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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 TiO₂ 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-gelatin microcapsule, poly(ϵ -caprolactone)/keratin nano fibrous mats, 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.

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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 Diseases¹. 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, biodegradability, 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 bones⁸. Polysaccharides offer a green alternative to synthetic polymers in the preparation of soft nanomaterials⁹. 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. A list of bacterial polysaccharides consists of the intracellular, capsular, or exo-based skeleton. 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	<i>In-vitro/in-vivo</i> 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.	<i>In-vitro</i> 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, <i>in vitro</i> gene transfection and gene expression experiments.
7.	3D Bioprinting of iPS Cells in a Nanocellulose/Alginate Bioink ²³	Confocal images, Fluorescence microscopy	Bioprinting iPS cells 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	<i>In vitro</i> 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	<i>In-vivo</i> bone regeneration study, <i>In-vitro</i> cell study

Ismail *et al.*, prepared gellan gum incorporated TiO₂ nanotubes using the solvent casting method for skin tissue engineering. TiO₂ nanotubes are a promising tool for cell growth and proliferation for wound healing¹³. They are biocompatible osseointegration¹⁴ and attenuate inflammatory mediators¹⁵. Aadil *et al.*, formulate poly(vinyl) alcohol-gellan gum-based nanofiber using electrospinning and found promising 3D nanofibrous scaffolds for various tissue engineering applications¹⁶. 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 applications¹⁷. Gellan and PVA cross-link nanofiber is prepared to enhance the physicochemical stability and made biocompatible to human dermal fibroblast (3T3L1) cells¹⁸. Cellulose nanocrystals offer to aggrandize Cytocompatibility and improved mechanical properties as compared to carbon or metallic nanotubes¹⁹. Nanocellulose reinforced gellan-gum hydrogels are helpful in Annulus fibrosus (AF) defects such as annular tears, herniation, and discectomy²⁰. 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 level²¹. Yvette and co-researcher also worked on nanocellulose based gene delivery and designed polyelectrolyte layer assembly of bacterial nanocellulose whiskers with plasmid DNA²². Nguyen *et al.*, developed nanocellulose/alginate Bioink for 3D Bioprinting of iPS Cells. The result suggests supporting cartilage production in co-cultures with irradiated chondrocytes²³. 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 regeneration²⁴, wood-based nanocellulose and bioactive glass modified gelatin–alginate bioinks for 3D bioprinting of bone cells²⁵ 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 engineering²⁶,

vascular tissue engineering²⁷, bone tissue engineering²⁸, skin tissue engineering²⁹, wound repair³⁰. 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/vivo* bone tissue engineering³¹. 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 $\beta(1-4)$ -linked d-glucosamine and N-acetyl-d-glucosamine³². Chitosan has been used to prepare collagen/chitosan porous scaffolds³³, injectable chitosan-based hydrogels³⁴, chitosan-nanohydroxyapatite composite scaffolds³⁵, chitin-based tubes³⁶, chitosan-alginate hybrid scaffolds³⁷, and chitosan/carbon scaffolds³⁸.

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

Medicinal Herb	Polysaccharides based Nano-composites	Application
<i>Lycium barbarum</i> ⁵²	<i>Lycium barbarum</i> polysaccharide encapsulated Poly lactic-co-glycolic acid Nanofibers	Peripheral nerve tissue engineering
<i>Elaeagnus angustifolia</i> ⁵⁴	EA extract was loaded onto poly(ϵ -caprolactone)-poly(ethylene glycol)-poly(ϵ -caprolactone) (PCL-PEG-PCL/EA) nanofibers	Bone tissue engineering
<i>Aloe barbadensis miller</i> ⁵⁵	Aloe vera incorporated poly(ϵ -caprolactone)/gum tragacanth nanofibers	Wound dressing
<i>Stryphnodendron adstringens</i> ⁵⁵	PVA/pineapple nanofibers/ <i>Stryphnodendron adstringens</i>	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 herbs⁴⁹. Functional polysaccharides have a wide variety of application in the field of biomedical engineering and tissue repair⁵⁰. Several medicinal herbs such as *Indigofera aspalathoides*, *Azadirachta indica*, *Memecylonedule* and *Myristica andamanica*, along with a biodegradable polymer, polycaprolactone has been used in combination for skin tissue engineering⁵¹. 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 engineering⁵².

Elaeagnus angustifolia is traditionally indicated in osteoarthritis⁵³. *Elaeagnus angustifolia* extract was loaded in poly(ϵ -caprolactone)-poly(ethylene glycol)-poly(ϵ -caprolactone) (PCL-PEG-PCL/EA) nanofibers for bone tissue engineering⁵⁴. Aloe vera is incorporated in poly(ϵ -caprolactone)/gum tragacanth nanofibers to develop the wound dressing⁵⁵. *Stryphnodendron adstringens* is indigenous to Brazil and a well-known wound healing herb on the eastern coast of South America⁵⁶. It has been used in combination with Polyvinyl alcohol and pineapple nanofibers for medical applications⁵⁷.

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 eczema⁵⁸. 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

CONCLUSION

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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CONFLICT OF INTEREST

No conflict of interest associated with this work.

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