent of nanotechnology there arises the possibility to deliver hydrophobic molecules without getting degraded inside the hostile environment of tissue [205]. Lierova et al. asserted that both animals as well as human models manifested a rise in HA levels in the lungs during chronic inflammation due to leukocyte infiltration which reinstate its equanimity once HA concentration reaches to baseline. Whereas, low molecular weight HA (LMW-HA) fragments correspond through CD44 which reinforce inflammatory cells recruitment at the site of inflammation. Mice model that were deprived of CD44 receptors indicated an upsurge in accretion of LMW-HA inside the lung tissues along with increased inflammatory gene expression. This substantiated that CD44 plays a crucial role in the renewal of homeostasis and for targeted drug release at the injury site in lungs

In case of lung fibrosis, water content in the mucus layer of tissue is lesser as compared to the normal mucus along with copious presence of mucin fibers which entangles and forms a mesh type network with decreased area, where these nano sized particles are able to pass through hence, penetration of the drug increases. As a result of hypersecretion of mucus in chronic fibrosis of lung, the sputum becomes highly adhesive that impedes the penetration of these NPs. To enhance delivery to the targeted tissue and to increase penetration through mucus, shielding of the surface of NPs is performed [206]. Due to diversity in charge present over these naturally occurring polysaccharide NPs, they can be altered with respect to patient's condition and targeting site. Hence, they are able to control severe inflammation and hypersecretion of mucus in the airway more effectively [207].

On the other hand, chitosan is being used for its mucoadhesive properties and high potency in protein binding. Various hydrophilic as well as hydrophobic molecules can be administered with chitosan NP by aerosol system. It showed great deposition to the target site with non-destructive intracellular delivery of the medication. Chitosan and its derivative, polylactide-co-glycolic acid (PLGA) have shown promising results in this domain[208]. It has shown excellent candidature for transmucosal administration. Elena at el., showed promising results from CFTR-specific LNA biopolymer based nanoparticles in the therapeutics of lung fibrosis as well as the stability

of CS-NP in biological system during incubation in Opti-MEM containing HEPES and mannitol. Inside the transfection media, an enhancement of average particle size was seen which was near to 350nm for the particles made up of animal chitosan and contrasting for the particles made up with synthetic chitosan. As stability of a nanocarrier in transfection medium is a crucial aspect for the estimation of drug effectiveness and its biodistribution where chitosan nanoparticles showed exciting results and remained stable throughout the study [209].

Likewise, alginates composed of 1, 4-linked D-mannuronic acid, a-L-guluronic acid and serves as an ideal carrier for sustained drug release. Carboxy methyl cellulose, another polysaccharide nanomaterial is being used to increase permeation and internalization through mucus membrane along with sustained release of drug in systemic circulation [172]. Similarly, carbopols have been used mainly for their mucoadhesive properties in liquid as well as semi solid pharmaceutical preparations. Nanospheres or nanocapsules can be easily prepared with the help of amphiphilic cyclodextrins. Hence, it seems to be clear that the use of polysaccharide nanoparticles provides an additional value in the therapeutics of lung fibrosis [210]. We have tabulated some of the polysaccharide nanoparticles with their potential applications in fibrosis in **Table 3.**

Table 3: The polysaccharide NPs studied against organ fibrosis.

S. No.	Nanoparticles	Drug	Testing method	Advantages	Reference
1.	**Hyaluronic Acid**	Silibinin	Both *in vivo* and *in vitro*	Anti-hepatic fibrosis effect *in vivo*; wound healing in lung tissue	[211]
2.	**Alginate**	Rifampicin	*in vivo*	*Staphylococcus aureus* induced cystic fibrosis	[212]
3.	**Chitosan**	Collagenase loaded	Both *in vivo* and *in vitro*	Improves scar in liver fibrosis	[213]
		siRNA	Both *in vivo* and *in vitro*	Drug delivery to fibrotic livers	[214]
		NF-κB oligonucleotide	*in vitro* and Cell based	Immunomodulation of cystic fibrosis epithelial cells	[215]
4.	**Cellulose**	Docetaxel	*in vivo*	Showed anti-fibrotic	[216, 217]

				effect in liver fibrosis	
5.	**Dextran**	siRNA	Both *in vivo* and *in vitro*	Aids in drug delivery	[218]

7.2. Polysaccharide nanoparticles for treatment of liver fibrosis

Liver fibrosis is the process of continual assemblage of extracellular matrix (ECM) as a wound healing response to undirected liver injuries that distorts hepatic architecture by developing a fibrous scar. It entails a variety of cells such as of proteins, different macromolecules, collagen, insoluble fibers and microfibrils that makes the process of drug delivery complicated. Due to this, various methods have been developed to digest the collagen rich extracellular matrix where fibrotic scar is present in case of chronic hepatic disease [219]. Liver encompasses primarily hepatic parenchymal cells (60%-70%) and non-parenchymal cells (30%-40%), out of which non-parenchymal cells contain Kupffer cells, hepatic stellate cells (HSC), macrophages and various immune cells. Amongst these, quiescent hepatic stellate cells are the foremost cells that secrete extracellular matrix (ECM) and interstitial collagen which plays a crucial role in the enhancement of liver fibrosis (**Figure 6**) [220].

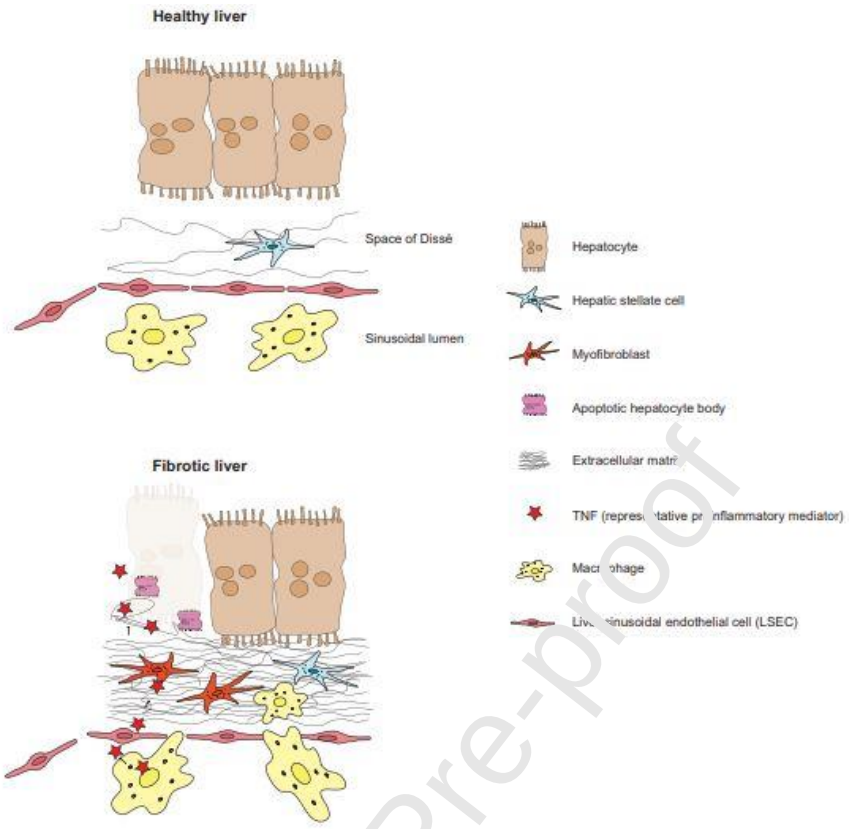

Figure 6: Different cell types present in liver under healthy and fibrotic conditions. Upon liver injury, macrophages recruited to injured site and secrete proinflammatory and profibrogenic activators that lead to hepatic stellate cells (HSC) activation. HSC transorms into myofibroblasts, that leads to excess extracellular matrix synthesis and fibrosis development. This figure is adapted from [221] under creative common license.

Due to any hepatocellular impairment that leads to liver injury can activate these hepatic stellate cells which then undergo into morphological as well as functional alterations and transformed to be proliferated. Hence, obstructing these activated HSCs is the conventional method of treatment. Because of their meagre presence and physiological location of these HSCs, it is difficult to target them specifically low tissue distribution, poor selectivity of the target tissue and lack of *in vivo* stability are the major pitfalls of traditional clinical treatment options [222]. To enhance drug efficiency, targeting the delivery of drugs to the discrete liver cells is highly important.

Polysaccharide NPs based drug delivery shows encouraging results to enhance the bioavailability, stability and targeting of drug. Tailoring of a polysaccharide nanoparticle can be achieved to deliver efficacious therapeutic precursors with specific targeting to the tissue site

without prompting systemic toxicity. In addition, they can perpetuate the sustained release of drug and refines its distribution to the target tissues which leads to the improvement of efficacy and depletion of adverse effects [127, 223, 224]. Moreover, a better control over the amount of targeting entities on nanoparticle surface can be achieved as chances of leakage of drug molecule are very low. Hyaluronic acid, a naturally occurring linear polysaccharide is highly used in regulation of fibrosis and inflammatory processes due to its non-immunogenic properties. It is one of the major constituent of extracellular matrix inside the organ. It indicatively recognizes and binds to the cell surface of overexpressed CD44 receptors present in HSCs that provides a conceptual basis for treatment of liver fibrosis using hyaluronic acid as a targeting molecule [225].

Alginates are also being widely used as a favorable drug delivery nanocarrier for various molecules at a regulated release of the drug by altering the pore size of alginate hydrogel. Their ingrained functional moieties can represent as attachment points for medication and targeting agents with the help of superficial chemical transformation to increase circulation time and target specific drug accumulation process [172]. The system containing losartan inside hyaluronic acid micelles serves as an effective alternative in the treatment of advanced liver fibrosis in a C3H/HeN mouse model. Coupling of the targeting entity on the surface of preformed nanomaterials has improved the designing of targeted drug delivery systems. The size of particle acting as a drug carrier must be small enough to reach the HSCs passing through these small openings. Furthermore, targeting any unintentional tissues can result in damage of contiguous normal healthy cells [226].

Nanomicelles comprising of semisolid hydrophobic core in its core shell structure can easily entrap water insoluble drugs that makes the drug more stable in systemic environment and due to its small size, active targeting of the drug was possible. To achieve directed HSC drug delivery Wenhao et al. developed a similar system of SLB-loaded HA-based nanomicelles. Amphipathic HA were procured by modifying partial side chains containing carboxylic group at the end with the help of deoxycholic acid (DOCA) and ethylenediamine as the linking group which was used in the process of fabricating the HA-functionalized nanomicelles. Targeted drug delivery to HSCs was attained by inserting hydrophobic side chains of HA conjugate inside the hydrophobic core along with surface of micelles encased around with hydrophilic main chains of the HA conjugate. Even the particle size was retained below 100 nm so that it could pass through the

small spaces in LSECs. Both, *in vivo* as well as *in vitro* studies were studied to evaluate to examine the targeting efficiency of these HA micelles, its biodistribution, therapeutic efficacy, systemic toxicity and biological half time in systemic circulation. It showed hampering and negating of liver fibrosis during in vivo studies and controlled release of drug during in vitro evaluation. In addition, these HA micelles showed targeted uptake to HSCs via CD44 receptor mediated cellular infiltration [211].

Chitosan is a biocompatible polysaccharide that has shown sufficient interaction and binding with collagen. They have the ability to encapsulate various therapeutic proteins and desired drug molecules by keeping their functional and constitutional form intact within the in vivo environment. Azzam et al. evaluated targeting efficiency and therapeutic efficacy with the help of *in vivo* and *in vitro* systems in which chitosan NPs were loaded with collagenase protein. Encapsulation magnitude of these nanoparticles was discerned to be more that 50% and it was able to release its content in active form. Furthermore, the surface of chitosan nanoparticle was altered by various densities of collagen binding peptides (CBP) to find out if this modification is necessary for nanoparticle collagen binding or is it the sole interaction of chitosan with collagen molecules.

It was demonstrated with the help of an *in vitro* collagen binding analysis that unaltered chitosan NPs were able to bind with the collagen molecules and showed reversal of fibrosis with 100% survival rate while modified CBPs did not manifested any reinforcement in collagen binding. This experiment indicated about the capacity of chitosan NPs in targeted delivery of functional collagenase at the site of liver injury [227]. Nanotechnology offers great possibility in the deterrence and treatment of chronic liver ailments. Conclusively, these are chosen as first generation nanocarriers with lesser side effects and variety of primacy over other traditionally used therapeutic methods in the treatment of liver fibrosis.

7.3. Polysaccharide nanoparticles in treatment of other fibrotic diseases

Chronic tissue injury predominantly results in the accumulation of extracellular matrix that makes up a scar tissue and eventually, fibrosis. Various types of stimuli that can be severe acute or chronic including autoimmune response, infection or any physiological injury can result into fibrosis. Repair of a damaged tissue occurs mainly in two phases, first one is a regenerative phase that includes substitution of damaged cells with healthy cells of equivalent archetype and

the other phase is fibrosis which involves replacement of parenchymal tissue by connective tissue. The latter can result into the genesis of permanent scar if it continues to transpire on the same injured tissue [228]. Contemporary clinical treatment options are present for targeting the inflammatory cascade of wide spectrum fibrotic disorders such as hepatic fibrosis, nephrogenic system fibrosis, systemic sclerosis, cardiac fibrosis and pulmonary fibrosis, but require more contemplation in the field [229]. Albeit, the causative mechanism might be different behind these disorders but they share the prevalent feature of continual accreditation of extracellular matrix at the site of tissue injury, leading to its dysfunction and sometimes, failure of the organ [230].

Application of nanotechnological principles in the treatment of fibrotic disorders has intensive transformative potential. Customization of nanocarriers according to the desired drug and location of targeting tissue is possible which greatly magnify its efficacy, targeted drug delivery capacity and tolerability. Its role in the treatment of liver fibrosis and lung fibrosis has already been discussed [221]. Treatment and management of fibrotic disease associated with kidney delineates an enormous field of attraction and research. Use of nanotechnology has upgraded the biodistribution and pharmacokinetics of the drug to enhance its efficacy. Targeted drug delivery approach has achieved with improved C_{max} and plasma area under the curve (AUC). The drug encapsulated inside nanoparticle shows low plasma concentration at first, but reaches to its C_{max} with progressive increment as the time goes by.

Nanomedicines show lesser cytotoxicity associated with drug as its pharmacokinetics depends on C_{max} which shows wider area under the curve as compared to the free drug which shows instant peak initially but steep decrease after some time. It implies lesser C_{max} associated cytotoxicity of nanomedicines in the treatment of fibrotic disorders [231]. Their assemblage has been shown to be cramped in the area of glomerular mesangium and extracellular matrix inside the kidney. The transference of NPs in systemic circulation is highly influenced by their morphology that plays an important role in its biodistribution [232]. Polysaccharide NPs have been remolded at nanometric scale boosting their range of potential application in various fibrotic disorders. Due to their less toxicity, versatility and biocompatibility, they have been substantially used in clinical therapeutics of different ailments. Amongst these, chitosan polysaccharide NPs have increasing attention as drug delivery system. It is the only impetuously occurring cationic polysaccharide in which chemical modification results into amphiphilicity [233].

Chitosan NPs have been reported in the process of encapsulation of various therapeutic proteins and assists in preserving their functionality from degradation inside an *in vivo* system. Hyaluronic acid, being a major component of various connective tissues has been widely utilized in different biomedical applications and therapeutics of fibrotic disorders. Cyclic oligosaccharide, cyclodextrins are subsisted by different hydrophobic surface which helps in the formation of inclusion complexes with various molecules. It has shown propitious results in improvement of drug solubility and its biodistribution with enhanced encapsulation efficiency. Their hydroxyl group offers as the active sites for surface alterations with variety of targeting entities including arginine-glycine-aspartic acid (RGD) and folic acid [234].

Likewise, cardiac fibrosis occurs due to the activation of fibroblast cells to myofibroblasts and start fabricating extracellular matrix in colossal amounts leading to the formation of scar tissue at the mangled site. There is an alteration in normal production and degradation process of extracellular matrix proteins that ultimately results into fibrosis. As a result, it builds up the rate of accumulation of collagen protein that affects both systolic as well as diastolic functions of the heart. Cyclodextran, a glucose polysaccharide nanoparticle intensifies the interaction between target and ligand molecule with the help of chemical alterations. McCarthy et al. studied the role of cross-linked dextran coating (CLIC) in thrombus targeted fibrinolytic therapy in which two different components of thrombus were earmarked including fibrin and activated factor XIII (FXIIIa) by peptide affinity ligands present on surface of nanoparticle. Moreover, in another experiment magnetic field was used to focus dextran coated iron-oxide magnetic nanoparticles to the target tissue and enhancement in thrombolytic efficiency of conjugate particles was observed [235]. With the help of various studies, it has been noted that nanoparticles carrying cationic or neutral charge have good internalization efficiency as it can easily bind with the cell membrane containing a negative surface charge. Due to the above stated parameters and having various attractive characteristic features such as biodegradability, non-toxicity, hydrophilicity, low production cost and target specific drug delivery efficiency, polysaccharide nanoparticles have been intensively developed in the clinical therapeutics of variety of organ fibrotic disorders.

8. Challenges

8.1 Fabrication of polysaccharide nanoparticles

Several methods, including crosslinking (chemical or ionic), nanoprecipitation, coacervation and emulsion-based methods have been employed in the fabrication of polysaccharide nanoparticles. Each method has its own merits and demerits. A separate cross-linker is used in the chemical crosslinking method that makes an irreversible covalent bond between polysaccharide molecules. Oppositely charged small ionic molecules are used in the ionic crosslinking method and polysaccharide molecules are connected using electrostatic interactions [236]. However, crosslinking methods are not preferred for the drug delivery applications as the cross-linkers pose additional toxicity. Nanoprecipitation is one of the widely used methods that employs two phases, i.e, aqueous and organic phases. First, hydrophobic compounds are dissolved in the water-miscible organic solvent and water or aqueous based buffer solutions are added subsequently. Finally, precipitated hydrophobic nano particles can be collected by evaporating the solvent [237]. Like nanoprecipitation, emulsion-based methods also use two phases. First, polysaccharide molecules will be dissolved in deionized water and subsequently dispersed in the oil phase. This method is called oil-in-water or water-in-oil emulsion and the polysaccharide NPs are prepared by gelation. In coacervation method, two oppositely charged aqueous polymer solutions are mixed and that results in dense liquid and dilute solution phases. Polysaccharide NPs are extracted from the dense liquid phase [238].

8.2 Stability

Stability of the polysaccharide NPs is closely linked to its preparation method. NPs prepared using chemical crosslinking has very high stability due to its covalent bonding. Whereas, NPs prepared using ionic crosslinking show lower stability susceptible to changes to ionic strength, temperature and pH. NPs synthesized using nanoprecipitation and emulsification methods have varying stability based on the particle size. Czabany et al. have recently reported an improved method that increases the stability of polysaccharide NPs [239].

8.3 Extraction

Polysaccharides can be extracted from natural sources such as animals, plants, microbes and fungi. Extraction methods are broadly divided into three categories, i.e., solvent extraction (water, organic and alkaline), physical extraction (microwave and ultrasonic) and enzyme assisted extraction [240]. However, achieving clinical grade purity is of another challenge.

Traditional solvent-based methods are often combined with physical extraction methods to improve the yield and purity. Moreover, extraction and purification methods significantly alter the functional and physicochemical properties of the polysaccharide [241]. Therefore, extraction and purification methods that yield lower chemical contamination and does not alter physicochemical properties of the polysaccharide should be chosen.

8.4 Regulatory status

Many of the polysaccharide moleculesdescribed in this review are already in use as drug carriers for many diseases including diabetes, arthritis and fibrosis. For example, FDA has already approved cellulose, alginate, HA, guar gum for ophthalmological treatments [242]. Both, FDA and European medicines agency approved chitosan NPs for drug delivery [243]. Since, polysaccharides are natural materials and various tissues in human body already contain them, they pose minimal side effects and toxicity. This is an additional advantage that polysaccharide based NPs can be easily approved by the regulatory agencies. However, chemical compounds used during polysaccharide extraction and NPs preparatory methods will pose toxicity. Further research is required to develop new NPs synthesis methods that use less or no chemical compounds to reduce the toxicity.

9. Future perspectives

In the last two decades polysaccharide-based NP formulation have emerged as potential therapeutic choice in different disease conditions. As polysaccharide based nanoformulations can be tailored easily so they can play an important role in the personalized medicine in clinical settings which will offer a great advantage in future therapeutics development. But still, most of the research for polysaccharide-based nanoparticles is confined to the preclinical setting. For clinical translation of these potentially valuable polysaccharide based NPs, considerable work is a pre-requisite. In modern era of science by using nanotechnology based tools we can design intracellular or subcellular drug delivery system for delivery gene or drug by incorporating polysaccharides. As evident from different pre-clinical reported studies, polysaccharide based NPs formulations appears to be a favorable strategy in delivering or releasing their content to the target site. Their inherent property of muco-adhesiveness can offer the opportunity to enhance the mean residence time, enhanced binding efficiency of nanoformulations at the site of absorption. Moreover, by coating specific ligand or by surface functionalization of

polysaccharide NPs the receptor ligand interaction can be modulated for better therapeutic outcomes. However, to assess the interaction of the cell membrane with polysaccharide NPs some study have also been performed to address the uptake mechanism and their intracellular fate that must be taken into consideration for designing novel drug therapeutics.

10. Conclusions

Herein, we have reviewed the naturally available polysaccharides for the drug delivery applications. It is apparent from the strength and extent of numerous studies that polysaccharide NPs are preceding as novel therapeutic option. A distinct number of preclinical studies proclaim the increased efficiency of drugs in conjunction with polysaccharide based modifications. Their capability to enhance the drug permeability, bioavailability, reduced toxicity and increased sojourn time makes them attractive beacon in drug development. Mechanistically, many polysaccharides based NPs have been found to show multiple effects like abrogation of ROS, impeding inflammatory signaling by modulating the Nrf-2, NFκB MAPKs, halting fibrotic cascade and many more. Indeed, polysaccharide NPs-based intervention can certainly be proved as an advantage against different sort of disease ailments. Furthermore, polysaccharide based NP interventions embrace ample possibilities for development of advanced therapeutic drug delivery systems.

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Graphical abstract