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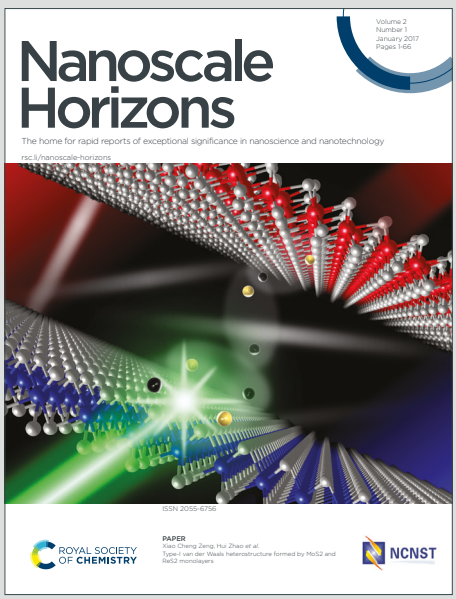

Polysaccharide-based Nanocomposites for Biomedical Applications: A Critical Review

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Abstract

Polysaccharides (PSA) are taking specific position among biomaterials for advanced applications in medicine. Nevertheless, poor mechanical properties is known as the main drawback of PSA, which highlights need for PSA modification. Nanocomposites PSA (NPSA) are a class of biomaterials widely used as biomedical platforms, but despite their importance and worldwide use have not been reviewed. Herein we critically reviewed application of NPSA by categorizing them into generic and advanced application realms. First, application of NPSA as drug and gene delivery systems, along with their role in the field as antibacterial platform and hemostasis agent is discussed. Then, applications of NPSA for skin, bone, nerve, and cartilage tissue engineering are highlighted, followed by cell encapsulation and more critically cancer diagnosis and treatment potentials. In particular, three features of investigations devoted to cancer, i.e. radiotherapy, immunotherapy, and photothermal therapy, are comprehensively reviewed and discussed. Since this field experience an early-stage maturity, some other aspects such as bioimaging and biosensing are reviewed in order to give a sensation of potential applications of NPSA for future developments—providing a support for clinical applications. It is well-documented that using nanoparticles/nanomaterials above a critical concentration brings about concerns to toxicity, so that their effect on cellular interactions would become a criticism. We compared nanoparticles used in fabrication of NPSA in terms of toxicity mechanism to shed more lights on future challenging aspects of NPSA development. Indeed, neutralization mechanisms underlying cytotoxicity of nanomaterials, which are expected to be induced by PSA introduction, should be taken into account for future investigations.

Keywords: Polysaccharide; nanocomposite; drug delivery; tissue engineering; biomedical engineering

1. Introduction

Polysaccharides (PSAs) are ubiquitous biomacromolecules, which can be found in every living organism. They contain sugar units (i.e., saccharoses) in their structure and there exist a wide spectrum of PSAs possessing monosaccharides of different type, molecular weight, and glycosidic bonds. Chitin, chitosan, cellulose, agarose, starch, hyaluronic acid, guar gum, heparin, alginate, pectin, pullulan, dextran, and cyclodextrin can be mentioned as the well-known PSAs with broad biomedical applications [1]. They are green alternatives to synthetic polymers and in combination with nanofiller, nanoparticles and nanosheets, they can be utilized

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instead of different synthetic polymer composites. There exist a wide range of PSAs with low or high molecular weight, linear or branched as well as mono- or multifunctional groups and mainly benefit from hydrophilicity, no/low level of toxicity, and non-immunogenicity which amplify their applications [1]. Noteworthily, in addition to metabolic conformity and enzyme-triggered degradation, these biomolecules are more stable in comparison to nucleic acids or proteins. Different types of PSAs are utilized for biomedical applications, food additives/packaging, agricultural purposes and water treatment [2]. For instance, sulfated PSAs have a unique ability to mimic the extracellular matrix (ECM) environment (i.e., heparan sulfate molecules in the ECM) leading to enhancement in alkaline phosphatase activity for bone regeneration [3] or nerve tissue engineering, where biodegradation of PSA plays an important role after the replacement surgery [4].

Development of PSA green nanocomposites has been the subject of plenty of papers. PSA nanocomposites containing bionanomaterials (e.g. silver, gold or titanium oxide, especially in the form of nanofibers/nanowire or nanocrystal), are promising scaffolds possessing Young's modulus of 100–200 GPa and higher specific surface area (hundreds of m^2/g) [5, 6]. Moreover, PSA-based fibrous scaffolds more closely mimic the heterogeneity of the native ECM. PSAs themselves micro- and nanoscale fibrous structures can be also fabricated through dry, wet, melt, gel, reaction or electrospinning processes [7]. The resulting nanocomposites fibers can be used as constructing components of tissue scaffolds (e.g., fiber-reinforced hydrogel) or they may be the only constituent of fibrous scaffolds. PSA-based nanocomposites can be applied as biomedical platforms through a-two-stage approach. In the first step, nanomaterials are blended with PSAs (as matrix) with appropriate distribution and dispersion, e.g. *via* solution mixing. In the second stage, the prepared nanocomposite undergoes a process, like electrospinning, to make a proper shape (e.g., electrospun fibers). **Figure 1** illustrates the most well-known methods used for shaping PSA nanocomposites [8, 9]. Between the figured approaches, electrospinning is the most practical and cost-effective one because of the ability of mimicking the fibrous structure of natural ECM, which affects the cells' biological behaviors [10-12].

Although PSA-based nanocomposites used for biomedical purposes are becoming more and more widespread, there is no review paper to summarize and interpret available reports on their application in biomedical engineering. This paper aims to summarize and discuss numerous studies that have utilized bio-nanocomposites with PSA as matrix or PSA-based nanostructure additives. A number of review papers and books have assorted PSA sub-families [13], their origins [14], their general applications (no focus on biomedical ones) [15], applications of PSAs

(not their nanocomposites) in tissue engineering (no other biomedical fields [16, 17]), methods of preparation and functionalization [8, 18], details about their pharmacogenomics [19], different possible bio-additives [20], the electrically conductive PSAs and existing challenges [4], and eventually their usage in some very few branches of biomedical engineering [21]. However, none of them have discussed the existing opportunities and challenges in all biomedical fields, ranging from delivery systems (both gene and drug), tissue engineering (skin, bone, nerve and cartilage), and cancer treatment (radiotherapy, immunotherapy and phototherapy) to bioimaging as well as biosensors. It is attempted to comprehensively review and discuss PSA nanocomposites in quest for developing scaffolds for biomedical application. Moreover, a concise glimpse at fabrication methodologies, and discussion about existing challenges (such as nonmaterial toxicity) and the future ahead of this field of research is taken into account. It is believed that such a well-organized review would help researchers working in the field in taking next steps toward a profound understanding of the limitations and possible remedies, all of which would endorse the future horizon.

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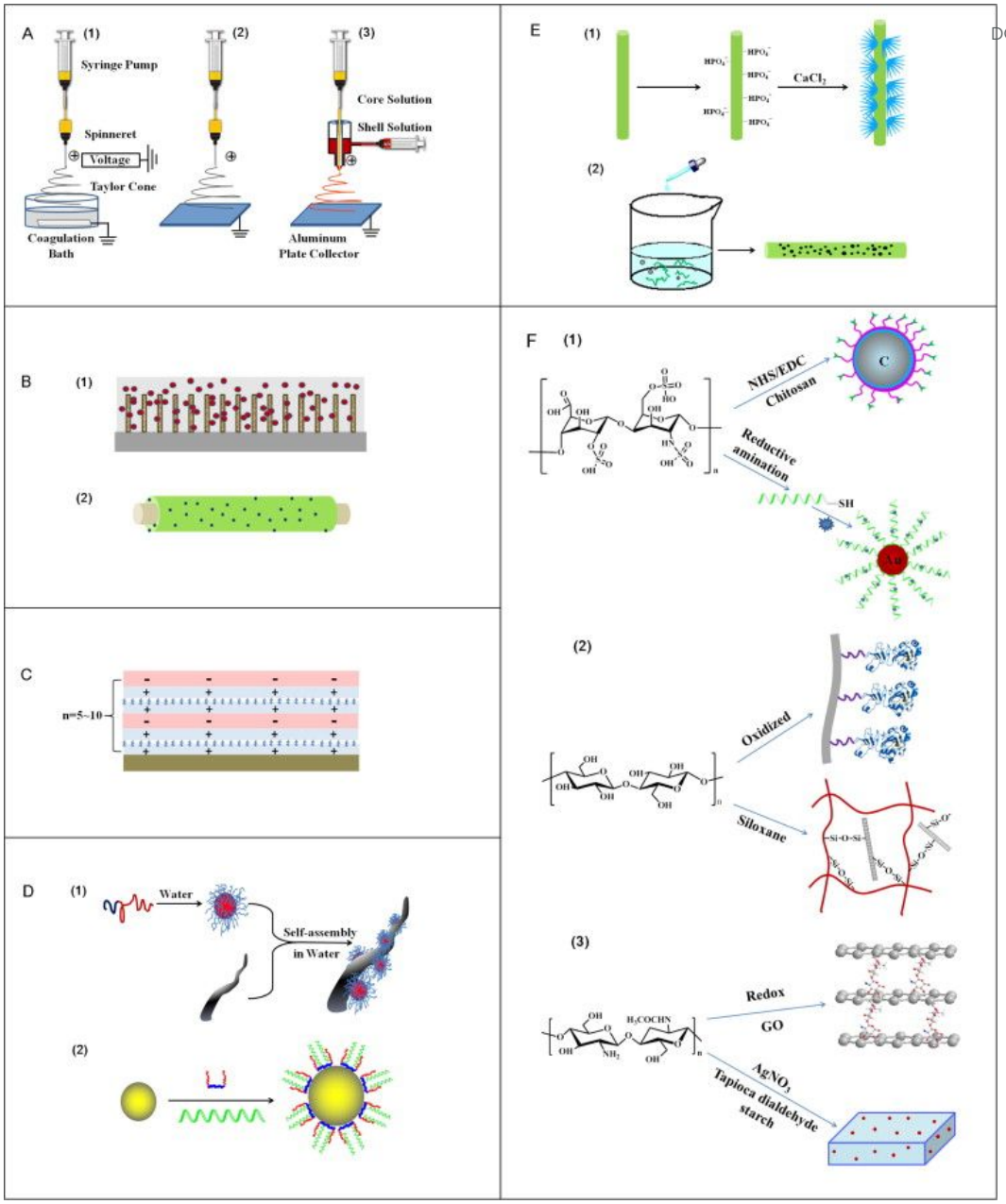

Fig. 1. Schematic illustration of the methods used for nanocomposites fabrication. **(A)** electrospinning process, which has utilized (1) wet-wet, (2) wet-dry, and (3) co-axial method, respectively, **(B)** film coating procedure, (1) to convert cellulose from sphere form to cylinder on silicon wafer surface, and (2) lactose modification with chitosan and enclosed Ag nanoparticles, **(C)** Layer-by-layer deposition method, **(D)** colloidal assembly, (1) self-assembling of block polymer on a fiber from anionic PSA core/shell structure, and (2) assembling of poly(lactide-co-glycolide) within the water **(E)** in situ nanoparticles preparation procedure, (1) phosphorylation of cellulose fibers and growth of hydroxyapatite nanocrystals, and (2) cellulose nanofibers within sodium borohydride (NaBH4) solution with addition of silver nitrate ($AgNO_3$) as well as **(F)** Covalent coupling, (1) coating of poly(methyl methacrylate) with carbon and heparin linked with chitosan which is labeled with fluorescent, and (2) coupling of cellulose oxidized lysostaphin or siloxane 3- grafting of chitosan with graphene oxide (GO) nanosheets [8].

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2. Polysaccharide family

PSAs can be found in various types and with different properties. There is a variety of PSAs with different molecular weights, functionalities (e.g., hydroxyl, amine, and carboxyl), and properties (e.g., hydrophilic or hydrophobic). The main motivation for development of PSA-based nanocomposites roots in their relatively poor mechanical properties, which has limited their potential applications. Utilization of PSAs in combinations with nanoscale materials enhances their properties, mechanically (like addition of graphene nanosheets) and in some cases, biologically (like adding silver nanoparticles for improving antibacterial performance) [4, 22]. On the other hand, it may induce other functions, e.g. electrical conductivity (like the addition of carbon nanotubes), to the base PSAs.

Generally speaking, alginate with biocompatible properties and ionic crosslinking has numerous biomedical benefits, such as cell delivery, 3D and 4D bioprinting as well as 3D cell culturing [12, 23, 24]. Additionally, reports have indicated that alginate has been proposing a strong intrinsic anticoagulant characteristic [25]. Pectin can be obtained from plant cell walls and pullulan with perfect water solubility and nontoxicity, is typically isolated from Aureobasidium [22, 25]. Dextran and hyaluronic acid with high water solubility can be mentioned as excellent candidates for food and medical applications [25]. Gums are reported as cheap and easy operable materials, which are well-known as water treatment agent [26]. Cellulose and chitosan with biodegradability, biocompatibility, good mechanical properties and facile chemical modifications are captivated by developers in medicine, food and paper industries and water treatment.

Some of PSAs like starch, have weak mechanical characteristics. For instance, starch suffers from poor mechanical properties when it is moist and fragile when it is dry [27]. Physical and chemical crosslinking are well-known strategies to enhance the mechanical properties of PSA. Physical interactions are generally weaker than the chemical crosslinking, but can induce dynamic features such as self-healing capability. It is worth mentioning that the pretreatment, like chemical modifications, may be necessary prior to crosslinking. Chemical crosslinking also affects the cytotoxicity and rheological behavior (e.g., gelation time, gel strength, swelling ratio and absolute viscosity). For instance, the gelation time and gel strength of dextran hydrogels can be controlled by altering the chain length of the chemical cross-linker agent [28, 29]. On the other hand, incorporation of nanomaterials with high mechanical properties is another general strategy to enhance the mechanical properties of starch. From a molecular

view, interfacial interactions between nanomaterials and PSA are key factors for property enhancement. **Table 1** shows different PSAs sub-families and their properties and **Table 2** summarizes PSAs extractions methods associated with its advantages and disadvantages, the purification methods as well as PSAs bioactivities.

Table 1. A summary of the PSAs and their properties together with discussion about benefits/consequences.

PSA family	Properties and applications	Refs.
Alginate	biocompatible/ionic crosslinking/cell delivery and 3D culture applications /strong anticoagulant properties	25, 30, 31
Pectin	achieved from plant cell walls/nontoxicity/biocompatibility	22, 25, 30
Pullulan	water solubility/nontoxicity/achieved from Aureobasidium	22, 25, 30
Dextran and hyaluronic acid	great biocompatibility/great water solubility	32
Gums	a cheap biomaterial/easily operable/usable for water treatment agent/biocompatibility	26, 32
Cellulose	biodegradability/biocompatibility/good mechanical properties/facile chemical modifications	33
Starch	poor mechanical properties/fragile/biodegradability/biocompatibility/	34
Chitin/chitosan	positive charge/solubility in acidic aqueous/pH responsive/electric sensitivity/magnetic sensitivity//biocompatibility	35

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Table 2. A summary of extraction and purification methods for PSAs as well as their bioactivities.

Extraction methods	**Advantage**	**Disadvantage**	**Refs.**
Hot water extraction	Facile operation, widely used and cost-effective	Low quality (in terms of purity), very time consuming and too repeated	36
Acid-base extraction	Short processing and fast rate	Too selective and hard controlling over the acid concentration	37
Enzyme extraction	High quality and purity, applicable in mild condition and fast speed processing	Enzymatic degradation byproducts, very high costs, high concentration of needed enzymes	38
Ultrasonic extraction	Widely used, facile, cost-effective, and low level of energy consumption	Possible alteration of PSA structural properties	39
Ultrahigh pressure extraction	Time saving and high yield	Not appropriate for the PSAs with high level of starch (carbohydrate)	40
Microwave extraction	Can be used for the thermally unstable PSAs and the most time saving technique	No possibility of large-scale production and possible degradation of PSAs under extraction process	41
Supercritical fluid extraction	No residue and a possibility to reuse the solvent	Complexity and high expenses	42
Purification	**Purification**		**Refs.**
Gel permeation chromatography	Anion Exchange chromatography		43
For PSAs with different molecular weights	For neutral and acidic PSAs		44
Bioactivities	**Bioactivities**	**Bioactivities**	
Antitumor activity	Anti-inflammatory activity	Immunomodulatory activity	
45	46	47	
Hypolipidemic activity	Hypoglycemic activity	Vascular protective activity	
48	49	50	
Antithrombotic activity	Ant obesity activity	Ant arteriosclerosis activity	
51	52	53	
Cryoprotective activity	Reno protective activity	Regulating gut microbiota	
54	55	56	
Antiviral activity	Neuro protective activity	Antibacterial activity	
57	58	59	
Prebiotic activity	Antioxidant activity	Whitening activity	
60	61	62	

2.1. Polysaccharide nanocomposites

Variety of synthetic polymers and biopolymers are eco-friendly and non-toxic. However, 'Nanotechnology' gives them another dimension for performance [63]. When it comes to nanocomposites, the addressed properties are extraordinarily of higher performance for appropriate tissue engineering, increasing drug release stability, gene delivery performance as well as antibacterial wound dressings [64-66]. Incorporation of nanoscale materials with high specific surface area and favorable inherent properties enhances the functionalities of PSA-

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based matrixes and enlarges their applications window. For example, PSA nanocomposites containing carbon nanotubes not only can be used as conductive hydrogels for nerve or cardiac tissue engineering, but also, reveal improved thermal stability. The combination of physicochemical properties of each component results in a nanocomposite with tunable properties, desirable for a specific application [67] . It is noteworthy to mention that utilization of these systems as drug delivery platforms is as sophisticated as it can be used for contact lenses to release desired drug within the eyes due to high stability of drug release profile [68-70].

The properties of the base PSA matrix can be enhanced *via* blending with synthetic polymers, which generally possess higher mechanical properties [71]. For example, chitosan was blended with poly(ε-caprolactone) prior to embedding with zinc-doped hydroxyapatite nanoparticles (Zn-HA). The obtained PSA-based nanocomposite benefits from biodegradation, appropriate cytocompatibility, bioactivity as well as mechanical properties (elastic modulus (3 times more than the controlled group) and tensile strength (1.5times more than the controlled group))[72, 73]. Some of the proposed biodegradable nanocomposite scaffolds serve excellent supports for cell attachment, spreading, growth, and ECM secretion. These scaffolds are so biologically compatible that can form cell sheets only within 14 days and the cells continue their metabolic activity up to 21 days [74]. On the other hand, blends of PSAs with proteins (as matrix) before the addition of nanomaterials can be used to adjust the degradation profile, thermal stability, bio-interface characteristics, and release behavior of PSAs. Some suggested a nanocomposite scaffold from chitosan nanoparticles and gelatin (the added protein) using gelation method. They loaded the basic fibroblast growth factors (bFGFs) within the scaffold and their results indicated that sustained release of bFGFs is possible. Such a system is invaluable to be used as tissue regeneration platform that requires vascularization such as wound healing platforms [75]. Similarly, Shokrani et al. reported that combination of gelatin and chitosan is a strong natural platform for improving angiogenesis density and tissue regeneration [76]. In some studies, PSAs have been utilized as the particles to enhance the cytocompatibility of graphene oxide nanostructures (GO) and to decrease its toxicity. For instance, a nanocomposite made of GO nanostructures/hyaluronan/chitosan with great cell adhesion and protein absorption properties has been suggested by Andreeva et al [77]. Their results revealed that in addition to unique thermal and mechanical properties, a range of platelet adhesion quality and thrombosis (74%) can be obtained using the mentioned platform [77]. Additionally, incorporation of some PSAs with silver (Ag) nanoparticles brings antibacterial properties for the nanocomposite scaffolds. For example, Chitlac (as a kind of PSA film) combined with Ag nanoparticles destroys *P.*

aeruginosa and *S. aureus* bacteria, for tooth tissue engineering applications [78]. Remarkably, Halloysite nanotubes (HNTs) and silica nanoparticles are promising nanostructures for wound healing applications, owing to exceptional mechanical stability as well as hemostatic features [79, 80]. Combination of HNTs and chitosan not only hinders bleeding, but also supports faster reepithelization [81].

2.2. Stimuli responsive polysaccharides

Different stimuli have been introduced to obtain the desired response from smart PSA nanocomposites. Almost all PSAs are responsive to pH and ions. However, there are some differences in responsiveness of PSAs in terms of their chemical structure and functional groups. For instance, chitosan is specifically responsive to electrical fields and glucose, which is a necessity in developing biosensors for diabetic patients. The mechanism of insulin delivery using glucose responsive chitosan is shown in **Figure 2** [35, 82]. On the other hand, alginate is responsive to the light and surfactants. **Table 3** summarizes the most frequent stimuli responsive PSAs. Many smart PSA nanocomposites may respond to physical stimuli like temperature, light, electricity, magnetic field or even pressure, while some others may respond to chemical species such as reactive oxygen species (ROS), redox species (e.g., glutathione), glucose, enzymes, and some ions (e.g., calcium). Among the chemical stimulus, glucose is the most prevalent one (**Figure 2**). Of note, incorporation of nanoparticles into PSAs may considerably change or get worse their responsiveness ability/mechanism.

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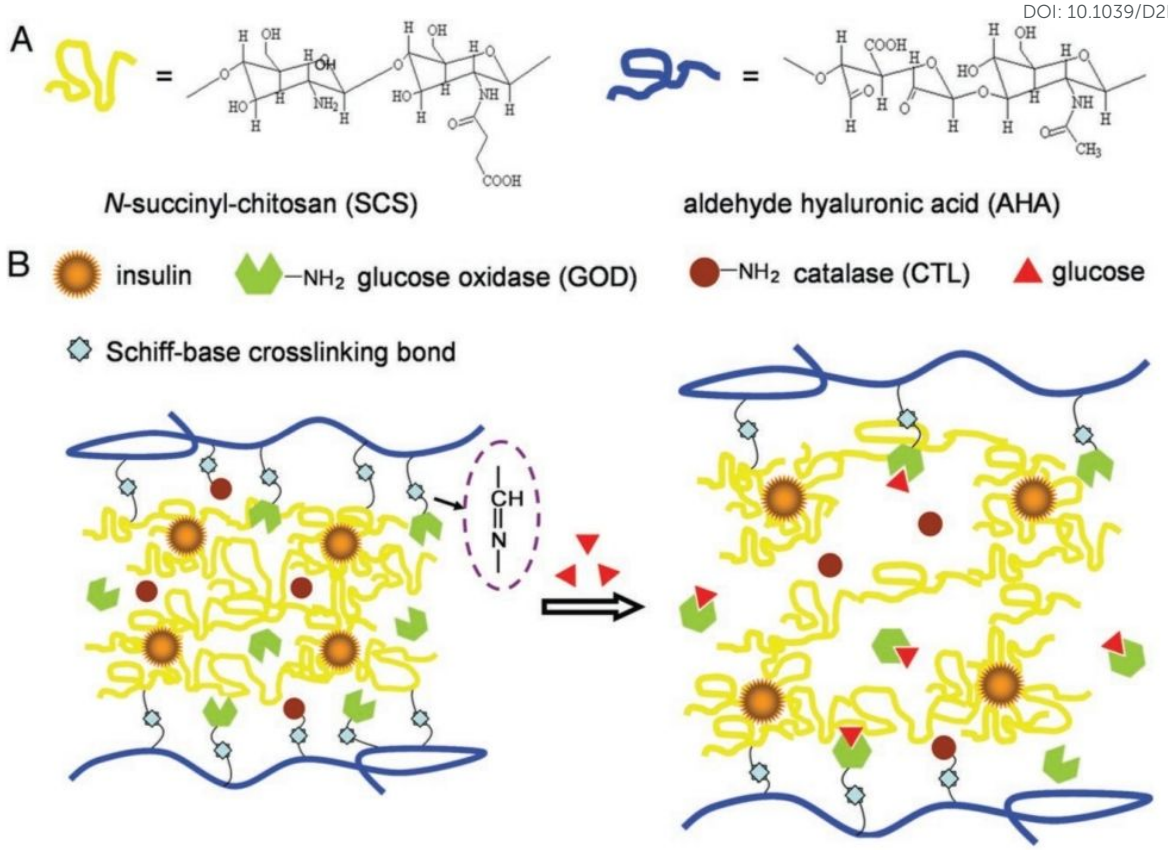

Fig. 2. (A) The chemical structure of chitosan and hyaluronic acid-based composite. **(B)** mechanism of glucose-responsive PSA hydrogel for delivery of insulin [83].

Table 3. A summary of the more frequently used stimuli-responsive PSAs, stimuli, their resources, and molecular weights.

Polysaccharide	Molecular weight ranges (Da)	Abundances	Responsiveness	Refs.
Chitosan	3.8×10^3 to 9×10^6	Exoskeleton of crabs and shrimps, and cell walls of fungi	Ions, pH, electrical field, glucose	84
Alginate	10^4 to 6×10^6	Cell walls of algae	Ions, pH, electrical field, surfactants, light	85
Heparin	3×10^3 to 3×10^4	Mucosal tissues	Ions, pH, redox	86
Hyaluronic acid	5×10^3 to 2×10^7	Extracellular matrix, epithelial and neural tissues	Ions, pH, electrical field, light, temperature, and redox	87
Cellulose	3×10^3 to 4×10^6	Microbes	Ions, pH, and temperature	88

Some PSAs such as chitosan, have basic amine groups, which results in pH responsiveness behavior. pH responsiveness of chitosan-based nanocomposites stem in protonation of amine groups under acidic conditions [89, 90]. Interestingly, Protonation of amine groups is the responsible driving force for its solubility in acidic aqueous media. In some cases, two or more different stimuli are introduced to take advantages of their synergistic effects. For instance, chitosan indicates both pH and electric sensitivity within an electric field, which enables one to make dual responsive biomaterial [35]. To add magnetic sensitivity to the scaffold, addition of magnetic nanoparticles to PSAs (like cellulose) seems to be a promising solution. It can be utilized for delivery of therapeutic drugs into a specific tissue or organ through directing of carriers with the aid of a magnetic field [91]. Moreover, according to Liu et al., addition of phenylboronic acid is one way to sensitize the scaffold to glucose [92]. Akbari et al. reported that combination of carboxymethyl cellulose and zinc oxide nanoparticles brings about a pH sensitive nanocomposite which is the result of synergistic effects of cellulose responsiveness as well as zinc oxide sensitiveness [93, 94]. Moreover, incorporation of acrylic acid and *N*-isopropyl acrylamide (NIPAM) with chitosan results in dual responsive scaffolds that respond to both pH and temperature fluctuations. This smart system has been utilized for doxorubicin (DOX) release for cancer therapy [95]. Collaboration of chitosan and (3-amino propyl) triethoxy silane is another smart pH/temperature-responsive platform for curcumin delivery in cancer treatment applications. In a molecular view, when pH or temperature increases, a higher swelling ratio leads to water penetration into the structure which can finally affect the drug release pattern [96]. A dual responsive nanocomposite platform based on aminated nano dextran and carboxylate nanocellulose containing GO nanoplatelets was used for pH and near-infrared (NIR) sensitive delivery of curcumin. To the best of our knowledge, such a system can be an inspiring option for bioimaging applications (because of being sensitive to NIR) [97]. Generally speaking, dual responsive nanocomposites (especially hydrogel nanocomposites) can be chiefly assorted to pH/temperature sensitive systems, pH/redox platforms, pH/electric field scaffolds, temperature/light systems, as well as pH/glucose nanocomposites [35].

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3. Generic applications of polysaccharides in biomedical engineering

3.1. Drug delivery

Drug delivery systems (DDSs) that target specific tissue or cells and release therapeutics in a sustained and controlled manner have attracted much interest in the biomedical fields [16, 98, 99]. Targeted DDSs for cancers enable to carry drug molecules to tumor cells, while ignoring healthy cells/tissue such that adverse side effects are minimized. Various PSAs have been utilized as constituents of delivery platforms formulation, since they benefit from advantages such as biocompatibility and low immunogenicity [100-102]. On the other hands, the nanotechnology strategies (such as making different nanostructures including nanoparticles, nanosheets as well as nanofillers) have always played crucial roles in development of DDSs [103]. Evolvement of biocompatible and stimuli-responsive PSA-based nanocomposites enable both passive and active targeting drug delivery benefiting from small dimensions and responsiveness [104, 105].

On the other hand, PSA-based nanocomposites (e.g. nanogels) can be decorated with targeting ligands to target specific receptors on the cell membrane (e.g., CD44 which is a cell surface glycoprotein [106, 107]). Remarkably, chemical modification strategies provide robust tools for conjugation of targeting moieties such as nanobodies [108]. In the PSA-based nanocomposites, the presence of accessible reactive functional groups, e.g. amines, enables facile and effective chemical functionalization. Brain targeting drug delivery is a good example of this case [109]. Although there are plenty of barriers in terms of biological or physical obstructions, nano-based DDSs can circumvent many of these barriers. These systems exhibit high capacity to carry various drugs (e.g., anticancer drugs, Alzheimer's medications) to the brain. Interestingly, they not only support sustained drug release which brings about a stable release profile, but also decreases the level of toxicity of administrated drug, especially when the drug has low water solubility [79, 110-112].

PSAs are great options among the existing biomaterials and their combinations with graphene-derivatives (as nanocomposites) can be a perfect recommendation to reduce the toxicity, increase the targetability, and accelerate their release efficacy. Moreover, this class of carriers can be responsive towards external stimuli such as NIR light or internal stimuli like pH and some ions [113]. Combination of HNTs with PSA is a novel platform to prime nanocomposites for drug delivery aims, which roots in their perfect super molecular interactions and mesoscopic features. Moreover, miscellaneous active molecules can be loaded within the

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HNTs and their ultimate characteristics can also be controlled by fabrication methods and modification strategies [79]. Additionally, PSAs can be a nanoscale component of another matrix. Noteworthily, the final release rate has a lot to do with biomaterial's molecular weight, constituents' ratios, crosslinker type, crosslinker concentration as well as drug curing time [114]. The applications of PSA-based delivery systems can be further expanded to theragnostic platforms that enable both delivery of therapeutics and imaging of internal body parts [115].

3.2. Gene delivery

Gene therapy is a novel treatment methodology for various diseases such as osteoarthritis or even cancer. This is why devising safe, practical and targeted gene carriers is crucial in biomedical engineering. PSA-based nanocomposites are among the existing options with exceptional ability in marker expressions. For instance, they prim a great media to support expression of early and late bone markers with bone marrow stem cells even in an environment that lacks osteo-inducive factors [116-119]. As another instance, Patnaik et al. proposed an interesting delivery system for siRNAs delivery, consisted of polyethylenimine (PEI) nanoparticles, alginate, alginic acid, and polyethylene glycol (PEG). PEG shell enhances the blood circulation and enables the DDS to evade the immune cells, while the cationic PEI nanoparticles enable gene transduction across plasma membrane and alginate increases the compatibility of the whole system. Their results revealed that the flexible structure with positive charge can easily interact with negative charge of cells' membrane [120]. However, the possibility of enzymatic degradation in this creative system can be alarming. After years, further studies demonstrated that surface coating of dopamine will postpone the enzymatic degradation which is very important in delivery systems, especially the sustained ones (that need to follow prolonged release pattern) [121]. Additionally, chitosan-*g*-polyethylene glycol nanocomposite is suggested for sustained delivery of genes with a great optimized circulation time in a rat model [122]. Utilization of hyaluronic acid and chitosan nanocomposite is a great platform for plasmid DNA delivery to corneal with great cytocompatibility toward corneal epithelial cells [123-127]. As another example of gene delivery using PSAs, Kashkouli et al. took advantages of chitosan nanocarriers, organosilane modified 5-amino-1H-tetrazol and Fe_3O_4 combination for plasmid delivery. Their results indicated an increase in gene expression for HEK-293T cell line (human embryonic kidney cells) for cancer therapy. Their assessments revealed that the percentage of transfected cells within magnetic field is three times more that the transfection without inducing any magnetic field (A 45% transection in magnetic field compared to 15% without field) [128]. Likewise, different types of chitosan-based nanostructures

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as a non-viral gene delivery vector have been investigated. In a typical study, pCRISPR (a family of DNA sequences) was selected as the gene, and different combinations of calcium nanoparticles along with chitosan were selected as the promising non-viral gene delivery vectors (**Figure 3**). The results showed that after the addition of different weight ratios of chitosan to the calcium and calcium phosphate nanoparticles, the zeta potential increased considerably and leads to considerable interactions with the pCRISPR [129]. Elsewhere they demonstrated that by addition of these PSAs to the nanostructures (nanocarriers), even highly toxic nanocarriers like $(ZnO)_x(GaN)_{1-x}$, the relative cell viability as well as the biocompatibility and biodegradability could be increased considerably on different cell lines leading to considerable and successful drug/gene delivery to the targeted tissues/cells [130]. **Table 4** has gathered various nanocomposite scaffolds that endorse drug/gene delivery.

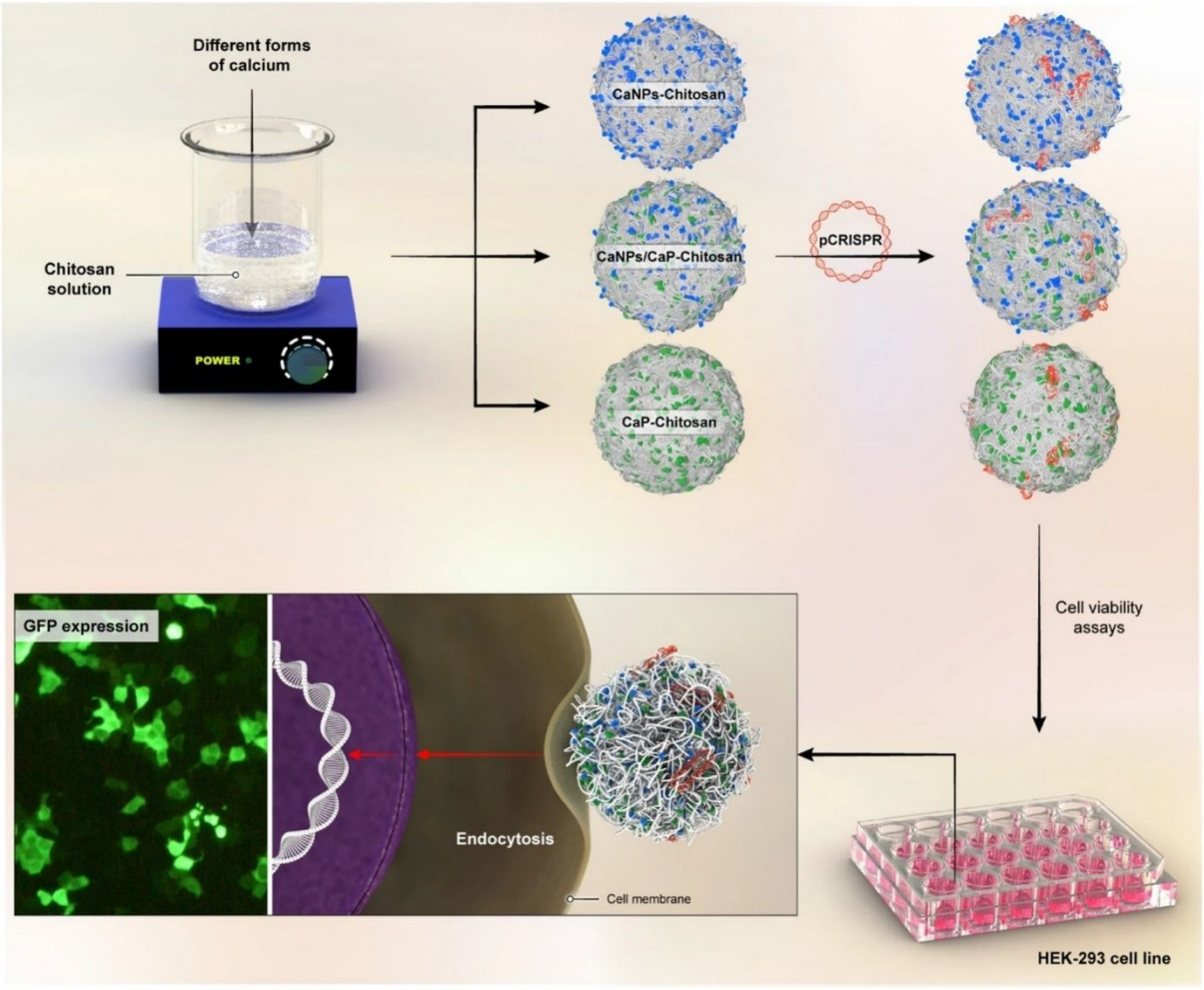

Fig. 3. A schematic illustrations on the preparation of nano-blends of chitosan and different calcium corms for the pCRISPR delivery on the HEK-293 cell lines [129].

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Table 4. A summary of nanocomposite scaffolds based on their based PSAs, other constituents and their outstanding features for drug/gene delivery).

Base Polysaccharide	Nano additive(s)	Payload	Comment	Refs.
Chitosan	Amino propyl silane nanoparticles	Metformin	An abrupt release within 22hr and the rest of that in 15days	131
	Zinc oxide nanoparticles	Naproxen	Great cytocompatibility for human dermal fibroblast cells with antibacterial activities	132
	Solid lipid nanoparticles	Atorvastatin	98% membrane degradation percentage after 5days/ 75-79% percentage of drug release	133
	GO sheets	5-FU	A great option for PH sensitive drug release	134
Cellulose	HNTs	Vanillin	A great option for antimicrobial or flavor release even in food industry or biomedical application	135
	Cupper (II) oxide nanoparticles	NPX	Excellent antibacterial properties and great swelling behavior for colon drug delivery	136
Starch	Sericin nanofibers	Doxorubicin	High capacity of drug encapsulation/great stability and biodegradability	137
Hyaluronic acid	Polyethylene glycol nanoparticles	Plasmid	Slightly increase of liver toxicity /24-96 h release time without polyethylene glycol	122
Chitosan	Fe_3O_4 nanoparticles	Plasmid	An increase in gene expression for HEK-293T cell line for cancer therapy	128

3.3 Polysaccharide nanocomposites as antibacterial platforms

Preparation of antibacterial and antimicrobial platforms has numerous merits not only in biomedical applications, but also in food industry. Antibacterial scaffolds can be utilized for different applications ranging from hemostasis agents and wound dressings [138] to bone tissue engineering [139] and food packaging [140]. PSA-based nanocomposites with excellent antibacterial activities toward *Escherichia coli* [141, 142] and *Staphylococcus aureus* [138, 143] play an essential

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role in this field. However, their nanocomposites are preferred because of the fact that some nanomaterials have strong antibacterial properties by themselves (such as silver and zinc oxide nanoparticles) and form a great platform with PSAs [144-147]. For example, Anugrah et al. reported that combination of zinc oxide nanoparticles with PSAs can accelerate the food life time due to hindering microbial activities. According to them, zinc nanoparticles increase the oxidative stress which harms the bacteria cell wall. Synergistically, Zn^{+2} release can penetrate the bacterial cell membrane and endanger their life [148]. **Figure 4** shows the mechanism of action of antibacterial activities of zinc oxide and a PSA-based stimuli responsive nanocomposite fabrication process [136, 148].

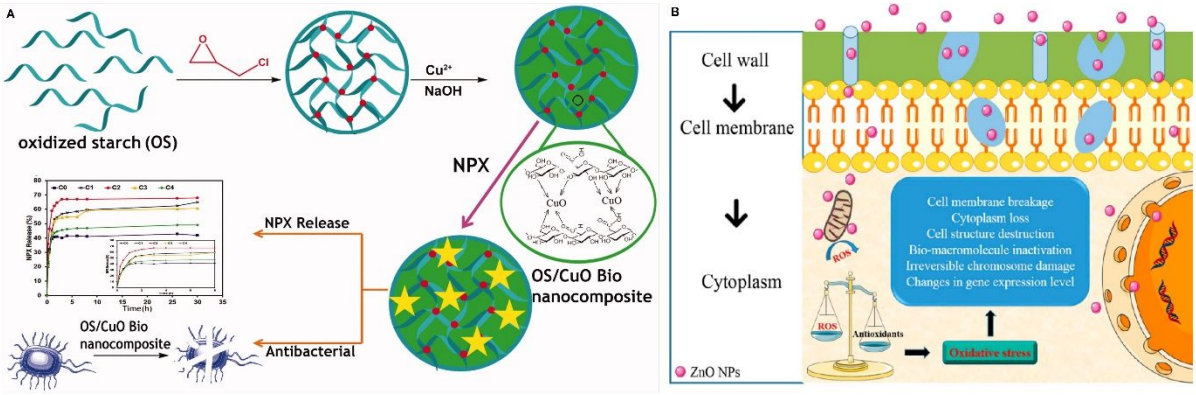

Fig. 4. Illustration of antibacterial mechanisms of two different scaffolds. **(A)** Shows a scaffold used for drug delivery with great antibacterial properties consisted of oxidized starch and cupper (II) oxide. **(B)** Shows the mechanism of action of antibacterial properties for zinc oxide [136, 148].

Noteworthily, nano-hydroxyapatite, chitosan and Trigonella foenum-graecum can form a nanocomposite (using co-precipitation method) with a very low hemolysis (below 4%), great compressive strength (6.7 MPa), excellent compressive modulus (100 MPa) as well as high antibacterial activities [149]. Interestingly, Lu et al. demonstrated that hydroxypropyl chitosan, lonely, has strong biocompatibility and antibacterial performance. However, the assigned biomaterial was not able to easily endorse desired mechanical properties. Hence, combination of nano hydroxyapatite with hydroxypropyl chitosan and genipin (as a crosslinking agent) brought about an improvement in compressive strength (from 19.1 KPa to 52.8 KPa with increasing the amount of nano hydroxyapatite) and capacity of fluorescence emission [150]. Moreover, to induce antibacterial activity toward *Staphylococcus aureus* and *Escherichia coli* using chitosan-based nanocomposite, polyethylene oxide nanofibers were loaded with an optimized amount of zeolitic imidazolate framework-8 nanoparticles [138, 143]. As it is above-

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mentioned, when Ag nanoparticles are constituents of a nanocomposite, a perfect level of antibacterial activities is observed. For instance, Shariatinia et al. demonstrated that a promising nanocomposite from chitosan, phosphor amide as well as Ag nanoparticles will leave a crucial antibacterial trace on two kinds of gram positive bacteria and two kinds of gram negative bacteria, simultaneously [151]. **Table 5** summarizes different kinds of scaffolds with PSA and their constituents, fabrication method, and their antibacterial features.

Table 5. A summary of different kinds of antibacterial scaffolds with PSA based and their constituents, fabrication methods, and their features.

Base Polysaccharide	Nano additive(s)	Fabrication method	Main findings	Refs.
Chitosan	Nano-hydroxyapatite	Co-precipitation method	Great capacity of water and protein absorption *via* the porous structure/excellent antibacterial properties/good choice for bone engineering	149
Chitosan	Nano hydroxyapatite	Co-precipitation	High antibacterial activity due to presence of Hydroxypropyl chitosan/good swelling ratio as well as fluorescence emission (as an unique feature)	150
Chitosan	Polyethylene oxide nanofiber mats/zeolitic imidazolate framework-8 nanoparticles	Electrospinning technique	Antimicrobial activity/antibacterial activity against Staphylococcus aureus and *Escherichia coli*	143
Chitosan	Polyethylene oxide nanofibrous mats/bioactive silver nanoparticles	Electrospinning technique	Antimicrobial activity/antibacterial activity against staphylococcus aureus and Escherichia coli/great option for wound dressing applications	138
Chitosan	Silver nanoparticles	Citrate reduction method	Excellent antibacterial activities against 2 kinds of Gram+ and 2 kinds of Gram- bacteria and the more Ag nanoparticle brings about higher antibacterial property	151
Gum	Nano-hydroxyapatite	Co-precipitation approach	Excellent mechanical properties (like compressive strength and compressive modulus)/great capacity of protein adsorption with nice ability to swell/powerful antibacterial properties/good choice for bone tissue engineering	152

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3.4. Polysaccharide nanocomposites as hemostasis agents

PSA-based nanocomposites are repetitively used as hemostatic platforms [153]. Great biocompatibility, intrinsic antibacterial features (chitosan) and natural hemostasis performance (chitosan, cellulose, oxidized cellulose, carboxymethyl cellulose) are the reasons behind the usage of PSAs as blood clotting biomaterials [154]. Importantly, they must be able to be excreted from the body by natural mechanisms (such as enzymatic degradation), especially if injected to the internal parts of body (such as liver [155]). So, high biodegradability of PSA-based nanocomposites is of a great importance. Addition of nanomaterials not only gives antibacterial and drug delivery properties to such systems, but also intensifies coagulation pathways and enhances interactions of the anti-bleeding agent with wounded tissue [156, 157]. In this regard, HNTs, bioactive glasses, and silica nanoparticles are the most frequently used nanoparticles that all own hemostatic performance. Combination of PSA with the mentioned nanomaterials will strongly increase their cytocompatibility as well as their hemostasis efficacy. Also, it helps regulating wound moisture and faster healing [158].

4. Advanced applications of polysaccharides in biomedical engineering

4.1. Tissue engineering

4.1.1 Skin tissue engineering

Skin plays an essential role in preserving body from assailing stimuli that come from outside. As the largest organ, it has a great control over heat and water loss [159-161]. There are two main approaches to rescue a damaged skin. Autografts and allografts are the practical approaches for saving highly injured skin (for instance a high percentage burnt skin), but they may cause immune response as morbidity [162, 163]. Hence, tissue engineering seems to be a perfect approach to heal tissue damages as an alternative for the natural skin [164]. In addition to owning good mechanical properties (skin stretching ratio is 70% which is drastic), appropriate biomaterials for skin scaffolds fabrication have to support cell attachment, growth, proliferation, differentiation, and migration; besides, enable cell-cell signaling (fibroblasts, keratinocytes as well as melanocytes as the foremost three types of skin cells) as well as the minimum possible immunogenic response [165-168]. A wide variety of PSA based biomaterials and nano-additives are reported owning good mechanical and biological properties [169]. Among various biomaterials that can be utilized for skin tissue engineering, PSAs are great potent options.

Although hydrophilicity is crucial in all biomaterials used in tissue engineering, it is underscored for skin scaffolds [170-172]. PSA-based nanocomposite can be referred to as a great biodegradable 3D structure to entrap large amount of water [173]. Also, there are plenty of reports on PSA-based nanocomposites simulating biological and mechanical properties of human skin for tissue regeneration purposes. For instance, composition of copper nanoparticles with chitosan and gelatin (using freeze drying method) is reported as a great scaffold for skin tissue engineering. Their result showed that in spite of enhanced physio-chemical properties (about 91% porosity), no negative effect was observed on cell behaviors (adhesion to scaffold or cell proliferation) after addition of cooper nanostructures and also, no negative influence on ROS production was revealed [174]. Combination of chitosan with bacterial cellulous and medical grade nano-diamonds (using electrospinning method) is another good example of scaffold for skin regeneration. The results indicated that scaffold strength increased from 13 to 25 MPa after addition of only 1 wt.% medical grade nano-diamonds without any damage to biological properties (up to 90% cell viability). They demonstrated that easier electrospinning process is another benefit of this combination with highly diminished size of fibers (80 nm) [175]. Ultimately, it is worth it to mention that chitosan-based nanocomposites [174], cellulose-based nanocomposites [176, 177], and gum-based nanocomposites [178-180] are the most widely used PSAs in skin engineering field. In addition to skin tissue engineering, wound healing can be referred to as another challenging fields. PSAs are also reported as practical structures in wound healing process [181, 182]. Typically, a natural PSA, like calcium alginate, comprises d-mannuronic and l-guluronic acid and plenty of calcium ions, which upregulate the glycosaminoglycan (GAG) activities. GAG is a kind of ECM molecule not only responsible for fibroblast production, but also for cell-cell and cell-matrix interactions. Therefore, upregulation of GAG can bring about improved interactions and more fibroblasts production, which itself helps the wound healing process as well as skin regeneration [183].

4.1.2 Bone tissue engineering

There are plenty of studies that have suggested PSA-based nanocomposites with chiefly acceptable performance and functionality. Therefore, tissue engineering has considerably contributed to progression in this field [119, 184-188]. However, the proposed scaffold has to own some features like preparation of a good media for cell differentiation, great cell attachment as well as desired mechanical properties (mechanical properties are underscored in bone

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engineering and even some times antibacterial activities are needed [139]). Anionic PSAs are outstanding considering the fact that GAGs (Glycosaminoglycans as the actual components of ECM) endorse cell signaling capability. In this regard, an inspiring platform was firstly suggested by Fricain et al. Natural hydrophilic pullulan combined with nanocrystalline hydroxyapatite particles are proposed as great structure to induce bone marker expression. Moreover, supportive behavior of this scaffold brought about Morphogenetic Protein 2 expression. Hence, the mentioned scaffold could mimic the demanded media for mesenchymal stem cells differentiation, which is practical in surgical procedures [116]. To enhance the mechanical properties similar to the real bone, combination of chitosan, chondroitin sulfate as well as hydroxyapatite was examined utilizing freeze drying method. The obtained nanocomposite endorses osteoblast cells growth and osteoblasts adhesion along with good mechanical properties [189]. However, without the presence of different nanostructures (organic, inorganic, and polymeric) near the PSA matrix, improving the mechanical features [190-192] was completely impossible.

4.1.3 Nerve tissue engineering

Nerve regeneration is reported as a sophisticated biological process that needs nerve gap bridging utilizing autologous grafts, which are a few by number of donors [193]. Other issues like non-functionality after the surgery as well as immune rejection of graft can be pointed out [194]. To prim some alternatives, tissue engineers propose some options. For instance, fabrication of appropriate scaffolds to host stem cells with differentiation capability is of demand. In this regard, polymeric nanocomposites seem to be really appealing due to their controllable features and electro conductive behaviors [195] (electroconductivity in nerve grafts is important [195]). Suitable scaffolds should also support cell attachment, differentiation, and growth because they simulate the real extracellular environment, which is demanded by nerve cells [196]. Among various biomaterials that can be utilized, PSAs are highly potent options. There are studies that have used PSA-based nanocomposites to emulate nerve autologous. Among all, chitosan-based nanocomposites [197-205] are the most frequent ones. To name but a few, Karami et al. utilized electrospinning method to fabricate a scaffold consisted of poly(hydroxybutyrate) nanostructures and chitosan, which is reported as a suitable nerve graft. Their results indicated that this biocompatible scaffold is highly hydrophilic and owns great mechanical/electrical and morphological properties similar to the real nerve [199]. Manzari et al. constructed a scaffold

consisted of polypyrrole (PPy), alginate and chitosan-based nanoparticles in which they utilized oxidative polymerization method to synthesize PPy. Their findings revealed that the fabricated scaffold is a great option for nerve engineering due to electrical conductivity (2:10 ratio of pyrrole and alginate) and the nice condition that scaffold prims for neural or fibroblast cells activation and proliferation 72hr after cell culturing [201].

4.1.4 Cartilage tissue engineering

Cartilage self-repair is a certain issue (because of very high mechanical properties (8.3 MPa tensile strength) and very low repair rate (due to lacking vascular network)) and the engineered alternative scaffolds must have specific and unique features [206]. Plenty of tissue engineers felt arduous task to fabricate a qualified scaffold for this target. PSA-based nanocomposites are proper options because of the biocompatibility and good mechanical properties inherited from embedded nanomaterials and/or acquired chemical crosslinking. Moreover, their similarity to the real tissue media (i.e., the ECM) make them more outstanding [207, 208]. Scientists did their best to fabricate a scaffold from multi-walled carbon nanotubes and poly (3-hydroxybutyrate) (PHB)-chitosan to exploit the desired mechanical properties similar to a real cartilage. The resulting scaffold not only supports chondrocyte adhesion and growth, but also owns excellent hydrophilicity and tensile strength due to the addition of carbon nanotubes to chitosan (8MPa yield strength and 20% elongation at break) [209]. Among other suitable nanostructure to be combined with PSAs, nano-hydroxyapatite plays important role. Using freeze-gelation method, a nanocomposite hydrogel from chitosan, collagen and nano-hydroxyapatite was fabricated with low cost and Young's modulus of 80–800 kPa, closely similar to modulus of cartilage [210]. **Table 6** summarizes different kinds of PSA based scaffolds with their constituents, fabrication methods, main findings as well as the targeted tissue.

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Table 6. A summary of different kinds of scaffolds with PSA based and their constituents, fabrication methods, main findings as well as the targeted tissue.

Base Polysaccharide	Nano additive(s)	Target tissue	Fabrication method	Main findings	Refs.
Chitosan	Gold nano particles	Bone	Tilting method/WAXS and UV-VIS techniques	Highly cytocompatible toward normal kidney epithelial cells/epithelial colorectal adenocarcinoma/positive human cervical tumor/and murine macrophage cells	211
Chitosan	Nano hydroxyapatite	Bone	Freeze-drying technique	Great condition for osteoblast cell adhesion/proliferation and growth	189
Chitosan	Nanohydroxyapatite	Bone	Combination of freeze-drying with a foaming agent method	Great hydrophilic media that endorses protein adsorption/great support for fibronectin binding/good osteoblast adhesion/great osteoblast proliferation	212
Chitosan	Hydroxyapatite nano crystallites	Bone	Coprecipitation procedure	Excellent compressive strength/ great condition for osteoblast proliferation	213
Chitosan	Methacrylated silk fibroin micro/	Cartilage	Photocrosslinking method	Excellent compressive modulus/ a great cytocompatibility for mouse articular chondrocytes	214
Chitosan	Alumina nanowires	Cartilage	Electrospinning method	High porosity/great hydrophilicity /Chondrocyte cytocompatibility	215
Chitosan	Nano-hydroxyapatite	Cartilage	Freeze-gelation method	Low-cost preparation/Young's modulus of 80–800 kPa	210
Chitosan	β-tricalcium phosphate nanoparticles	Cartilage	Sol-gel method	Good degradation rate/hydrophilicity/porosity	216
Chitosan	Multi-wall carbon nanotubes	Cartilage	Electrospinning method	Weak mechanical properties without carbon nanotubes and enhanced mechanical features after addition of carbon nanotubes	217
Chitosan	Multi-walled carbon nanotubes	Cartilage	Electrospinning method	High tensile strength/Chondrocyte cytocompatibility	209
Chitosan	Graphene nano-sheets	Nerve	Solution casting method	Excellent electrical conductivity/ great cell proliferation after 72 hours	197
Chitosan	Polycaprolactone and chitosan nanofiber	Nerve	Electrospinning method	Excellent condition for mesenchymal stem cells differentiation to neuron-like cells	205
Chitosan	Chitosan-based nanoparticles	Nerve	Oxidative polymerization method	Great electrical conductivity/ nice condition for neural or	201

				fibroblast cells activation and proliferation	
Chitosan	Poly(hydroxybutyrate) nanostructures	Nerve	Electrospinning method	Great hydrophilicity and mechanical properties similar to nerve tissue	199
Chitosan	Copper nanoparticles	Skin	Freeze-drying method	In spite of enhanced physico-chemical properties, no effect was observed on cell behaviors (adhesion to scaffold or proliferation) after addition of cooper, no influence on ROS production	174
Chitosan	Medical grade nano-diamonds	Skin	Electrospinning method	Scaffold strength increase from 13 MPa to 25 MPa after addition of only 1 wt % MND /easier electrospinning process / diminished size of fibers	175
Chitosan	HNTs	Skin	Simple solid liquid interaction technique	Reepithelization and reorganization of fibroblast cells/ great capacity for wound healing	218
Chitosan	polystyrene sulfonate nanofibers	Cardiac	Electrospinning method	Great mechanical properties/electrical conductivity /increasing the tensile strength only with addition of 1 wt% of synthetic polymers	219
Chitosan	SrAl2O4: Eu2 +/Dy3 + nanophosphor	Eye	Sol-gel method	Promising growth and differentiation of Recognized retinal progenitors within the scaffold	220
Cellulose	HNTs	Bone	Freeze-drying technique	Injectability in various conditions	221
Cellulose	Nano-hydroxyapatite	Bone	Free radical polymerization	Great compressive strength and elastic modulus consistent with bone tissue	222
Cellulose	Nano hydroxyapatite	Bone/cartilage	Freeze-drying technique	Excellent cytocompatibility toward wide range of cells (osteosarcoma cells, human articular chondrocytes as well as human adipose-derived mesenchymal stem cells)	223
Cellulose	Cellulose nanofibers	Cartilage	Freeze-drying technique	High porosity (95%)/high compression moduli=1Mpa/great similarity with natural cartilage due to viscoelasticity behavior	224
Cellulose	Cellulose nanocrystals	Skin	Electrospinning technique	Great cytocompatibility toward 3T3 Fibroblast cells/ great hydrophilicity	176
Cellulose	Bacterial cellulose nanofibers	Skin	Colorimetric method/Shindai extraction method	Support for adhesion of keratinocyte cells/skin fibroblast cells	177
Guar gum	poly (ε-caprolactone) nanofibers	Skin	Electrospinning method	Great elongation and tensile strength similar to skin tissue	180

Guar gum	gum arabic nanofibers	Skin	Electrospinning method	Elongation and tensile strength similar to skin tissue/antibacterial activity/support for L929 cells proliferation	179
Guar gum	gum arabic nanofibers	Skin	Suspension, two-nozzle and multilayer electrospinning	Appropriate fibroblast cells adhesion and proliferation	178
Alginate	GO nanosheets/nanohydroxyapatite	Bone	Freeze-drying process	Great compressive strength similar to bone/low rate of biodegradation/cytocompatibility for MG-63 bone cells	225

4.2. Polysaccharide nanocomposites for cell encapsulation

Nanocomposite hydrogels are highly examined as platforms in which cells can be encapsulated and protected from high shear forces and successfully delivered to the aimed region. One approach is to add 2D or 3D nanomaterials to the PSAs in order to make them strongly interacted and accelerate their shear thinning behavior [226, 227]. As an instance, 2D nano-silicate reinforced kappa–carrageenan (κCA) hydrogel was prepared in order to give it shear thinning characteristics, higher mechanical stiffness, elastomeric properties, and physiological stability. Scientists utilized this new platform for delivery of human mesenchymal stem cells and their analysis demonstrated the high cell viability (85% cell viability) (**Figure 5**). This study seems to be promising for cell delivery aims (such as cartilage tissue regeneration systems) as well as 3D bioprinting [228]. In this regard, utilization of stimuli-responsive PSAs (such as chitosan) will also endorse the possibility of 4D printed scaffold fabrication for cell encapsulation (4D printed scaffolds have the ability to deform and change the release pattern as a function of time, which is of a great importance, if needed [229]). Another study reports successful encapsulation of ATDC5 cells **(**mouse teratocarcinoma cells**)** within a Xanthan gum-based micro-scale system (Xanthan gum is a high weight type of PSA) and their results suggested that their PSA-based platform can preserve the cellular metabolic activities up to 21 days after incubation with a great level of viability, shear-thinning and gelling behaviors [21]. Additionally, a sort of pH-responsive (responsive to the pH less than 4.2) PSA nanocomposite consisting chitosan (CS), and oxidized hydroxypropyl cellulose (HPC) nanofibers with great mechanical property and 49 s gelation time, shows a perfect stable network for high percentage delivery of stem cells. Their analysis could demonstrate a promising stability, cytocompatibility (more than 93%) as well as biodegradability (after 15 days at 37 C°) [230].

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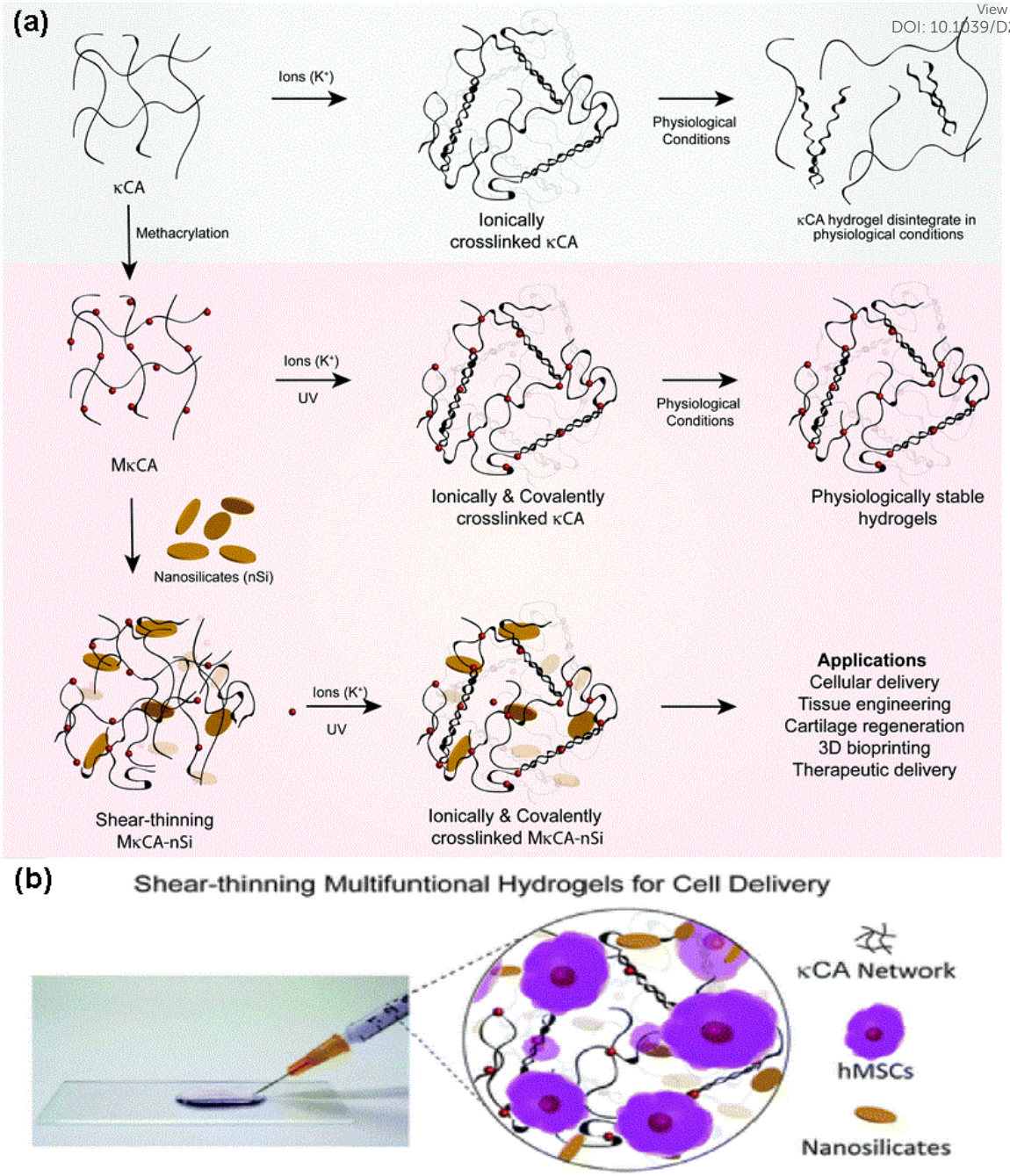

Fig. 5. (A) The illustration of the synthesis process of a hydrogel with PSA base (kappa–carrageenan (κCA)) using potassium ions coated with nano-silicates, which gives it shear thinning properties and bioactive features. **(B)** Encapsulation of human mesenchymal stem cells within the synthesized network for cell delivery applications [228].

4.3. Polysaccharide nanocomposites for cancer diagnosis and treatment

Some PSAs or chemically-modified PSAs possess inherent bioactivities for cancer early diagnosis and therapy. The effectiveness of PSA-based nanocomposites for cancer emanates from embedded nanomaterials. For example, gold nanoparticles with NIR-absorbing properties, can be incorporated to PSA nanogels for photothermal therapy (PTT) of various

cancers. As another instance, nanometals incorporated with PSAs create great platforms for selectively targeting tumor cells (**Figure 6**) [231, 232]. Another study demonstrated that combination of gold nanoparticles and immune-active PSAs can successfully enhance the dendritic cell and T cell activation in parallel with inhibition of tumor growth and metastasis when loaded with doxorubicin [233]. In addition to the mentioned examples, surface biofunctionalization of graphene with PSAs can be employed for cancer diagnosis and treatment due to increased water solubility, drug capacity, large surface area and photo thermal properties. These systems are promising owing the fact that they underline the cancer cell responses to internal and external stimulus, which help us trap cancerous cells [234].

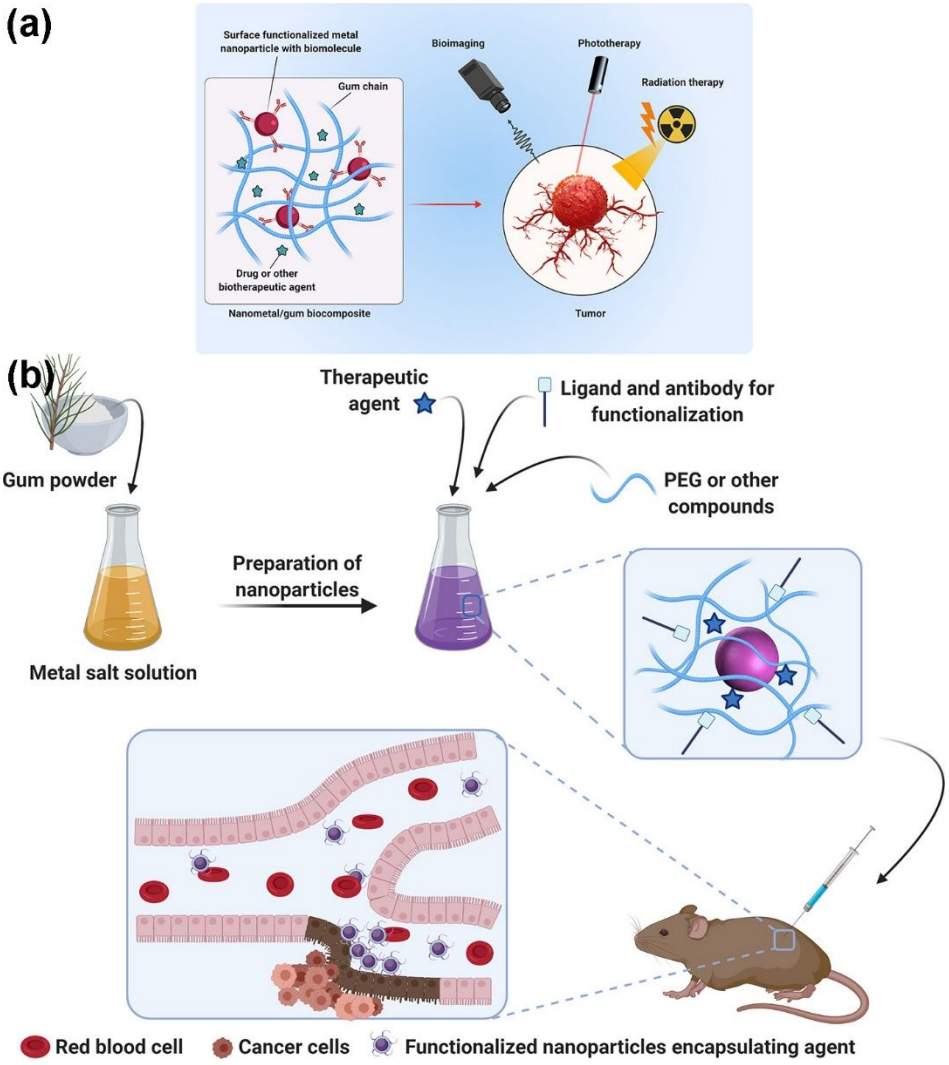

Fig. 6. (A) A schematic illustration of PSA-based platform incorporated with nanometal usable in cancer treatment and diagnosis, detectable *via* phototherapy, bioimaging, as well as radiation therapy. **(B)** The schematics of synthesis and functionalization process of the encapsulated agent as well as the tumor cell detection strategy after reaching the targeted site [232].

Recent studies have achieved unexampled progress in graphene nanocomposites fabrication for cancer therapy. In spite of this progression, toxicity is sometimes an unavoidable problem that walk hand in hand with inorganic-nanomaterials utilization [235]. Nonetheless, tunable properties of graphene nanocomposites help scientists to utilize it in the field of oncology. For instance, combination of GO with chitosan supports the prepared scaffold to have sustained Doxorubicin release and excellent stability as well as biocompatibility [236]. Thus, combination of graphene or GO with biocompatible materials like PSAs (specifically chitosan) provides the user with a great opportunity to use these materials as smart nanoprobes for cancer treatment or diagnosis. For example, combination of chitosan, hyaluronic acid, and GO is proposed for SNX-2112 (it is a heat shock protein with anticancer properties) delivery. Results indicated that this scaffold enhances the ability of recognition of the cancer cells with higher efficacy in sustained SNX-2112 release within an acidic condition which causes A549 cells death (human lung carcinoma cell line) [237]. Combination of hydroxyapatite and chitosan for celecoxib delivery ended in an excellent sustained release, which brought about apoptosis for colon cancer cells [238]. Rabiee et al. showed that addition of PSAs like chitosan to the highly toxic nanomaterials containing $CoNi_2S_4$ (**Figure 7**) [239] could lead to increasing the relative cell viability, considerably. This approach is promising due to the wide range of nanocarriers based on inorganic-components possessing poor biocompatibility/bioavailability. Moreover, they have shown that addition of chitosan leads to reduction in the interactions between the toxic components and cell walls, in both of the HeLa (cervical cell line) and HEK-293 cell lines (human embryonic kidney 293 cells), but increases the constructive interactions for the chemotherapy drug delivery [239]. Also, combination of chitosan with alginate nanoparticles for antisense oligonucleotide delivery has the ability to downregulate the EGFR (epidermal growth factor receptor) expression for the ones suffer from breast cancer cell [240, 241]. Additionally, ganoderma lucidum PSA and gold are a promising amalgamate for doxorubicin delivery and increase the T cells growth due to acceleration of dendritic cells activities, which ultimately brings about hindering 4T1 tumor cells proliferation for pulmonary cancer [233]. **Table 7** compares different scaffolds, their base PSA, constituents, and the loaded anticancer and main findings. However, the main findings based on the usage of PSAs on the surface of the nanostructures (nanocarriers) for the cancer therapy was a challenge between the routine synthetic co- and/or triblock polymers including poly (HEMA), poly (NIPAM) and etc. It should be noted that by addition of these PSAs, some of the advantageous of the synthetic polymers including well-defined interactions to the cells as well as the considerable biocompatibility decreased. The synthetic polymers could lead to well-defined nanostructures

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(nanocarriers), but they are not simple to prepare, cost-effective and highly green. Thus, the need for using PSA-based polymers instead of synthetic polymers has been felt seriously. Moreover, the need for combination of these PSAs with the inorganic- and organic-based nanomaterials have been felt.

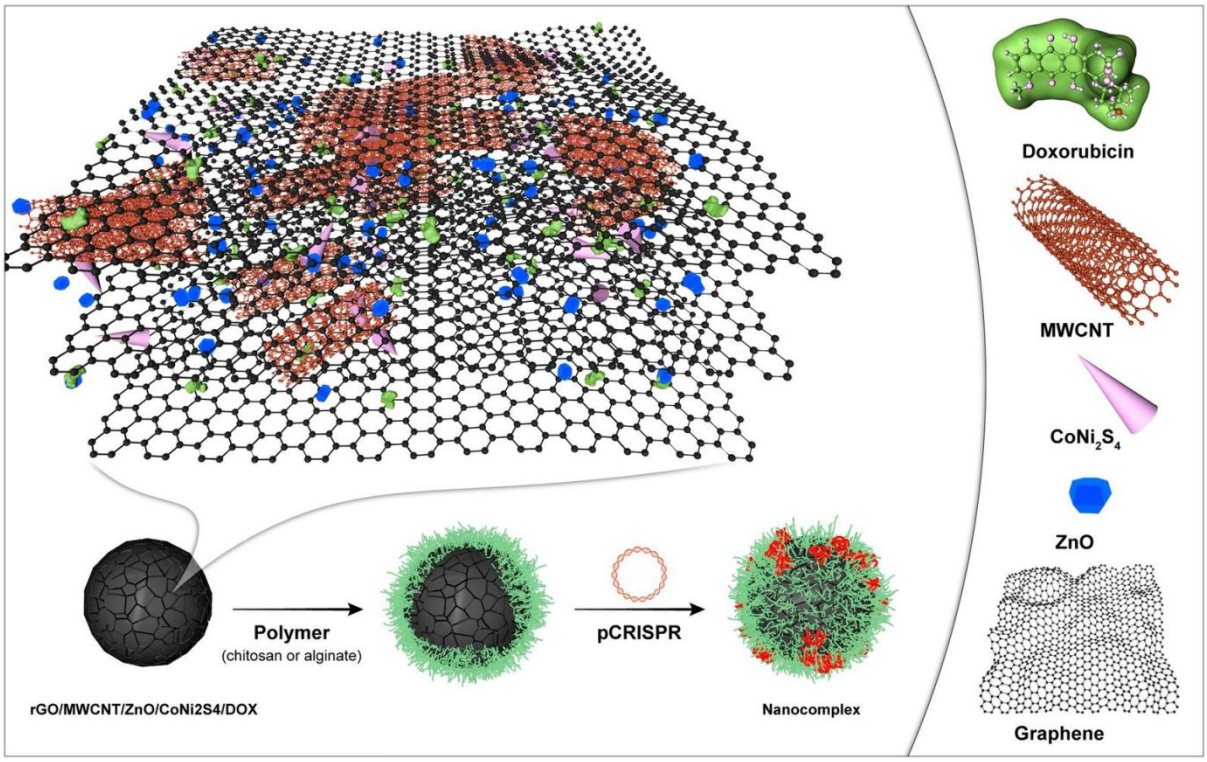

Fig. 7. A schematic illustration on the highly toxic nanomaterial based on $CoNi_2S_4$ coated with chitosan for targeted DOX delivery orientated towards cancer therapy [239].

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Table 7. A summary of different scaffolds, their base PSA, their constituents, the loaded anticancer and their main findings).

Base PSA	Nano additive(s)	Payload	Main findings	Refs.
Pullulan	Gold nanorods	-	Due to acidic environment in addition to concentrated amount of glutathione (that endosomes have)/ self-destruction behavior /great influence on cancer cells inactivation	242
Hyaluronic acid	GO nanoparticles	SNX-2112	Enhanced ability of recognition of the cancer cells/high efficacy in sustained SNX-2112 release within an acidic environment caused A549 cells death	237
Alginate	Poly-deoxy adenylic acid nanostructure	Phosphorothioated antisense oligodeoxyribonucleotide of TNF-α	A great option for intestine inflammation/influence on macrophage Cells performance/great reduction of TNF-α secretion	243
Cellulose	Nanocellulose	5-fluorouracil	PH sensitive/ability to destroy the colon cancer cells	244
Ganoderma lucidum PSA	Gold nanoparticles	Doxorubicin	Accelerated T cells growth due to acceleration of dendritic cells activities/hindering 4T1 tumor cells proliferation for pulmonary cancer	233

4.3.1. Polysaccharide nanocomposites for Cancer Radiotherapy

Advent of X-rays was a significant revolution in cancer treatment. Radiation therapy (derived from X-rays technology) is a big improvement in controlling cancer progression. However, safer and more efficient radiation delivery is the reason behind the usage of biomaterials.

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Nowadays, biomaterials have turned the field of theragnostic and combination therapy upside down [245]. In this regard, PSA-based nanocomposites are utilized to deliver immunostimulatory radioisotopes and they can also be modified with radiosensitizer moieties (see **Figure 8** [245]). Remarkably, utilization of PSAs for siRNA delivery to a desired area is of a great importance in order to overcome a possible radiation resistance [246]. Among different PSAs, chitosan-based nanocomposite is the outstanding one because this biopolymer can easily maintain its structural integrity before being exposed to acidic media of cancerous cells. For instance, According to Yang et al, the encapsulated substance can be stored inside the chitosan loaded Polylactic-co-glycolic acid (PLGA) nanoparticles without any leakage [247, 248].

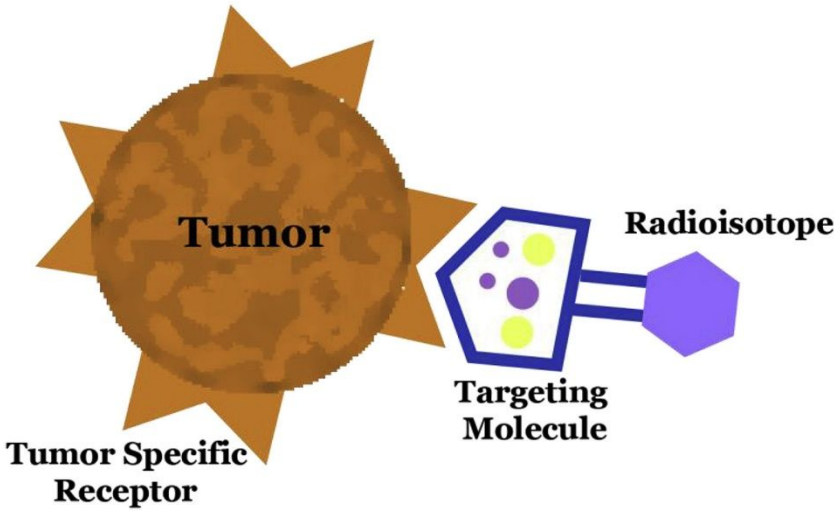

Fig. 8. A schematic illustration of radioisotope delivery to cancer cells using biomolecules [245].

4.3.2. Polysaccharide nanocomposites for Cancer Immunotherapy

Immunosuppression (known as Immunotherapy) is a very powerful tool for cancer cells eradication [249]. Immunotherapy has made a significant progress and also has a very long way to go. However, inappropriate specificity of this method is a serious limitation. Natural and synthetic biomaterials have been utilized to realize efficient immunotherapeutic targeting and address the existing challenges [250]. In this regard, immunotherapy agents such as immunostimulatory small molecules [251], some nucleic acid adjuvants [252], different proteins [253, 254] or antibodies [255, 256], as well as exogenous immune cells [257] can be encapsulated inside the nanocomposite in order to induce a gradient of agent's concentration. Among different biomaterials and platforms, PSA-based nanocomposites and especially alginate nanocomposites are able to play the role of reservoir for the above-mentioned factors (see **Figure 9** [258]). The main reasons behind using alginate as a matrix are being FDA approved,

being cost effective, its potential for large scale manufacturing, low immunogenicity, as well as inherent ionic behavior and hydrophilicity [259]. As an instance, one group utilized an alginate nanocomposite scaffold for codelivery of programmed CAR T cells in conjunction with cyclic-dinucleotide (CDN) which was an effective platform for treating sild tumors [250]. Despite advances in immunotherapy conjugated materials and nanotechnology, a great of deal of time and energy must be expended to translate the ideas to clinic. The major challenges that may hinder the clinical translation of immunotherapy are designing pre-clinical models translating to human immunity, determining the main drivers of cancer immunity process, discerning the organ-specific tumor immune contexture and the molecular and cellular diversity of the immune escape. Moreover, developing the advanced personalized approaches for cancer immunotherapy as well as understanding the effect of immune suppression on autoimmune toxicities must be taken into consideration in the way clinical implementation of immunotherapy [260].

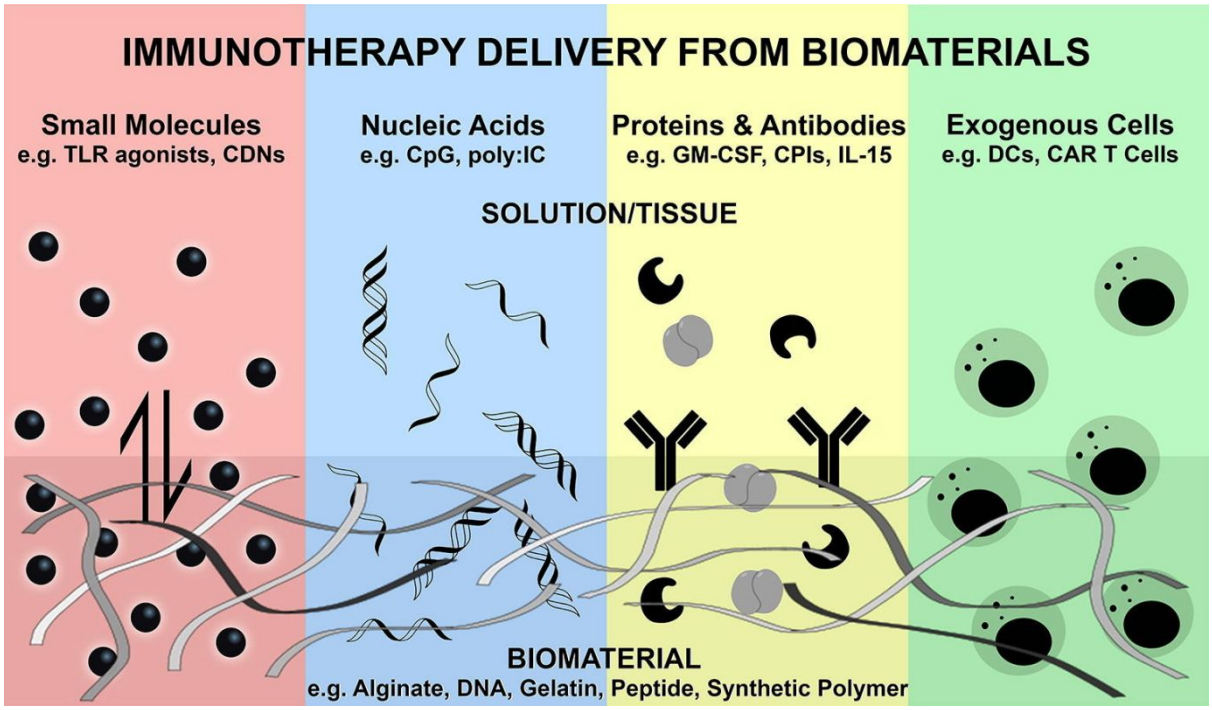

Fig. 9. A schematic illustration of biomaterial for controlled release of bioactive immunotherapies [258].

4.3.3 Polysaccharide nanocomposites for cancer Phototherapy

Light induced cancer treatment which is also called phototherapy is a state of art and progressing field of cancer treatment. Tumor associated antigens (TAAs) release (from the cancerous cells that are dying after being exposed to phototherapy) as well as damage

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associated molecular patterns (DAMPs) have been considered as phototherapeutic immunological responses that must be amplified. Amplification of the above-mentioned responses is a perfect cue for immune cells to recognize and kill the cancerous cells [261]. If amplifying of the responses is done, auxiliary methods such as immune checkpoint blockade (ICB) may also be available [262]. In this regard, different types of biomaterials have been served as photo absorbers or sensitizing agents to improve the performance of the therapeutics as well as minimize the possible side effects of this new technique. For instance, encapsulation of oligodeoxynucleotides inside chitosan coated hollow Copper Sulfide (CuS) nanoparticles was an effective template as a photoabsorbent agent (**Figure 10** [263]). Under laser irradiation (near-infrared laser (900 nm, 2.0 W/cm^2, 40 s)), structural breaking of chitosan-CuS is the result of cancer cells rise in temperature until they burn. Then, oligodeoxynucleotides will be released and tumor will be affected [263, 264]. Another study indicated that Polydopamine nanoparticle is also a great option as a photothermal additive agent [265, 266] to be combined with PSAs [267-269]. Remarkably, gold nanoworms (5 ± 1.5 nm) can strongly enhance the light-heat conversion efficiency [270, 271].

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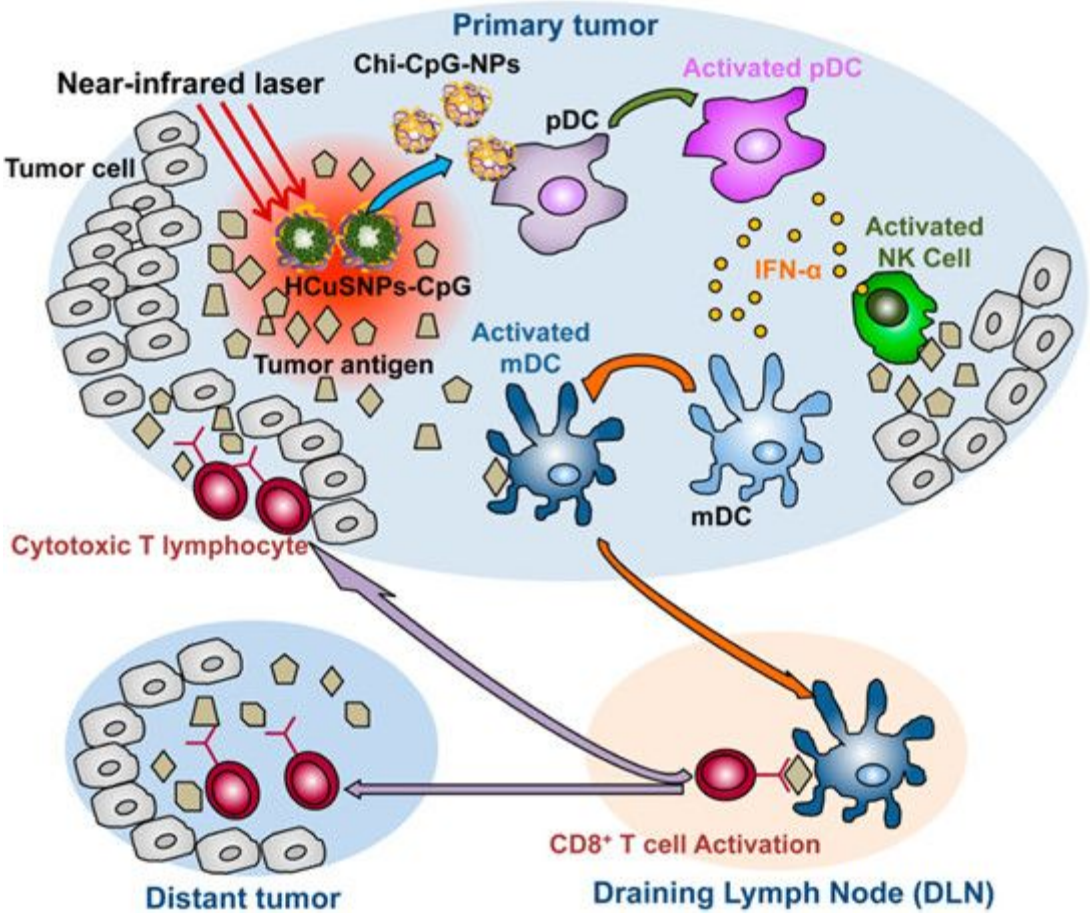

Fig. 10. Mechanism of chitosan-CuS oligodeoxynucleotides loaded photothermal therapy for both primary and distant tumors [263].

4.4. Polysaccharide nanocomposites for Bioimaging

There exist many imaging techniques (such as optical and magnetic resonance imaging) that play a significant role in diseases recognition and treatment. However, state of art bioimaging probes are urgently required to enhance the sensitivity and specificity. Recently, chemistry and bioimaging scientists have opened a new window of bioimaging which is known as polymer-based bioimaging. In this regard, biomaterials and imaging modalities have been combined to produce effective bioimaging probes [272]. The designed structures need to have specific features in order to be qualified. For instance, prolonged half-life, stability, low toxicity as well as target specificity. Among various biomaterials, PSAs are of a great interest in bioimaging field owing the fact that their nanocomposites have excellent stability, very high biocompatibility and they are great stimuli responsive platforms [273]. Chelation of Gadolinium-based contrast agents (GBCAs) (as a very frequently used magnetic agent in bioimaging) with PSAs will strongly

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enhance the compatibility of Gadolinium (Gd) due to the fact that diffusion of Gd to the surrounding media (it is a low molecular weight component that can diffuse in the vein) will decrease the imaging quality. Dextran and starch conjugated Gd nanocomposites have repetitively used as MRI bioimaging probes [68]. Noteworthily, PSAs' modifiable backbone (presence of different chemical structures on their backbone which facilitates the modification) as well as good biodegradability are the other factors that make PSAs desirable options in this regard.

4.5. Polysaccharide nanocomposites as Biosensors

Ever expanding utilization of biosensors has been observed in recent years. It is expected that the value of biosensors sale reaching from 0.58 U.S. dollars in 2017 1.4 billion U.S. dollars globally by 2027 (almost 2.5. times increase in income over one decade) [274]. The applications of biosensors are extremely diverse and some of them are as follows: clinical and diagnostic applications, environmental applications as well as industrial ones. The most effective factor for producing a sensitive and efficient biosensor is accurate immobilization of biological elements on the polymeric matrix surface [275, 276]. PSA-based biomaterials and their nanocomposites can be mentioned as a great matrix for surface immobilization [277]. The reason behind the high usage of PSA-based nanocomposites (as a matrix) is that they own plenty of chemical functionalities (useful for immobilization of biological elements), high permeability, great biocompatibility, no toxicity, as well as cost-effectiveness and very high availability [278]. Being low cost and highly available as a biosensor matrix is invaluable because biosensors are usually mass-produced and they should be available to all segments of the population. Among different members of PSA family, chitosan nanocomposite is of a great importance for biosensor production and bio detection applications [278-281]. Presence of amino and hydroxyl groups on chitosan backbone (for facile modification or chelation of nanoparticles), very good sensitivity to different stimuli (such glucose, pH (under acidic conditions, due to the presence of basic amine groups) or even an electric field), and high stability for detection of various kinds of targets [84] (such as different proteins, DNA structures, various biomolecules and even bacteria) are the reasons that highlight the usage of chitosan nanocomposites in biosensors [278]. Additionally, the very porous structure of chitosan effectively increases not only the loading capacity, but also the sensitivity to the outside's signals [282]. Remarkably, biodegradability, renewability, being very safe for humans as well as very low immunogenicity are the other

important behaviors of chitosan as a matrix for bioagents [283]. According to Zhang et al. combination of chitosan with carbon nanotubes will be a great platform not only for aflatoxin B1 (a kind of contaminants in variety of food such as grains) detection, but also for antibody binding [284]. Noteworthily, Guner el al. suggested the combination of chitosan and gold nanoparticles for antibody immobilization as well as Escherichia coli (E. coli) detection [285]. Chemical modification of chitosan (such as chitosan–poly (acrylic acid)-metal ions nanospheres) is also suggested for preparation of reliable binding sites to immobilize antibodies. Conjugation of chitosan and graphene nanosheets is also an interesting option to provide adequate sites for DNA hybridization reactions [286, 287].

5. Limitations and challenges

Nanocomposites are a new class of platforms that have plenty of applications in biomedical engineering. The most important reason for the development of these systems is that despite their excellent biological properties, biomaterials, lonely, were not able to provide excellent physical and mechanical properties. In addition to increasing mechanical stability, the addition of nanomaterials enhanced some biological properties such as cellular adhesion and antibacterial features. Also, the possibility of loading the drug into these nanoparticles is one of the attractiveness of these systems. However, we have to keep it in mind that nanomaterials can be very toxic (dependent on the used weight percentage [288]). In this regard, a holistic understanding of their toxicity mechanisms will be a huge step toward neutralizing the toxic behaviors [289]. In this section, we briefly discuss the cellular view of toxicity mechanisms.

Silver nanoparticles are among the most repetitively used nanostructures in biomedical engineering (silver is highly antibacterial). However, it strongly affects the mitochondrial respiratory chains and will bring about production of reactive oxygen species (ROS) (reactive molecules containing oxygen). The more the mitochondria are poisoned, the more the cells' energy chains will be distracted which finally harms cells' DNA and will lead to cell apoptosis [290]. The mechanism underlying the titanium oxide toxicity is ROS production, inflammation responses as well as genotoxicity which finally eradicates the cells. Interestingly, the cell poisoning is not only a function if titanium oxide weigh percentages, but also its physical properties such as size, crystal structure as well as photo-activation [291, 292]. It is worth it to address that the possible mechanism of zinc toxicity is the penetration of nanostructures into the pits or protrusion of the cell walls which kills cells trough extrusion of cytoplasmic contents

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[293]. Finally, and importantly, the potent machoism of toxicity of gold and copper nanoparticles are almost somewhat similar. Poisoning of cells' redox system, mitochondrial damage as well as proteins and DNA injuries will prostrate cells [294, 295].

Besides possibilities with nanocomposite PSAs in biomedical applications, there are some serious limitations mainly caused by the natural resources from which PSAs are originated, which discombobulates their pharmaceutical and biological applications. To name but a few, batch-to-batch variations, the possibility of microbial contamination, viscosity drop during the storage stages, viscosity thickening, as well as uncontrolled rate of hydration can be addressed. Moreover, extraction and purification of PSAs in view of the amalgamated nature of PSAs presence in the nature with proteins and lipids [296]. Thus, a precise isolation of PSAs requires smarter methods other than co-extraction, which may contaminate them [297]. Eventually, a comprehensive understanding of structural reactivity of PSAs has been recognized as another challenging aspect, which narrowed the widows of pharmaceutical and biological applications down [298].

6. Concluding remarks and future perspective

Recent advances in applications of PSAs in biomedical engineering witnesses the importance of dealing with improvement of their properties, mainly poor mechanical strength, by the use of reinforcing agents, mainly nanomaterials. Taking the advantage of nanoparticles such as silver, copper, gold, titanium oxide, zinc, etc., in giving mechanical strength along with antioxidant, antibacterial and/or conductivity, the use of PSA nanocomposites is becoming widespread as reliable biomedical platforms—leading to a paradigm shift from fantasy to practical use for clinical purposes. The resulting stimuli-responsive systems not only prim great medias endorsing drug, gene, and cell delivery templates, but also induce nano characteristics with multidimensional physicochemical features for skin, bone, nerve and cartilage tissue engineering. Moreover, they can play an essential role in cancer diagnosis and treatment (radio-, immune- and photothermal therapy), bioimaging as well as biosensing. Form the biosensing application, enzyme engineering offers precise and efficient enzyme immobilization techniques, which localizes the enzymes (e.g., laccase) onto PSA backbone [299]. From immobilization perspective, PSAs are promising biomaterials because of being chemically modifiable. PSA composites are also able to improve the life time as well as the stability of the immobilized enzyme in catalytic reactions [300]. Notably, the selectivity of the immobilized

enzyme is effectively preserved for any particular application after immobilization on the surface of PSA [301].

In this review, we have looked over superiority of PSA-based nanocomposites over neat PSA, which are treated into two main categories, as generic and advanced applications of PSA nanocomposites. After precise analysis of the literature, we understood that there are some existing challenges such as nanomaterial toxicity and also some opportunities for the future studies ahead of PSA-based nanocomposites in biomedicine. To name, some unsolved problems and unanswered questions can be counted accordingly:

1) Difficulties in controlling over PSA-based nanocomposites fabrication techniques, in order to achieve desired properties, specifically electrical and mechanical features are of importance. For instance, one can address thermal sensitivity of plenty of PSA-based systems, which leads to degradation even before the melting point. This is the case when especially it requires thermomechanical stability or mechanical toleration and durability in surgical procedures (if needed).

2) An increasing demand still exists for devising new PSA-based nanostructures for personalized diagnostic outputs as well as therapeutic such as personalized anticancer delivery in order to minimize the side effects.

3) Weak immunogenic response, toxicity or immunogenicity of their modification or collaboration with other materials, or discovering new toxicity neutralizing mechanisms to diminish nanomaterials toxicity

To overcome the above-mentioned obstacles, we suggest four main approaches. First of all, we believe that devising more complicated systems by combination of different PSAs with different fortes can lead to making up for the existing weaknesses. Secondly, we anticipate that deeper investigations on the effects of each component in a composite and the exact mechanism for each effect can be a huge step toward the future progression in this field. In fact, we need to be aware of the details and mechanisms more explicitly. Thirdly, it would be great to utilize the most state-of-the-art systems (such as electrospinning, 3D and 4D printing, artificial intelligence) in order to improve our understanding of details or to enhance the manufacturing and biomodification processes. For instance, devising methods to optimize composites' features utilizing artificial intelligence can be a great topic for future studies. In addition to technological advances, the ability to use and apply them in various fields purposefully is a key factor. Ultimately, considering the limited number of practical PSAs, there is a huge demand

for modification of their properties, which can be obtained *via* addition of nanoparticles or bulk modification that boosts the matrix and additive surface bio-interactions. Based on the above-mentioned discussion, in spite of excellent progress in this field, a long way should be paved. Moreover, still we are in early stage of using PSA nanocomposites, taking clinical implementation of recipes the ultimate objective.

Table 8. Abbreviation table.

Full name	Abbreviation
Polysaccharides	(PSAs)
extracellular matrix	(ECM)
zinc-doped hydroxyapatite nanoparticles	(nZnHA)
human adipose derived stem cells	(hAD-MSCs)
basic fibroblast growth factors	(bFGFs)
graphene oxide	(GO)
Halloysite nanotubes	(HNTs)
silver	(Ag)
reactive oxygen species	(ROS)
N-isopropyl acrylamide	(NIPAM)
near-infrared	(NIR)
Drug delivery systems	(DDSs)
polypyrrole	(PPy)

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poly (3-hydroxybutyrate)	(PHB)
photothermal therapy	(PTT)
doxorubicin	(DOX)
silver nitrate	(AgNO3)
polyethylenimine	(PEI)
polyethylene glycol	(PEG)
sodium borohydride	(NaBH4)
polystyrene sulfonate	(PSS)
Glycosaminoglycan	(GAG)

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