Trends In Carbohydrate Research, Vol.13, No.1 (2021) 71-81 0975-0304/09

Trends in Carbohydrate Research

website: www.trendscarbo.com

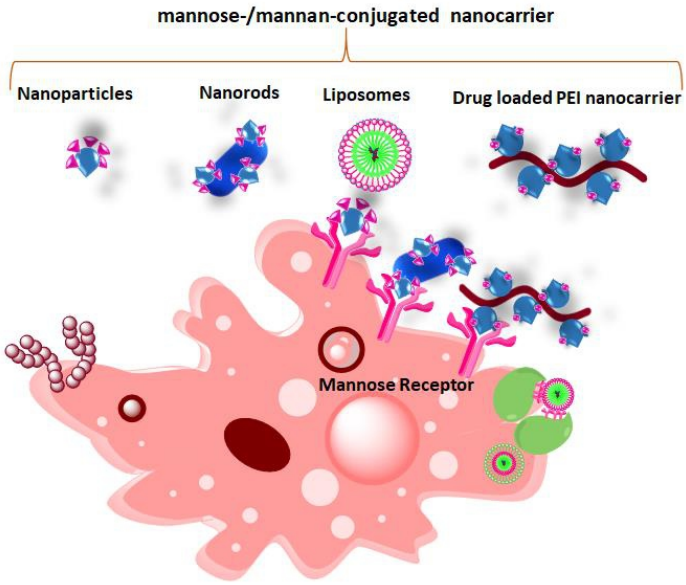
Mannosylated and mannan-modified nanovectors targeting Resident Tissue Macrophages (RTM) for efficient pharmacotherapy

Indu Singh,[1,2] Seema Gupta,[2] Gagan Dhawan,[2] Pradeep Kumar[1,*]

[1]CSIR-Institute of Genomics and Integrative Biology, Mall Road, Delhi-110007, India
[2]Acharya Narendra Dev College (University of Delhi), Govindpuri, Kalkaji, New Delhi- 110019, India

Received: January 01, 2021, Revised: March 28, 2021, Accepted: March 30, 2021

Graphical Abstract



Abstract

Nanovectors advocate extensive scientific advancement for feeding safe and efficient pharmaceutical delivery systems. Embraced as both organic and inorganic vectors, these nanovectors can be designed and engineered with various layers of complexity to achieve therapeutic targeting and ensuring effective pharmacotherapy for disease management. A substantial challenge that the most therapeutic agents face is an inability to penetrate effectively to the target site. Chemical methods offer a solution to allow safe, controlled release and specific delivery of therapeutic molecules to the target tissue. Chemical targeting of vectors to diseased tissues or macrophages can utilize molecular recognition units for decorating the surface of particles or molecular units responsive to diseased microenvironments or remote stimuli. This review aims to provide insights into the sophisticated chemical vectors designing and characterization that can be used as carriers for implication in nanotechnology. Further, desired characteristic properties of nanovectors essential for therapeutic delivery have been stressed in the communication. Additionally, the current trends and novel concepts for mannose receptor macrophage-specific drug or gene or antigen targeting that use conjugation or encapsulation pathways for binding targeting moieties have been addressed.

***Keywords*:** Nanovectors; macrophages; mannose receptors; drug delivery; mannose; galactomannan.

* Corresponding author : Pradeep Kumar
E-mail: pkumar@igib.res.in

1. Introduction:

Targeted drug/gene delivery has encouraged the development of nanovectors owning complex structures and functionalized surfaces. Vectors must navigate a series of obstacles before the therapeutic payloads, e.g. all forms of biological molecules such as proteins, peptides, nucleic acids (i.e., DNA/RNA/PNA/LNA as genes and ribozymes/DNAzymes), lipids and fatty acids, etc., could target a diseased tissue. Chemical vectors include polymeric nanoparticles, liposomes, micelles, nanocapsules, solid lipid nanoparticles (SLN), lipid–polymer hybrid systems, peptides, dendrimers, and biopolymers, which are potentially non-toxic, easy to be produced on a large scale, and easily modified.[1-4] The therapeutic ligand can be encapsulated or conjugated chemically or interact electrostatically with these chemical vectors. Surface modification of these vectors could improve their longevity, bioavailability, tissue targeting, and intracellular penetration, and, therefore, provide a range of opportunities for efficient delivery of anticancer drugs, genes, and diagnostic agents. A wide range of chemical vectors (viral and non-viral) have been established and exploited for intended utility which sufficiently reflect the scope of envisioned applications and vibrancy underlying this field. Following the development in the area of delivery systems, next comes the ability to potentially enhance the therapeutic efficacy by cell-specific targeted delivery of therapeutic agents.

Macrophages are known as "doubled-edged sword" that act as an immune monitor as well as have an inhibitory effect against infection. Prominently, Resident Tissue Macrophages (RTM) are involved in all types of inflammatory and pathological states including atherosclerosis, rheumatoid arthritis, cancer and neuro-inflammatory diseases, where they play a crucial role in the initiation and maintenance of the inflammatory processes that ultimately lead to tissue destruction.[5] Macrophages reside and express in different cell types such as Kupffer cells in liver, microglia in neural tissues, alveolar in lungs, osteoclast in bone, and monocytes in blood, as depicted in **Figure 1**. Accordingly, activation of these resident macrophages occurs due to disparate stimuli such as a microbial attack, necrotic cells and activated lymphocytes that trigger the release of different macrophage polarization states. The monocyte upon migration in the tissues differentiates into macrophages which lead to the expression of various cellular receptors allowing macrophages to efficiently sense and internalize particulate matter.[5,6]

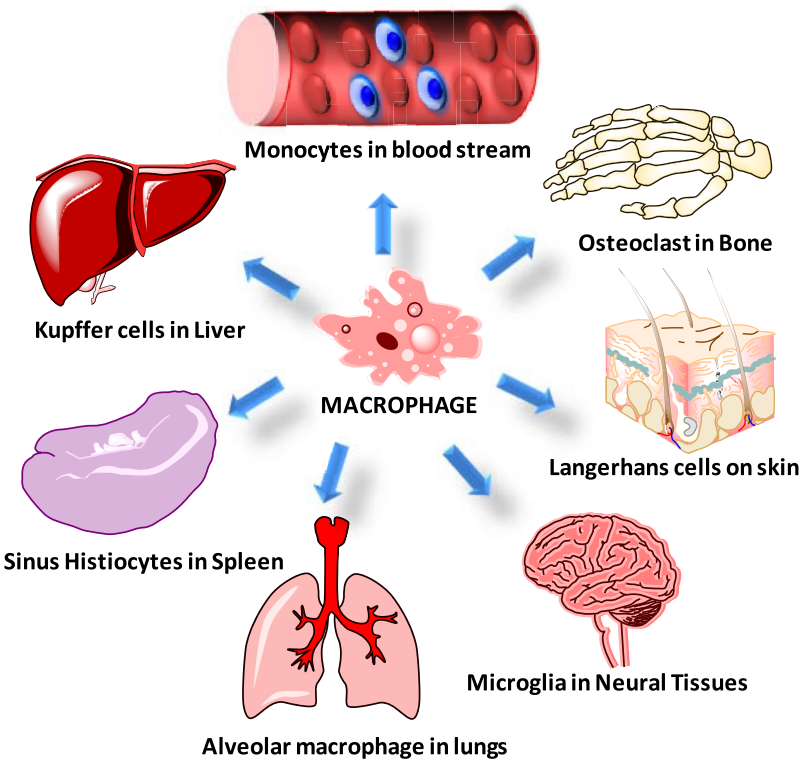


Figure 1. Graphic illustration showing presence of resident macrophages in different tissues

In general, macrophages have been categorized into two types depending on their functions and phenotypes i.e. macrophage M1 (pro-inflammatory) and macrophage M2 (anti-inflammatory).[7] M1 and M2 are converted from other macrophages by the action of IFN-γ and Th2 cells, respectively. Due to the participation of these macrophages as sole or mixed phenotypes in a large number of inflammatory diseases and malignancy, these have been considered as the potential target intended for targeted drug delivery.[8] The specific development of therapeutic drug targeting to macrophages would be considerably facilitated if the mechanisms of interaction between the macrophage membrane and the carrier, along with the subsequent uptake mechanisms could be explored. Macrophage surface expresses a variety of plasma membrane receptors (scavenger, mannose, folate, tuftsin, and Toll-like receptors TLRs) that recognize susceptible binding ligand.[9] Apart from other receptors, our primary focus is to elaborate mannose receptor (MR) and identify molecules with a similar range of MR binding efficiency such as mannose, fucose, glucose, maltose, glucan, mannan and other ligands. Over the past several decades, many important discoveries in the field of biomedical sciences have been inspired by MR targeting macrophages as a therapeutic intrusion. The present review stresses specifically on the carbohydrate-based nanovectors and targeting ligands and their role in achieving MR macrophage target-specific delivery and intracellular pharma-cotherapeutics.

1. Macrophage Plasma Membrane Receptors (MPMR)

Macrophage expresses a variety of membrane receptors enabling recognition and uptake of foreign substances. These include the family of scavenger receptors (collagenous and non-collagenous), Toll-like receptors (TLRs), carbohydrate-binding lectins (mannose, fucose, *N*-acetyl glucosamine, glucose, xylose and galactose as the targeting agent), phagocytic receptors, complement receptors, Fc receptors (Fc as the targeting agent), tuftsin receptor (tuftsin as the targeting agent), dectin (NK-like C type lectin-like) with major emphasis on mannose receptors, as shown in **Figure 2**. The membrane receptors perform their functions by various modifications on self-ligands and their uptake occur either directly or through opsonization process in different body compartments.[10] Therefore, delivery of a therapeutic molecule to macrophages may be enhanced through surface modification resulting in penetration of bioactive molecule at the specific site of infection. Opsonization is the vital immune response mechanism for invading pathogens that encompass on recognizing and engulfing pathogens/microbial clearance. Mechanistically, drug molecule coated with opsonin molecules, for instance, complement proteins such as C1q complex, C3b and iC3b antibodies (notably IgG and IgM isotypes), fibronectin and circulating protein aggravates phagocytosis.[11,12] Particles of different physicochemical properties may attract different arrays of opsonin. Herein, varieties of receptors have been explained superficially, but we have restricted our concern to mannose receptors and its subfamilies.

2. Structure and role of Macrophage Mannose Receptors (MMR) in pathological conditions

Mannose receptors belong to C-type lectin receptors (CLRs) superfamily and are 180 kDa Type I transmembrane proteins composed of a single subunit of *N*- and *O*-linked glycosylation, and distinct five domains present on the extracellular regions listed as N-terminal cysteine-rich region that recognizes sulfate sugar residues (Cys-MR), 8 C-type lectins Carbohydrate-Recognition Domains (CRDs) performing Ca^{2+} dependent mannose recognition, a fibronectin II like insert, elongated cytoplasmic tail containing motifs intended for endocytosis and endosomal activity in the cytoplasmic region,[13] briefly illustrated in **Figure 2**. Mannose receptors are expressed on different cell surfaces such as dendritic cells (DCs), Kupffer, alveolar region, dermal, endothelial as well as mucosal lining which enable the delivery of active molecule at the specific site resulting in significant improvement in the therapeutic index. Mannose receptors can recognize mannose, fucose, maltose, glucan, mannan, galactose and polysaccharides present on the surface of pathogenic bacteria, thus have significant role for cell specific drug delivery resulting in antimicrobial and anti-inflammatory effects.[14] Prominently, MMR has two main subtypes such as Mannose Receptor C type1 (MRC1) and Mannose Receptor C Type 2 (MRC2) along with four important members that exist in mammals as CD206 cluster, endo180 (CD280), Phospholipase A (2) receptor (PLA (2) R), CD-205 which advocate for variety of biological responses such as activation of innate and adaptive immune responses in tumor/malignancies, tuberculosis, viral infections and engulfing/phagocytic behavior against various pathogenic microorganisms. Significantly, CD206 is endowed with immune recognition of a broad spectrum of pathogens, antigen internalization and presentation, tissue repair as a novel therapeutic target. CD206 is a biomarker for alternatively activated

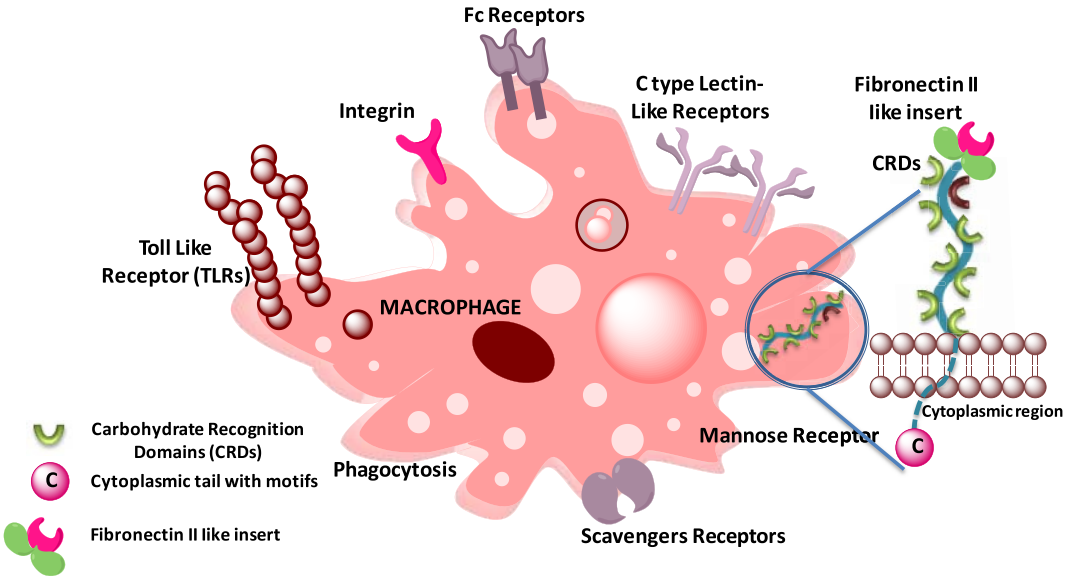


Figure 2. Pictorial visualization of macrophages expressing different cell surface receptors, specifically targeting mannose receptors (MRs).

macrophage M2 and specifically recognizes mannosylated and sulphated carbohydrates.[15] Mannose receptors endowed as a prognostic marker in disparate pathological conditions such as liver cirrhosis,[16] hepatitis,[17] rheumatoid arthritis,[14] dengue viral infection.[18] Mannose receptors are overexpressed on Antigen Presenting Cells (APCs) at the infection/inflammation sites and macrophages considered as appropriate candidates for targeting the diseased state. This way, mannose receptors have become center of attention in the development of an active targeting nanocarrier system for therapeutic drug and gene delivery.

3. Mannosylated nanovector for MMR targeting

Mannose is widely used monosaccharide for treating various pathological diseases and the generation of immune responses. Mannose effectively combines with disparate drugs, gene, antigen, photosensitizer for enhancing immunotherapy, photothermal therapy, and chemotherapy and microbiocidal action.[19] Nanocarrier systems for macrophage delivery render several benefits over traditional delivery including improved treatment strategies, declined peripheral side effects, augmented drug shelf life and worthwhile intracellular targeting. Remarkably, physicochemical properties of a nanovector must render cationic charge and mannose structure which would be recognized by mannose receptors present on the infected macrophages. Over the last few years, enormous research has been implicated for the development of mannosylated nanocarrier system using different biomolecules/ organic/ inorganic molecules such as polymeric nanovectors, lipid-based, cyclodextrin, mannosylated liposomes, niosomes, nanodots, nanoparticles, galactomannan (guar gum) based nanoparticles.[20] A recent study by Shahnaz et al. has revealed that mannose-linked thiolated chitosan (TC) nanocarrier, loaded with amphotericin B, has been explored for treating visceral leishmaniasis. It has been observed that combinatorial nanocarrier improves bioavailability, pharmacodynamic and pharmacokinetic profile of the active drug, consequently enhances treatment outcome. Modification of TC polymer with mannose ameliorates particle loaded drug uptake by macrophages surrounding *Leishmania* amastigotes.[21] Vossen and co-workers have demonstrated the accumulation of PEGylated dendritic polyglycerol (PG–PEG), decorated with mannose and conjugated with the anti-parasitic drug (amphotericin B), in the phagolysosomes in leishmaniasis-infected macrophages and these nanosynthesized conjugates target specifically CD205 receptors overexpressed in parasite infections.[22] In another study, Zhang et al. demonstrated that mannosylated hyaluronan based

nanohybrids for transfection studies showed enhanced transfection of its plasmid DNA complexes because of the improved uptake facilitated by a receptor-mediated phenomenon.[23] The authors showed that higher uptake of the complexes in macrophages provided evidence to support this concept exhibiting potential of such nanohybrids as macrophage targeted gene delivery vectors. Mannose-mediated transfer of therapeutic cargos into dendritic cells was also achieved successfully expressing the mannose receptors. The study demonstrated the targeted delivery of mannose and immune adjuvant CpG oligonucleotide loaded with tumor-specific TRP2 peptide as theranostic against tumor upregulation in dendritic cells.[24] Recent research by Li et al. has shown the efficacy of siRNA delivery as a therapeutic agent, employed for the management of malignant bone tumor. They designed layered double hydroxide (Aluminium and magnesium) nanoparticle fabrication, functionalized with mannose, with siRNA for efficient gene delivery to osteosarcoma site. Mannose-decorated nanocomposites reported efficient cellular uptake via receptor-mediated internalization due to strong affinity for receptor binding that was highly expressed on the cancer cell membrane. Protonation of amine groups present in nanocomposite promoted siRNA release through the "sponge effect" in the endosome.[25] Recently, polyethylenimine (PEI) functionalized single-walled carbon nanotubes conjugated with viral antigen protein and mannose for delivery of nanovaccine in fish for the cure of viral outbreak has been reported. It has been clearly mentioned that insertion of mannosylated peptides, as well as therapeutic agent, provoke T cells production leading to more robust immune responses.[26] Macrophages present on the surface of the alveolar region perform dual behavior via phagocytic action and systemic clearance of nanocarrier for maintaining bioavailability. Such peculiar behavior encouraged Costa et al. for synthesizing mannose anchored solid lipid nanoparticles (SLN) encapsulating isoniazid (antitubercular drug) targeting *mycobacterium tuberculosis*-infected alveolar macrophages that are overexpressed on the alveoli. Lipid matrix in solid shell is widely used for delivering hydrophobic drug without enzyme degradation but herein isoniazid (hydrophilic drug) was conjugated using solvent emulsification-evaporation method and delivered to infected macrophages. Cellular uptake and internalization slowed down by mannose anchored SLN due to competitive receptor binding and non-specific interaction with lungs epithelium and alveolar surface.[27] Another research by Prabhakar et al. depicted mannose linked polymeric nano-vehicle loaded with rifampicin-Zn^{2+} for targeted drug delivery. Plausibly, mannose receptor binding mechanism is similar to other nanocarrier, but herein Zn^{2+} of polymeric nanoparticle inflates concentration of rifampicin in the intercellular matrix leading to enhanced antitubercular activity.[28]

He et al. investigated dual targeting nanocarrier comprised of mannose anchored carboxymethyl chitosan and hyaluronan embedding protamine sulfate-CpG oligodeoxynucleotide (ODN) complex via self-assembled scaffold formation. Mannose modified nanocarrier specifically targeted macrophages due to overexpressed mannose and CD44 receptor at the infection site. It has been illustrated that positive charge of protamine sulfate and negative charge of ODN formed complex and penetrated easily into cell membrane endorsing nuclear translocation along with biocompatible and biodegradable behavior. Dual targeted delivery system inflates pro-inflammatory cytokines level owing to strong immuno-stimulatory capability in malignancy state.[29] Mannose receptors have been specifically approached for efficient gene delivery for improving anticancer therapy. Galactomannan (guar gum) conjugated with low molecular weight PEI formed a self-assembled complex where anticancer drug was entrapped within the shell. This complex interacted with mannose receptors overexpressed on macrophages residing in Triple-Negative Breast Cancer (TNBC). Ligand binding and cellular uptake revealed conformation for penetration via endocytosis. Further, endosomal swelling due to "proton sponge effect" led to endosomal release, which triggered gene release and transfer to nucleus and subsequently achieving effective gene therapy. The fabricated non-viral gene delivery vectors exhibited least toxic effects, non-immunogenicity, biocompatibility and sufficient cationic charge.[30]

Macrophage (M2) promotes tumor development via downregulating immune response mechanism, alternatively called Tumor-associated macrophages (TAM). Furthermore, TAM is considered as a promising therapeutic target for cancer therapy. In an order to establish this fact, Gao et al. designed a theranostic probe targeting TAM, comprised of aggregation induced emission core embedded in two flanked TAM targeting α-mannoside molecules. Mechanistically, TPE-Man interacted specifically with mannose and CD206 receptors, vastly expressed in TAM. On excitation with visible light radiations, internalized AIE sensitizes and TPE-Man generates reactive oxygen species (ROS) that ablate malignant cells and down-regulate M2 action, thus suppressing tumor growth.[31] Delivering an antigen for generation of inherent immunity in the cancer patients is the new

approach as a noble treatment strategy. This concept was adopted by Dong et al. for transporting ovalbumin (antigen) which was adsorbed on multi-walled mannose linked carbon nanotubes. Antigen-presenting nanodots bound mannose receptors and subsequently engulfed by dendritic cells activating major histocompatibility complex (MHC)/peptide complex on their surface; which further stimulated effective activation of both $CD8^+$ and $CD4^+$ T lymphocytes as well as released cytokines and finally initiated immune response which proved as a key strategy for cancer immunotherapy.[32] Mannose has been exploited drastically over the last five years with the motive to enhance disease treatment strategies. For enumerating better understanding, mannose functionalized nanocarrier have been illustrated diagrammatically in **Figure 3.**

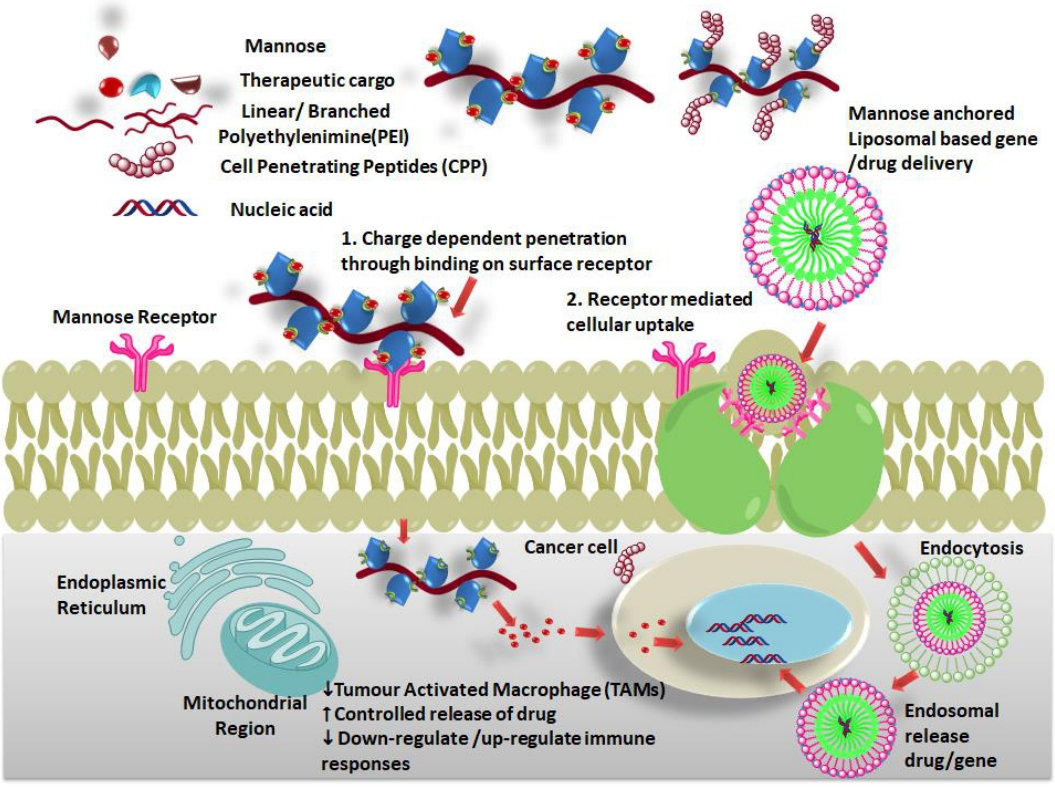


Figure 3. Diagrammatic representation of mannose receptor mediated cellular uptake of mannose-bearing nanovectors.

3. Mannan enriched nanovectors for effective drug/gene delivery

Mannan is the plant polysaccharide that owns linear structure containing mannose residues with β-1-4 linkages. Mannose and glucose carve the backbone and their different linkages allow the formation of three different variants of natural polysaccharides such as mannan, glucomannan and galactomannan. Recently, mannan has been explored as nanocarrier due to strong binding affinity with mannose receptors (MR) and endocytosis mediated cellular uptake followed by specific delivery of a drug to the target site without imparting any peripheral adverse effects. Mugade et al. have demonstrated that mannan sulphate is an efficient reducing/capping agent and can be utilized for the production of silver nanoparticles. The synthesized mannan sulphate capped AgNPs have been shown to be efficiently uptaken via mannose receptor-mediated endocytosis which can be further used for the designing of theranostics, wound dressings, biosensor and for other biomedical applications.[33] A recent study by Bartheldyova et al. demonstrated efficient drug delivery by using monosaccharide, oligosaccharide and polysaccharide-conjugated liposomal/lipid-based

nanoparticles. The basic mechanism for drug delivery depicted as receptor-mediated endosomal engulfment and release of active drug at the target region along with activation of antigen-presenting cells, up-regulating the immune response.[34] Glucomannan is another polysaccharide present extensively in plants and microorganisms. It consists of a backbone structure of D-mannose and D-glucose linked with β-1-4 glycoside linkage. It has several benefits such as outstanding stability, least toxicity, water solubility, biocompatibility, and biodegradability. Glucomannan and its derivatives, and their nano/microparticles elicit varieties of biological activities such as anti-inflammatory,[35] anti-colitis,[36] initiate cellular immune response,[37] anti-diabetic,[38] in cancer immunotherapy,[39] antioxidant,[40] anti-atherosclerotic,[40] promote angiogenesis,[41] ameliorate bone regeneration,[42] help in diabetic wound healing,[43] anti-obesity,[44] antibacterial,[45] as probiotic,[46] bifidogenic effect,[47] antitumor activity,[48] potentiate osteointegration,[49] hypolipidemic,[50] immunomodulator,[51] treat PCOS subjects with insulin resistance,[52] perform hemorrhage control via hemostatic management,[53] antitubercular activity,[54] etc. Aforementioned therapeutic effects of the glucomannan-containing formulations are summarized in **Table 1** along with their efficacy. Guerreiro et al. have described the effect of konjac glucomannan (KGM) microparticles loaded with isoniazid and rifabutin. The mannose backbone marks KGM susceptible for macrophage targeting, and the resulting effect could be arbitrated by macrophage surface lectin receptors. Furthermore, particles persist suitable properties regarding surface topography/geometry and size to reach the alveolar region and stimulate macrophage induced phagocytosis.[55] Glucomannan "all in one" scaffold was synthesized by Niu et al. which entailed bone repair by triggering macrophages to release pro-regenerative cytokines. Moreover, released

Table 1. Tabular representation of therapeutic effects of glucomannan-containing formulations along with their efficacy rate

S. No.	Glucomannan-formulations	Therapeutic effects	Efficacy Rate	Ref.
1.	Konjac glucomannan (KGM), ginsenoside, polyphenol, fish scale collagen nanocomplex	Anti-inflammatory, anticancer	~80-90% inhibition of cancer cells	35
2.	OKGM peptosome–MIR31 microspheres	Anti-colitis	Inhibit expression of Il7R and Il17RA (inflammatory cytokine)	36
3.	Carboxymethylated KGM and Quaternized KGM	Inflate cellular immune response	Higher IL-2 and IFN-ϒ production	37
4.	Glucomannan from *Amorphophallus albus*	Diabetes mellitus (Types 2)	~70-80% hypoglycaemic effect	38
5.	Alendronate-glucomannan (ALN-BSP conjugate)	Cancer immunotherapy	~80-83% depletion of tumour associated macrophages	39
6.	Glucomannan/spirulina-Restructured Pork	Antioxidant, Atherosclerosis	Inflate antioxidant enzymes and decline cholesterol level	40
7.	Glucomannan -tyramine conjugate	Promote angiogenesis	~80-90% increased production of growth factors	41
8.	Acemannan	Bone regeneration	~70-90% increased bone surface, bone volume	42
9.	Glucomannan-keratin grafted *Avena sativa* scaffold	Diabetic wound healing	~80-95% wound healing	43
10.	BC/KGM fiber	Anti-obesity	~60-90% increased adipocytokines and adipogenesis associated proteins	44

11.	Ag-loaded KGM-montmorillonite film	Antibacterial	Prolonged effect ~80%	45
12.	Oxidized KGM	As probiotic	Inflate intestinal and gut flora	46
13.	Ultrasound and acid hydrolyzed KGM	Bifidogenic effect	~60-70% and 80-90% bifidobacterial growth	47
14.	Selenium modified KGM oligosaccharide	Antitumor activity	~90-95% increased apoptotic activity	48
15.	Acemannan hydrogel	Osteointegration	~70-80% Inflation in bone regeneration	49
16.	Konjac extracted Glucomannan	Hypolipidemic	Inflation in HDL with declining low density lipoprotein cholesterol, triglycerols, total cholesterol	50
17.	2,3-*O*-acteylated -1, 4-β-D-glucomannan (DOP-1-1) from *Dendrobium officinale*	Immunomodulator	Upregulate expression of CCL-4 and IP-10 thus stimulate NF-κB signaling pathway,	51

cytokines helped in the induction of osteogenesis within bone progenitor cells. These promising scaffold agents were used for healing critical wounds via activating immune feedback mechanism.[56] Diversified studies have been conducted for transporting drug, gene, peptide, antigen using glucomannan as multifunctional nanovehicles, which directly target mannose receptors and its associated families for escalating therapeutic efficacy. Simultaneously, controlled and sustained drug release, shelf life, stability get boosted when glucomannan is incorporated in nanocarriers.

Galactomannan (GM), a natural polysaccharide comprised of linear D-mannan chains linked D-galactose by glycosidic bonds, have intrinsic capability for macrophage internalization via lectin like receptors, i.e. mannose receptors (CD206). Target binding susceptibility of galactomannan is supposed to enhance in TAMs owing to their overexpressed mannose receptors (CD206) and galactose-type C-lectins. These peculiar properties of galactomannan were utilized by Manisha et al. for delivering anticancer drug via synthesizing self-assembled hydrazinocurcumin (HC) loaded PEGylated GM nanoparticles (NPs). Inflated cellular uptake and internalization down regulated M2 phenotype and treatment with PSGM-HCNPs initiated production of the ROS, curbed the protein expression, and altered the secretory cytokines' profile. Synthesized nanoparticles acted as potential therapeutic nanocarriers in cancer therapy.[57]

5. Conclusions and outlook

With the approach of improvising treatment strategies for various disorders, targeted delivery of therapeutic molecule/gene at infection site leads to surpassing unwanted adverse effects observed due to peripheral action of the drug molecules. Systemic/peripheral release of drug reduces blood plasma concentration and stability thus allowing drug molecules to freely move in peripheral compartments away from target site. Bypassing this serious concern, targeted drug delivery has proved itself as the best alternative. The controlled rate of delivery and specific binding with target cells via receptors are the explicit features of targeting. The targeting ligand has to be precise for the macrophages of interest to reduce the dose regimen, improve the patient compliance and reduce side effects associated with a vector/therapeutic. Further studies should consider other cells to confirm the specificity of nanocarriers in the evaluation of cellular uptake.

Similarly, targeted gene delivery has become the most appreciable method for treating malignancy like diseases. The prominent messenger would be inculcated as “nanocarrier” for effective drug delivery. Nowadays, mannose receptor has become a most burgeoning family of receptors present on the infected macrophages. Due to the overexpression of MR (CD205, CD206, CD208, Endo180) on macrophages, these reside on the infected cell surface. MR enhances cellular uptake of a nanocarrier via receptor-mediated endocytosis; thereupon, boosts the drug release in a controlled manner due to charge difference and elicits profound therapeutic action, downregulates TAMs in tumor cells, suppresses alveolar macrophages, produces oxidative stress that kills infected

macrophages and pathogen-infected macrophage region. In current state of art, various studies have been progressing day by day for generating vaccine therapy, gene therapy, efficient drug therapy using mannose, mannan, glucomannan, galactomannan in the nanocarriers. Due to their low toxicity, biocompatibility, biodegradability and excellent stability as well as profound pharma-codynamic/ pharmacokinetic profiles, researchers have been using such naturally occurring polysaccharides as nanovehicles conjugated with another polymer/ peptide/lipid-based NPs/carbon nanotubes. The desired clinical experiment is, however, likely to be greatly hampered by cytotoxicity and instability in circulation. To be successful in clinics, problems associated with the manufacturing of carriers, long term stability and low cost should be addressed. Notably, more confirmative studies are warranted that will generate a mechanism of action to clearly explain the therapeutic efficacy of these receptor-based therapeutic delivery systems.

Acknowledgement

Authors gratefully acknowledge the financial support from the CSIR project (OLP1144). IS is thankful to the Department of Science and Technology (DST), New Delhi, India for awarding DST-INSPIRE fellowship. Authors acknowledge Perkin Elmer Chem Draw® professional version 15.0.0.106 and Microsoft Office for graphical sketches.

References

1. Masood, F., Polymeric nanoparticles for targeted drug delivery system for cancer therapy. *Mater. Sci. Eng. C,* **2016,** *60*, 569-578.
2. Jain, K.; Mehra, N. K.; Jain, V. K.; Jain, N. K., IPN Dendrimers in Drug Delivery. In *Interpenetrating Polymer Network: Biomedical Applications* **2020**; 143-181.
3. Khoee, S.; Yaghoobian, M., Niosomes: A novel approach in modern drug delivery systems. In *Nanostructures for Drug Delivery* **2017**, 207-237.
4. Jacob, J.; Haponiuk, J. T.; Thomas, S.; Gopi, S., Biopolymer based nanomaterials in drug delivery systems: A review. *Mater. Today Chem.,* **2018,** *9*, 43-55.
5. Hu, G.; Guo, M.; Xu, J.; Wu, F.; Fan, J.; Huang, Q.; Yang, G.; Lv, Z.; Wang, X.; Jin, Y., Nanoparticles targeting macrophages as potential clinical therapeutic agents against cancer and inflammation. *Front. Immunol.,* **2019,** *10*, 1998.
6. Munsell, E.V.; Ross, N.L.; Sullivan, M.O., Journey to the center of the cell: current nanocarrier design strategies targeting biopharmaceuticals to the cytoplasm and nucleus. *Curr. Pharm. Des.,* **2016,** *22*, 1227-1244.
7. Yuan, Y.; Long, L.; Liu, J.; Lin, Y.; Peng, C.; Tang, Y.; Zhou, X.; Li, S.; Zhang, C.; Li, X.; Zhou, X., The double-edged sword effect of macrophage targeting delivery system in different macrophage subsets related diseases. *J. Nanobiotechnol.,* **2020,** *18*, 168.
8. Ponzoni, M.; Pastorino, F.; Di Paolo, D.; Perri, P.; Brignole, C., Targeting macrophages as a potential therapeutic intervention: impact on inflammatory diseases and cancer. *Int. J. Mol. Sci.,* **2018,** *19*, 1953.
9. Ardura, J. A.; Rackov, G.; Izquierdo, E.; Alonso, V.; Gortazar, A. R.; Escribese, M. M., Targeting macrophages: Friends or foes in disease? *Front. Pharmacol.,* **2019,** *10*, 1255.
10. Gordon, S.; Plüddemann, A.; Mukhopadhyay, S., Plasma membrane receptors of tissue macrophages: functions and role in pathology. *J. Pathol.* **2020,** *250*, 656-666
11. Nelemans, L. C.; Gurevich, L., Drug delivery with polymeric nanocarriers—Cellular uptake mechanisms. *Materials,* **2020,** *13*, 366.
12. Papini, E.; Tavano, R.; Mancin, F., Opsonins and dysopsonins of nanoparticles: Facts, concepts, and methodological guidelines. *Front. Immunol.,* **2020,** *11*, 2343.
13. Jahagirdar, P.; Lokhande, A. S.; Dandekar, P.; Devarajan, P. V., Mannose receptor and targeting strategies. In *Targeted Intracellular Drug Delivery by Receptor Mediated Endocytosis*, Devarajan, P. V.; Dandekar, P.; D'Souza, A. A., Eds. Springer International Publishing: Cham, 2019, *39*, 433-456.
14. Hagert, C.; Sareila, O.; Kelkka, T.; Jalkanen, S.; Holmdahl, R., The macrophage mannose receptors regulate mannan-induced psoriasis, psoriatic arthritis, and rheumatoid arthritis-like disease models. *Front. Immunol.,* **2018,** *9*, 114.
15. Suzuki, Y.; Shirai, M.; Asada, K.; Yasui, H.; Karayama, M.; Hozumi, H.; Furuhashi, K.; Enomoto, N.; Fujisawa, T.; Nakamura, Y.; Inui, N.; Shirai, T.; Hayakawa, H.; Suda, T., Macrophage mannose receptor, CD206, predict prognosis in patients with pulmonary tuberculosis. *Sci. Rep.,* **2018**, *8*, 1-9.
16. Rainer, F.; Horvath, A.; Sandahl, T. D.; Leber, B.; Schmerboeck, B.; Blesl, A.; Groselj-Strele, A.; Stauber, R. E.; Fickert, P.; Stiegler, P.; Møller, H. J.; Grønbaek, H.; Stadlbauer, V., Soluble CD163 and soluble mannose receptor predict survival and decompensation in patients with liver cirrhosis, and correlate with gut permeability and bacterial translocation. *Aliment. Pharmacol. Ther.,* **2018,** *47*, 657-664.
17. Laursen, T. L.; Wong, G. L. H.; Kazankov, K.; Sandahl, T.; Møller, H. J.; Hamilton-Dutoit, S.; George, J.; Chan, H. L. Y.; Grønbæk, H., Soluble CD163 and mannose receptor associate with chronic hepatitis B activity and fibrosis and decline with treatment. *J. Gastroenterol. Hepatol.,* **2018,** *33*, 484-491.
18. Alzate, J. F. A.; Rodenhuis-Zybert, I. A.; Hernández, J. C.; Smit, J. M.; Urcuqui-Inchima, S., Human macrophages differentiated in the presence of vitamin D3 restrict dengue virus infection and innate responses by downregulating mannose receptor expression. *PLOS Negl. Trop. Dis.,* **2017,** *11*, e0005904.
19. Wei, Z.; Huang, L.; Cui, L.; Zhu, X., Mannose: Good player and assister in pharmacotherapy. *Biomed. Pharmacother.,* **2020,** *129*, 110420.
20. Patil, T. S.; Deshpande, A. S., Mannosylated nanocarriers mediated site-specific drug delivery for the treatment of cancer and other infectious diseases: A state of the art review. *J. Control. Rel.,* **2020,** *320*, 239-252.
21. Shahnaz, G.; Edagwa, B. J.; McMillan, J.; Akhtar, S.; Raza, A.; Qureshi, N. A.; Yasinzai, M.; Gendelman, H. E., Development of mannose-anchored thiolated amphotericin B nanocarriers for treatment of visceral leishmaniasis. *Nanomedicine,* **2017,** *12*, 99-115.
22. Vossen, L. I.; Domínguez-Asenjo, B.; Gutiérrez-Corbo, C.; Pérez-Pertejo, M. Y.; Balaña-Fouce, R.; Reguera, R. M.; Calderón, M., Mannose-decorated dendritic polyglycerol nanocarriers drive antiparasitic drugs to *Leishmania infantum*-infected macrophages. *Pharmaceutics,* **2020,** *12*, 915.
23. Zhang, Y.; Wang, Y.; Zhang, C.; Wang, J.; Pan, D.; Liu, J.; Feng, F., Targeted gene delivery to macrophages by biodegradable star-shaped polymers. *ACS Appl. Mater. Interfaces,* **2016,** *8*, 3719-3724.
24. Lai, C.; Duan, S.; Ye, F.; Hou, X.; Li, X.; Zhao, J.; Yu, X.; Hu, Z.;

Tang, Z.; Mo, F.; Yang, X.; Lu, X., The enhanced antitumor-specific immune response with mannose- and CpG-ODN-coated liposomes delivering TRP2 peptide. *Theranostics,* **2018**, *8*, 1723-1739
25. Li, L.; Zhang, R.; Gu, W.; Xu, Z. P., Mannose-conjugated layered double hydroxide nanocomposite for targeted siRNA delivery to enhance cancer therapy. *Nanomedicine: NBM,* **2018,** *14*, 2355-2364.
26. Zhu, B.; Zhang, C.; Zhao, Z.; Wang, G.-X., Targeted delivery of mannosylated nanoparticles improve prophylactic efficacy of immersion vaccine against fish viral disease. *Vaccines,* **2020,** *8*, 87.
27. Costa, A.; Sarmento, B.; Seabra, V., Mannose-functionalized solid lipid nanoparticles are effective in targeting alveolar macrophages. *Eur. J. Pharm. Sci.,* **2018,** *114*, 103-113.
28. Praphakar, R. A.; Munusamy, M. A.; Alarfaj, A. A.; Kumar, S. S.; Rajan, M., Zn^{2+} cross-linked sodium alginate-g-allylamine-mannose polymeric carrier of rifampicin for macrophage targeting tuberculosis nanotherapy. *New J. Chem.,* **2017,** *41*, 11324-11334.
29. He, X.-Y.; Liu, B.-Y.; Wu, J.-L.; Ai, S.-L.; Zhuo, R.-X.; Cheng, S.-X., A dual macrophage targeting nanovector for delivery of oligodeoxynucleotides to overcome cancer-associated immunosuppression. *ACS Appl. Mater. Interfaces,* **2017,** *9*, 42566-42576.
30. Jana, P.; Ghosh, S.; Sarkar, K., Low molecular weight polyethyleneimine conjugated guar gum for targeted gene delivery to triple negative breast cancer. *Int. J. Biol. Macromol.,* **2020,** *161*, 1149-1160.
31. Gao, X.; Mao, D.; Zuo, X.; Hu, F.; Cao, J.; Zhang, P.; Sun, J. Z.; Liu, J.; Liu, B.; Tang, B. Z., Specific targeting, imaging, and ablation of tumor-associated macrophages by theranostic mannose–AIEgen conjugates. *Anal. Chem.,* **2019,** *91*, 6836-6843.
32. Dong, Z.; Wang, Q.; Huo, M.; Zhang, N.; Li, B.; Li, H.; Xu, Y.; Chen, M.; Hong, H.; Wang, Y., Mannose-modified multi-walled carbon nanotubes as a delivery nanovector optimizing the antigen presentation of dendritic cells. *ChemistryOpen* **2019,** *8*, 915-921.
33. Mugade, M.; Patole, M.; Pokharkar, V., Bioengineered mannan sulphate capped silver nanoparticles for accelerated and targeted wound healing: Physicochemical and biological investigations. *Biomed. Pharmacother.,* **2017,** *91*, 95-110.
34. Bartheldyová, E.; Turánek Knotigová, P.; Zachová, K.; Mašek, J.; Kulich, P.; Effenberg, R.; Zyka, D.; Hubatka, F.; Kotouček, J.; Čelechovská, H.; Hézová, R.; Tomečková, A.; Mašková, E.; Fojtíková, M.; Macaulay, S.; Bystrický, P.; Paulovičová, L.; Paulovičová, E.; Drož, L.; Ledvina, M.; Raška, M.; Turánek, J., *N*-Oxy lipid-based click chemistry for orthogonal coupling of mannan onto nanoliposomes prepared by microfluidic mixing: Synthesis of lipids, characterisation of mannan-coated nanoliposomes and in vitro stimulation of dendritic cells. *Carbohydr. Polym.,* **2019,** *207*, 521-532.
35. Ngo, D. Q.; Nguyen, T. C.; Nguyen, T. D.; Phung, T. L.; Vu, Q. T.; Thai, H., A novel biopolymer nano-complex based on fish scale collagen, konjac glucomannan, camellia chrysantha polyphenols and ginsenoside Rb1: Preparation, characterization and its bioactivity. *J. Polym. Environ.,* **2021**, doi:10.1007/s10924-020-02022-0
36. Tian, Y.; Xu, J.; Li, Y.; Zhao, R.; Du, S.; Lv, C.; Wu, W.; Liu, R.; Sheng, X.; Song, Y.; Bi, X.; Li, G.; Li, M.; Wu, X.; Lou, P.; You, H.; Cui, W.; Sun, J.; Shuai, J.; Ren, F.; Zhang, B.; Guo, M.; Hou, X.; Wu, K.; Xue, L.; Zhang, H.; Plikus, M. V.; Cong, Y.; Lengner, C. J.; Liu, Z.; Yu, Z., MicroRNA-31 reduces inflammatory signaling and promotes regeneration in colon epithelium, and delivery of mimics in microspheres reduces colitis in mice. *Gastroenterology,* **2019,** *156*, 2281-2296.
37. Chen, N.; Zhu, P.; Du, T.; Han, K.; Wang, D.; Ye, J.; Xiao, S.; Ye, X.; Wang, Y., Preparation of modified konjac glucomannan nanoparticles and their application as vaccine adjuvants to promote ovalbumin-induced immune response in mice. *Pharm. Res.,* **2018,** *35*, 105.
38. Wu, C.-Y.; Zhou, J.; Long, F.; Zhang, W.; Shen, H.; Zhu, H.; Xu, J.-D.; Li, S.-L., Similar hypoglycemic effects of glucomannan and its enzyme degraded products from *Amorphophallus albus* on type 2 diabetes mellitus in mice and potential mechanisms. *Food Funct.,* **2020,** *11*, 9740-9751.
39. Zhan, X.; Jia, L.; Niu, Y.; Qi, H.; Chen, X.; Zhang, Q.; Zhang, J.; Wang, Y.; Dong, L.; Wang, C., Targeted depletion of tumour-associated macrophages by an alendronate–glucomannan conjugate for cancer immunotherapy. *Biomaterials,* **2014,** *35*, 10046-10057.
40. González-Torres, L.; Matos, C.; Vázquez-Velasco, M.; Santos-López, J. A.; Sánchez-Martínez, I.; García–Fernández, C.; Bastida, S.; Benedí, J.; Sánchez-Muniz, F. J., Glucomannan- and glucomannan plus spirulina-enriched pork affect liver fatty acid profile, LDL receptor expression and antioxidant status in Zucker fa/fa rats fed atherogenic diets. *Food Nutr. Res.,* **2017,** *61*, 1264710.
41. Feng, Y.; Li, Q.; Wu, D.; Niu, Y.; Yang, C.; Dong, L.; Wang, C., A macrophage-activating, injectable hydrogel to sequester endogenous growth factors for in situ angiogenesis. *Biomaterials,* **2017,** *134*, 128-142.
42. Godoy, D. J. D.; Chokboribal, J.; Pauwels, R.; Banlunara, W.; Sangvanich, P.; Jaroenporn, S.; Thunyakitpisal, P., Acemannan increased bone surface, bone volume, and bone density in a calvarial defect model in skeletally-mature rats. *J. Dental Sci.,* **2018,** *13*, 334-341.
43. Veerasubramanian, P. K.; Thangavel, P.; Kannan, R.; Chakraborty, S.; Ramachandran, B.; Suguna, L.; Muthuvijayan, V., An investigation of konjac glucomannan-keratin hydrogel scaffold loaded with *Avena sativa* extracts for diabetic wound healing. *Coll. Surf. B: Biointerfaces,* **2018,** *165*, 92-102.
44. Zhai, X.; Lin, D.; Zhao, Y.; Li, W.; Yang, X., Enhanced anti-obesity effects of bacterial cellulose combined with konjac glucomannan in high-fat diet-fed C57BL/6J mice. *Food Funct.,* **2018,** *9*, 5260-5272.
45. Zhu, W.; Li, J.; Lei, J.; Li, Y.; Chen, T.; Duan, T.; Yao, W.; Zhou, J.; Yu, Y.; Liu, Y., Silver nanoparticles incorporated konjac glucomannan-montmorillonite nacre-like composite films for antibacterial applications. *Carbohydr. Polym.,* **2018,** *197*, 253-259.
46. Zhang, L.; Wu, Y.; Xu, H.; Yao, Y., Effects of oxidized konjac glucomannan on the intestinal microbial flora and intestinal morphology of *Schizothorax prenanti*. *Aquac. Int.,* **2017,** *25*, 233-250.
47. Song, A.-X.; Mao, Y.-H.; Siu, K.-C.; Wu, J.-Y., Bifidogenic effects of *Cordyceps sinensis* fungal exopolysaccharide and konjac glucomannan after ultrasound and acid degradation. *Int. J. Biol. Macromol.,* **2018,** *111*, 587-594.
48. Li, K.; Qi, H.; Liu, Q.; Li, T.; Chen, W.; Li, S.; Piao, H.-l.; Yin, H., Preparation and antitumor activity of selenium-modified glucomannan oligosaccharides. *J. Funct. Foods,* **2020,** *65*, 103731.
49. Pachimalla, P. R.; Mishra, S. K.; Chowdhary, R., Evaluation of hydrophilic gel made from Acemannan and *Moringa oleifera* in enhancing osseointegration of dental implants. A preliminary study in rabbits. *J. Oral Biol. Craniofac. Res.,* **2020,** *10*, 13-19.
50. Chen, H.; Nie, Q.; Hu, J.; Huang, X.; Zhang, K.; Pan, S.; Nie, S., Hypoglycemic and hypolipidemic effects of glucomannan extracted from konjac on Type 2 diabetic rats. *J. Agric. Food Chem.,* **2019,** *67*, 5278-5288.
51. Huang, Y.-P.; He, T.-B.; Cuan, X.-D.; Wang, X.-J.; Hu, J.-M.;

Sheng, J., 1,4-β-d-Glucomannan from *Dendrobium officinale* activates NF-κB via TLR4 to regulate the immune response. *Molecules,* **2018,** *23*, 2658.
52. Troisi, J.; Cinque, C.; Giugliano, L.; Symes, S.; Richards, S.; Adair, D.; Cavallo, P.; Sarno, L.; Scala, G.; Caiazza, M.; Guida, M., Metabolomic change due to combined treatment with myo-inositol, D-chiro-inositol and glucomannan in polycystic ovarian syndrome patients: A pilot study. *J. Ovar. Res.,* **2019,** *12*, 25.
53. Shi, Z.; Lan, G.; Hu, E.; Lu, F.; Qian, P.; Liu, J.; Dai, F.; Xie, R., Puff pastry-like chitosan/konjac glucomannan matrix with thrombin-occupied microporous starch particles as a composite for hemostasis. *Carbohydr. Polym.,* **2020,** *232*, 115814.
54. Guerreiro, F.; Swedrowska, M.; da Costa, A.M.R.; Grenha, A.; and Forbes, B.; *In vitro* behaviour of konjac glucomannan microparticles aimed at pulmonary tuberculosis therapy. *J. Aerosol Med. Pulm. Drug Deliv*., **2020**, *33*, A12-A12.
55. Guerreiro, F.;.Pontes, J. F.; da Costa, A. M. R.; Grenha, A., Spray-drying of konjac glucomannan to produce microparticles for an application as antitubercular drug carriers. *Powder Technol.*, **2019**, *342*, 246-252.
56. Niu, Y.; Wang, L.; Yu, N.; Xing, P.; Wang, Z.; Zhong, Z.; Feng, Y.; Dong, L.; Wang, C., An "all-in-one" scaffold targeting macrophages to direct endogenous bone repair *in situ*. *Acta Biomaterialia,* **2020**, *111*, 153-169.
57. Kumari, M.; Purohit, M. P.; Pahuja, R.; Patnaik, S.; Shukla, Y.; Kumar, P.; Gupta, K. C., Pro-inflammatory macrophage polarization enhances the anti-cancer efficacy of self-assembled galactomannan nanoparticles entrapped with hydrazino-curcumin. *Drug Deliv. Transl. Res.,* **2019,** *9*, 1159-1188.