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REVIEW ARTICLE

LONG CHAIN POLYMERIC CARBOHYDRATE DEPENDENT NANOCOMPOSITES IN TISSUE ENGINEERING

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Abstract

The use of nanomedicine has increased enormously, especially in the field of gene delivery and targeted drug delivery. The objective of current review to identify long-chain polymeric carbohydrate dependent nano-composites in tissue engineering such gellan gum incorporated TiO_2 nanotubes, Poly(vinyl) alcohol-gellan gum-based nanofiber, cross-linked gellan/pva nanofibers, nanocellulose reinforced gellan-gum hydrogels, dextran and sol-gel derived bioactive glass-ceramic nanoparticles, aminated β-cyclodextrin-modified-carboxylated magnetic cobalt/ nanocellulose composite, chitosan-chitin nanocrystal composite scaffolds, sodium alginate-xanthan gum-based nano-composite scaffolds, nano-hydroxyapatite pullulan/dextran polysaccharide composite, chitosan/carbon nanofibers scaffolds, nano-bio composite scaffold of chitosan–gelatin–alginate–hydroxyapatite, alginate/gelatin scaffolds with homogeneous nano apatite coating, nano-hydroxyapatite-alginate-gelatinmicrocapsule, poly(ε-caprolactone)/keratin nano fibrousmats, keratin nanoparticles-coating electrospun PVA nanofiber, nano-hydroxyapatite/chitosan/chondroitin sulfate/hyaluronic acid and chitosan/chondroitin sulfate/nano-bioglass. The current review has identified a list of medicinal herbs that have been incorporated into long chain polymeric carbohydrate-based nano-composites.
Keywords: Nano-composites, nanomedicine, polymeric carbohydrate.

INTRODUCTION

Nanomedicine has gained a lot of interest due to its vast application. Physical and chemical attributes of nanomaterials have lengthened its application in the field of biological science and biomedical engineering such as biological imaging, drug delivery, biomolecular sensing, and Infectious Diseases[1]. There are different types of nanomaterials such as Inorganic nanomaterials (Graphene, mesoporous silica, gold, magnetic, quantum dots, and layered double hydroxides) and metal-organic frameworks (Zirconium -based metal-organic frameworks, Lanthanide-Based Metal-Organic Frameworks, Oligo nucleotide-Functionalized Metal-Organic Framework)[2,3]. Inorganic nano materials possess intrinsically physicochemical properties and good biocompatibility, as a result, they are used in different applications such as bio imaging, targeted drug delivery, and cancer therapies, whereas the Metal-organic framework is porous hybrid polymer-metal composites[4,5]. They possess many biomedical applications due to their excellent porosity, high loading capacity, biodegrade-bility, and ease of surface modification when compared to others[6,7].

The selection of material depends upon the biological activity, biocompatibility, and biodegradability. The materials provide an analogous environment to the extracellular matrix (ECM) and provide an induced rate of synthesis or growth of new tissues. Extracellular matrix consists of collagen fibril, glycoproteins such as fibronectin and laminin for attachment. In addition to the extracellular matrix, connective tissues are characterized by fibroblasts and ground substances which are usually fluid, but it can also be mineralized and solid, as in bones[8]. Polysaccharides offer a green alternative to synthetic polymers in the preparation of soft nanomaterials[9]. Monosaccharides and disaccharides are bonded through covalent linkage to develop a long chain of polymer-based carbohydrates. They also consist of other functional groups such as pyruvate, sulfate, and methyl. They can range from linear to branched structure. Exo based polysaccharides are Dextran, alginate, hyaluronic acid, and xanthan, which are synthesized extracellularly by cell wall-anchored enzymes[10,11,12].

Table 1: Long chain polymeric Carbohydrate dependent nano-composites in tissue engineering.

No.	Material Composition	Characterization Techniques	Application	*In-vitro/in-vivo* Testing relevant to TE and GD
1.	Gellan gum incorporated TiO_2 nanotubes[13]	FTIR, XRD and SEM	Skin tissue engineering	Cell viability and proliferation testing
2.	Poly (vinyl) alcohol-gellan gum based nanofiber[16]	SEM and FTIR	3D nanofibrous scaffold.	*In-vitro* embryonic stem cells (ESCs)
3.	Cross-linked gellan/PVA nanofibers[18]	FESEM	Human dermal fibroblast (3T3L1) cells in tissue engineering application	Cell proliferation behaviour of human dermal fibroblast cells (3T3L1)
4.	Nanocellulose reinforced gellan-gum hydrogels[20]	TEM	Annulus fibrous tissue regeneration	Bovine annulus fibrosus culture
5.	Dextran and sol–gel derived bioactive glass ceramic nanoparticles[31]	FESEM, SEM	Bone tissue engineering	Normal human osteoblasts (HOB) Cells, Cell viability assay
6.	Aminated β-Cyclodextrin-Modified-Carboxylated Magnetic Cobalt/Nanocellulose Composite[21]	FTIR, XRD, SEM, ESR	Tumor Targeted Gene delivery	DNA Binding Studies, MTT cytotoxicity assay, *in vitro* gene transfection and gene expression experiments.
7.	3D Bioprinting of iPS Cells in a Nanocellulose/Alginate Bioink[23]	Confocal images, Fluorescence microscopy	Bioprintingi PSCs to support cartilage production in co-cultures with irradiated chondrocytes	Immuno histochemical analysis, Microscopy, Gene expression assays
8.	Chitosan-chitin nanocrystal composite scaffolds[39]	SEM, XRD	Bone tissue engineering	Cell adhesion and proliferation
9.	Sodium alginate-xanthan gum based nano-composite scaffolds[40]	FESEM	Bone tissue engineering	Cell viability
10.	Nano-hydroxyapatite Pullulan/dextran polysaccharide composite[41]	ESEM	Orthopaedic and maxillofacial surgical applications.	Experimental models performed in rat and goat
11.	Chitosan/Carbon nanofibers Scaffolds[38]	SEM	Cardiac Tissue Engineering	Culture of Neonatal Rat Cardiomyocytes, Gene Expression
12.	Nano-bio composite scaffold of chitosan–gelatin–alginate–hydroxyapatite[42]	ESEM	Bone tissue-engineering	*In vitro* cell culture using osteoblast cell line, Cell viability, proliferation and attachment over the scaffold, Gene expression study, RNA extraction study
13.	Alginate/gelatin scaffolds with homogeneous nano apatite coating[43]	SEM, EDS	Bone tissue engineering.	Proliferation and differentiation of cells on scaffolds The
14.	Nano-hydroxyapatite-alginate-gelatin microcapsule[44]		Modular bone tissue engineering	Osteogenesis activity
15.	Poly(ε-caprolactone)/keratin nanofibrous mats[45]	SEM	Vascular tissue engineering	Fibroblast viability assay, Cell attachment
16.	Keratin nanoparticles-coating electrospun PVA nanofiber[46]	SEM	Neural tissue applications	Cell morphology, adhesion and proliferation
17	Nano/hydroxyapatite/chitosan/chondroitin sulfate/hyaluronic acid[47]	SEM	Bone tissue engineering	Cell biocompatibility
18	Chitosan/chondroitin sulfate/nano-bioglass[48]	XRD, FT-IR, FE-SEM and TEM.	Bone tissue engineering	*In-vivo* bone regeneration study, *In-vitro* cell study

Ismail *et al*., prepared gellan gum incorporated TiO_2 nanotubes using the solvent casting method for skin tissue engineering. TiO_2 nanotubes are a promising tool for cell growth and proliferation for wound healing[13]. They are biocompatible osseointegration[14] and attenuate inflammatory mediators[15]. Aadil *et al*., formulate poly(vinyl) alcohol-gellan gum-based nanofiber using electrospinning and found promising 3D nanofibrous scaffolds for various tissue engineering applications[16]. Poly (d, l-lactide-co-glycolide acid) (PLGA) nanofiber is an alternative biodegradable polymer when compared with polysaccharide-based nanofiber, which is used in medical devices and drug delivery applications[17]. Gellan and PVA cross-link nanofiber is prepared to enhance the physicochemical stability and made biocompatible to human dermal fibroblast (3T3L1) cells[18]. Cellulose nanocrystals offer to aggrandize Cytocomp-atibility and improved mechanical properties as compared to carbon or metallic nanotubes[19]. Nanocellulose reinforced gellan-gum hydrogelsare helpful in Annulus fibrosus (AF) defects such as annular tears, herniation[20].

Nanocellulose Composite for also useful in the tumor-targeted gene delivery. Anirudhan and Rejeena have developed a novel non-viral gene vector consists of aminated b-cyclodextrin modified carboxylated magnetic cobalt/nanocellulose composite, which helps reduce the toxicity but also increased the transgene expression level[21]. Yvette and co-researcher also worked on nanocellulose based gene delivery and designed polyelectrolyte layer assembly of bacterial nanocellulose whiskers with plasmid DNA[22]. Nguyen *et al*., developed nanocellulose/alginate Bioink for 3D Bioprinting of iPS Cells. The result suggests supporting cartilage production in co-cultures with irradiated chondrocytes[23]. The other researcher also supports the evidence for the development of 3D bioprinting using nanocellulose such as 3D bioprinting of human chondrocyte-laden nanocellulose hydrogels for patient-specific auricular cartilage regeneration[24], wood-based nanocellulose and bioactive glass modified gelatin–alginate bioinks for 3D bioprinting of bone cells[25] and development of nanocellulose-based bioinks for 3D bioprinting of Soft Tissue. The problem in all the above research lacks pre-clinical and clinical trials. This leads to motivation for researchers to design a randomized double-blind clinical trial for future commercial prospective. Dextran based hydrogel is prevalent in a different kind of tissue repair such as cartilage tissue engineering[26], vascular tissue engineering[27], bone tissue engineering[28], skin tissue engineering,[29], wound repair[30]. Nikpour and their co researcher-developed Dextran based bioactive glass-ceramic nano-composite scaffold. They synthesized nano bioactive glass-ceramic particles (nBGC) by sol-gel method, whereas the chemical cross-linked technique is used for the preparation of the nano-composite scaffold. They identify silicon dioxide improves surface reaction to contact with body fluids, and develops active surface area for *in vitro/v*ivo bone tissue engineering[31]. Some important Polysaccharide-based Nano-composites for tissue engineering and gene delivery are mentioned in Table 1. The researcher excluded several nano-composite as of lack of available literature on *in-vitro* or *in-vivo* evaluation. Chitosan-based biomaterial has been well known for the preparation of nontoxic, biodegradable, and biocompatible polysaccharide of β(1-4)-linked d-glucosamine and N-acetyl-d-glucosamine[32]. Chitosan has been used to prepare collagen/chitosan porous scaffolds[33], injectable chitosan-based hydrogels[34], chitosan-nanohydroxyapatite composite scaffolds[35], chitin-based tubes[36], chitosan-alginate hybrid scaffolds[37], and chitosan/carbon scaffolds[38].

Table 2: Some medicinal herbs incorporated into long-chain polymeric carbohydrate-based nano-composites for tissue regeneration.

Medicinal Herb	Polysaccharides based Nano-composites	Application
Lycium barbarum[52]	*Lycium barbarum* polysaccharide encapsulated Poly lactic-co-glycolic acid Nanofibers	Peripheral nerve tissue engineering
Elaeagnus angustifolia[54]	EA extract was loaded onto poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCL-PEG-PCL/EA) nanofibers	Bone tissue engineering
Aloe barbadensis miller[55]	Aloe vera incorporated poly(ε-caprolactone)/gum tragacanth nanofibers	Wound dressing
Stryphnodendron adstringens[55]	PVA/pineapple nanofibers/*Stryphnodendron adstringens*	Medical Application

2. Medicinal herbs incorporated into long-chain polymeric carbohydrate-based Nano-composites

Plants are the essential foundation of medicine. Some essential drugs that are still in use today are derived from traditional medicinal herbs[49]. Functional polysaccharides have a wide variety of application in the field of biomedical engineering and tissue repair[50]. Several medicinal herbs such as *Indigofera aspalathoides*, *Azadira chtaindica, Memecylonedule* and *Myristica andamanica*, along with a biodegradable polymer, polycaprolactone has been used in combination for skin tissue engineering[51]. Table 2 represents some of the medicinal herbs that are used in combination with polysaccharides based Nano-composites. *Lycium barbarum* polysaccharides have encapsulated Poly lactic-co-glycolic acid Nanofibers is indicated for peripheral nerve tissue engineering[52]. *Elaeagnus angustifolia* is traditionally indicated in osteoarthritis[53]. *Elaeagnus angustifolia* extract was loaded in poly(ε-caprolactone)-poly (ethylene glycol)-poly(ε-caprolactone) (PCL-PEG-PCL/EA) nanofibers for bone tissue engineering[54]. Aloe vera is incorporated in poly (ε-caprolactone)/gum tragacanth nanofibers to develop the wound dressing[55]. *Stryphnodendron adstringens* is indigenous to Brazil and a well-known wound healing herb on the eastern coast of South America[56]. It has been used in combination with Polyvinyl alcohol and pineapple nanofibers for medical applications[57].

3. Clinical trials of long-chain polymeric carbohydrate-based Nano-material

Limited available literature on the clinical trial of polysaccharides based Nano-material. Although several material is available and examined *in-vitro* or *in-vivo* a very few materials went for the clinical trial. Most of the available literature does not seem able to proceed further for clinical trials. A pilot randomized clinical trial of a customized nanotextile wet garment treatment was performed on moderate and severe atopic dermatitis and found useful in the treatment of eczema[58]. A couple of randomized, double-blind clinical trials have been performed on nano-hydroxyapatite toothpaste and nano-hydroxyapatite plus 8% Arginine in dentine hypersensitivity intervention[59,60]. Table 3 represent clinical trials with polysaccharides based Nano-material.

Table 3: Clinical trials with long-chain polymeric carbohydrate-based nano-material.

Product	Clinical trial	Application
Nano-hydroxyapatite Toothpaste[59]	Double-Blind Randomized Clinical Trial	Dentine hypersensitivity
Nano-hydroxyapatite and 8% Arginine[60]	Double-Blind Randomized Clinical Trial.	Dentine hypersensitivity
Nanofibrillar cellulose wound dressing[61]	Preliminary Clinical trial	Wound healing
Tinidazole functionalized homogeneous electrospun chitosan/poly (-caprolactone) hybrid nanofiber membrane[62]	Preliminary Clinical trial	Chronic periodontitis

CONCLUSIONS

Polymer-based carbohydrate molecules composed of long strings of simple sugars (i.e., monosaccharides or disaccharides) that are covalently linked together by glycosides. They are readily usable and can be used for development, assembling, and modification. Polysaccharides also provide 'natural' alternatives to oil-based synthetic polymers.The creation of nanoparticles from polysaccharides is accomplished by ion or covalent cross-linking, ion-complex, and self-assembly following the grafting of the hydrophobic segments onto the polymer backbone. Polymeric chain length and their charges are an important factor in the selection of appropriate methodology for the development of new nanoparticles.

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AUTHOR'S CONTRIBUTION

Aslam MS: Writing original draft, review, literature survey, editing, methodology, data curation.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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