Applications of mannose-binding lectins and mannan glycoconjugates in nanomedicine

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Abstract Glycosylated nanoparticles (NPs) have drawn a lot of attention in the biomedical field over the past few decades, particularly in applications like targeted drug delivery. Mannosylated NPs and mannan-binding lectins/proteins (MBL/MBP) are emerging as promising tools for delivery of drugs, medicines, and enzymes to targeted tissues and cells as nanocarriers, enhancing their therapeutic benefits while avoiding the adverse effects of the drug. The occurrence of plenty of lectin receptors and their mannan ligands on cell surfaces makes them multifaceted carriers appropriate for specific delivery of bioactive drug materials to their targeted sites. Thus, the present review describes the tethering of mannose (Man) to several nanostructures, like micelles, liposomes, and other NPs, applicable for drug delivery systems. Bioadhesion through MBL-like receptors on cells has involvements applicable to additional arenas of science, for example gene delivery, tissue engineering, biomaterials, and nanotechnology. This review also focuses on the role of various aspects of drug/antigen delivery using (i) mannosylated NPs, (ii) mannosylated lectins, (iii) amphiphilic glyco-polymer NPs, and (iv) natural mannan-containing polysaccharides, with most significant applications of MBL-based NPs as multivalent scaffolds, using different strategies.

Keywords Mannans · Mannose-binding lectins · Biomaterials · Nanoparticles · Lectin-mediated targeting · Targeted drug delivery · Drug delivery systems · Nanomedicine · Nanostructures

Introduction

Lectins are glycoproteins which adhere to specific sugars and cause agglutination and precipitation amongst cells and glycoconjugates without affecting their covalent linkages [1]. They are ubiquitously present and found in all kinds of plants [2], animals [3], and microorganisms [4]. Lectins exhibit specificity towards different kinds of sugars and can be categorized under four major classes as (i) glucose and/or mannos specific, (ii) galactose and N-acetyl-d-galactosamine or glucosamine specific, (iii) l-fucose specific, and (iv) sialic acid specific [5]. They initiate cell–cell interactions in biological systems [5]. The capacity of a lectin to attach to a specific carbohydrate imparts them with an exceptional property. Few
Lectins and their sugar specificities have been categorised in Table 1. Carbohydrates which are extensively dispersed in tissues and are found on cell surfaces have a function in a range of biological processes, including cell adhesion, inflammation, cell activation, and immunological responses via lectin interactions [6]. Usually, plant lectins are hardy proteins and can withstand highly acidic environment of the stomach. Because of their sugar specificity, lectins may bind to the membrane in the gut and ruin the cell permeability or may enter the circulation and cause allergic reactions [7]. Such lectins cause severe toxicity in humans [8, 9].

Few disorders where sugar-based drugs have an influence include AIDS, pneumonia, diabetes, cancer, bacterial infections, and rheumatoid arthritis [10]. Some endogenous lectins have been related to immunological roles in animal systems, including innate immunity to pathogens, cell trafficking, and immune control. Lectins are recognised by cell surface carbohydrates present in glycolipids, glycoproteins, and proteoglycans so they are of utmost importance. As lectins have an ability to react with lymphocytes and induce blast cell transformation, these molecules have significant importance in immune responses. Lectins provide a known method of optimizing medication and vaccine absorption as bio-adhesins on mucosal surfaces [11, 12].

One of the important animal lectins includes mannos-binding lectin (MBL) or mannan-binding protein (MBP) that imparts innate immunity and functions as opsonin through the pathway of lectin complement [13, 14]. Due to the growing significance of lectins, their interactions with carbohydrates and glycoconjugates in biosystems, and the paucity of information on the use of MBL in nanomedicine, the present study reviews the applications of mannan glycoconjugates and their interacting lectins as ligands in nanomedicine [15]. Conjugating MBL/MBP with a nanosystem can identify and specifically bind to the mannan moieties of glycoproteins expressed on cell surfaces, leading to the development of several MBL/MBP-functionalized nanoparticles to target drugs to various tissues. Such efficient lectin-functionalized NPs have not been reviewed earlier. The goal of the present study is to do an in-depth review of the nanomedical applications of MBL and mannose receptors in drug targeting, as well as their potential future applications in the development of targeted drug delivery systems (DDS).

| S. no | Sugar specificity | Role | Common name | Abbreviation |
|-------|------------------|------|-------------|--------------|
| 1     | d-Glucose/d-mannose | *Galanthus nivalis* | Snowdrop | GNA |
|       | *Canavalia ensiformis* | Jack bean | Con A |
|       | *Lens culinaris* | Lentil | LCA |
|       | *Pisum sativum* | Garden pea | PSA |
| 2     | N-Acetyl-d-glucosamine | *Triticum vulgare* | Wheat germ | WGA |
|       | *Ulex europaeus* | Gorse/Furze | UEA-II |
|       | *Griffonia simplicifolia* | Bandeiraea simplicifolia | GSA-II |
| 3     | N-Acetyl-d-galactosamine | *Erythrina crista-galli* | Coral tree | ECL |
|       | *Dolichos biflorus* | Horse gram | DBA |
|       | *Helix pomatia* | Escargot, a snail | HPA |
|       | *Glycine max* | Soybean | SBA |
|       | *Vicia villosa* | Hairy vetch | VVA |
| 4     | d-Galactose | *Dolichos lablab* | Hyacinth bean | DLL-II |
|       | *Ricinus communis* | Castor bean | RCA-I & RCA-II |
|       | *Arachis hypogaea* | Peanut | PNA |
|       | *Maclura pomifera* | Osage orange | PMA |
|       | *Griffonia simplicifolia* | Bandeiraea simplicifolia | GSA-1 |
| 5     | l-Fucose | *Aspergillus fumigatus* | A type of fungus | AFL |
|       | *Lotus tetragonolobus* | Asparagus- pea/winged pea | LTA |
|       | *Ulex europaeus* | Gorse/Furze | UEA-1 |
| 6     | Sialic acid | *Sambucus nigra* | Elderberry | SNA |
|       | *Limulus polyphemus* | Horseshoe crab | LPA |
Ubiquitous nature of lectins

Lectins are ubiquitously present in living organisms. They are dispersed in separate families in plants and are thus consumed regularly by humans and animals in large amount. A multitude of protein domains of animal lectins may bind unique carbohydrate recognition domains (CRDs) or glycans found on cell membranes, extracellular matrix, and secretory components [3, 4, 12, 13].

Microbial lectins

Lectins are found on fimbriae or pili, which are tiny appendages found on the surface of bacteria [16]. Only mannose-specific bacterial lectins, such as type-1 fimbriated lectins FimH in E. coli, were known until 1980s [17]. Since then, E. coli strains with a variety of specificities have been identified, including urinary strains with P fimbriae specific for galabiose [Gal4Gal] and neural S fimbriated strains specific for NeuAc [2, 3] Gal3GalNAc [16]. There have also been reports of bacteria showing affinities for other sugars, such as Neisseria gonorrhoea, a genital infection that detects N-acetyllactosamine [Gal4GlcNAc, LacNAc]. Helicobacter pylori, the bacterium that causes peptic ulcers, has a variety of binding specificities [2, 4].

Several of these lectins identify NeuAc [2, 3] Gal4Glc [Sia3’Lac] and its N-acetylglucosamine analogue [Sia3’LacNAc], whilst others detect the Leb determinant Fuc2Gal3[Fuc4]GlcNAc [18]. Plant and animal lectins with different specificities of carbohydrates demonstrated that lectins associate mainly, but not necessarily, with the O-side chain of H. pylori LPS [19]. A wide spectrum of proteins, similar to bacteria, bind high-mannose carbohydrates found on HIV’s envelope protein gp120, offering a novel strategy to regulate HIV infection [20, 21]. In-depth knowledge of host–pathogen interaction is essential for production of vaccines or repressive drugs that favourably target the identified lectin receptors [22].

Plant lectins

Lectins with high biological activity may be found in a variety of foods, including cereals, grains, seeds, spices, and vegetables. They can be categorized into one of the seven groups based on structure and evolution, as follows: (i) amaranth family, (ii) chitin-binding family, (iii) Cucurbitaceae phloem lectins, (iv) jacalin-associated lectins, (v) legume lectins, (vi) monocot lectins, and (vii) type-2 ribose inactivating lectin [5, 6, 23]. Mannose-specific lectins from the Amaryllidaceae family like Hippeastrum hybrid (HHA) and Galanthus nivalis (GNA) suppress HIV infection of human lymphocytes, and syncytium formation between HIV-1-infected cells and uninfected CD4+ T cells. Monocot lectins only react with mannose and mannose-containing N-glycans, whereas legume lectins interact with both mannose and glucose [1, 2, 11, 12]. A growing number of mannose-specific lectins structurally similar to jacalin (lectins from Jerusalem artichoke, banana, or rice) have been identified. The structural variation of glycans in high-mannose side chains emphasises the role of mannose-specific lectins in drug targeting [23–27].

Concanavalin A (Con A), a plant lectin from Canavalia ensiformis, precisely binds α-d-mannopyranoside or α-d-glucopyranoside rings at 3, 4, and 6 positions with unmodified hydroxyl classes. Con A stimulates T cells and controls the entry of Ca2+ in human neutrophils when polyclonal activation takes place. It explicitly defines the pentasaccharide core of N-linked oligosaccharide [12]. Mannose-specific lectins from seaweeds consist of different structural scaffolds possessing one or more CRDs which recognize carbohydrates containing complex high-mannose type glycans and show potent anticancer and antiviral properties [25]. Grateloupia chiangii lectin (GCL) has a high affinity for maltotetraose-β-Sp1 and maltotetraose-β-Sp1 suggesting that it might be used as an antiviral agent to defend against viral infection [26]. Plant lectins such as Griffithsin and Urtica dioica agglutinin have also significantly reduced the virus’s incidence and replication, allowing therapeutic treatment targets against SARS, MERS, and SARS-CoV to be identified [26–28].

Animal lectins

Animal lectins have functionally diverse protein domain groups that can bind to a variety of CRDs or oligosaccharide structures on cell membranes, extracellular matrix, and secretory proteins after glycosylation. Four of the 14 well-recognized superfamilies of animal lectins function...
primarily intracellularly and other four act more broadly beyond the cell [3, 13]. Intracellular lectins include (i) the calnexin family (calnexin and calreticulin), (ii) M-type (ER and cis-Golgi alpha-mannosidases), (iii) L-type (ERGIC-53), and (iv) P-type (phosphomannosyl receptors). They are located in luminal secretory pathway compartments and play a function in mature glycoprotein trafficking, processing, and targeting [3, 13]. Extracellular lectins include C-type (collectins, selectins, mannose receptors, etc.), S-type (galectins), and siglec family (siglec-1, 2, 3 and 4) and R-type. Mannose receptor–type proteins are extracellularly found either in or within the plasma membranes and facilitate multiple roles including cell adhesion, cell signalling, glycoprotein deletion, and pathogenicity [13].

**Animal lectins as receptors for receptor-mediated targeting**

**Mannan-binding lectin/protein (MBL/MBP)**

Serum MBL (or MBP) is a Ca\(^{2+}\)-dependent lectin synthesized in the liver and found in the serum of rodents, rabbits, and humans [29]. MBL recognizes high-mannose form of glycans in foreign microorganisms or plant pests. MBL is a circulating protein that acts as a soluble pattern recognition molecule in the innate immunity. MBL recognises carbohydrate structures expressed on the surfaces of a wide range of bacteria; triggers carbohydrate-mediated complement activation; and has complement-dependent bactericidal action [29].

Evidence suggests that pathophysiology of ischemia–reperfusion injury and other disorders is caused by MBL, and its inhibitors provide promising therapeutic strategies because they block MBL from interfering with its target sugar array [30]. MBL concentration in blood decreases following insulin therapy in type-1 diabetic patients and can have a role of therapeutic target in traumatic brain injury [31]. MBL is present in the contusion zone of traumatic brain injury patients and traumatised mice with brain injury, where MBL-C dominates MBL-A. De Blasio and colleagues investigated the effects of Polyman9, a multivalent glycomimetic MBL ligand, after traumatic brain damage in mice. Polyman9 has a one-of-a-kind neuroprotective action. MBL-C as a novel traumatic brain injury treatment target is one of Polyman9’s neurobehavioral successes [32]. Endocytosis of glycoproteins containing desialylated galactose or acetylgalactosamine residues from circulation is mediated by the asialoglycoprotein receptor (ASGP-R), a hepatic lectin [33, 34]. MBL-C lectins are highly expressed in a variety of cancer cells, macrophages, endothelial cells, and dendritic cells (DCs), including ManR-CD206 and DC-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) lectins, which may serve as interesting therapeutic targets [35]. The CRD-associated collagenous-multimeric proteins on the MBPs help to bind polysaccharides to the microbial surfaces.

MBL deficiency has also been correlated with enhanced sensitivity to respiratory infections like influenza, SARS-CoV-1, and SARS-CoV-2 [36–39]. A particular carbohydrate on the surface of the parasites in *Leishmania braziliensis*’ exterior allows serum MBL to attach to it and through antibody-independent pathways, serum MBL activates the complement system [40]. Polymorphism in the MBL gene in the Chinese population has recently been related to tuberculosis sensitivity [41]. Martin and colleagues employed up to 360 units of 1,2-mannobiosides linked to tridecafullerenes in biocompatible multivalent systems to block the entrance of the Zika virus and dengue virus [42]. MBL undergoes post-translational modifications such as disulphide bond formation, hydroxylation of proline and lysine residues, and hydroxylation of lysine residues. Through collagen prolyl-4-hydroxylase, the collagen-like MBL domain is prolyl hydroxylated [43].

**Lectins as antigen-presenting cells**

C-type lectin receptors (CLR), present on antigenic surfaces as antigen-presenting cells (APC), act not only as cell adhesive molecules but also as phagocytic receptors and are therefore potentially useful for vaccine antigens. DCs are specialized APCs, which initiate humoral and cellular immune responses. APCs must identify and respond to microbes to initiate immune reactions to infection. Recognition is accomplished by APC communicating with the surface receptors present on respective exterior molecules of contagious agents. The three kinds of specialized APCs are as follows:
i) Mature DCs, located in the lymphoid tissue and derived from immature DCs interacting with several different types of pathogens.

ii) Macrophages, particularly when covering with antibodies that enable them to internalize and display their antigens.

iii) B cell antigen-specific receptors to assist them in internalizing, sorting, and presenting specific antigens to the naive T cell for activation.

Pattern recognition receptors (PRR) communicate specifically with pathogenic receptors. PRR contains CLR in addition to scavenger receptors and toll-like receptors that attach several glycan structures on pathogenic organisms [4]. CLR includes (i) mannose receptors, (ii) MBL, (iii) DC-SIGN and its receptors for mannose, and (iv) dectin-1 and dectin-2 (Fig. 1) [39, 44].

Mannose receptor (ManR)

ManR is a molecular scavenger found in macrophages and epithelial and endothelial cells that binds to and internalises a variety of pathogenic bacteria and toxic glycoproteins. Macrophage mannose receptor (MMR; CD206: 180 kDa) is a prototype member of a family of multi-lectin receptors that identify carbohydrates on pathogenic organisms’ cell walls [4, 45]. The function of ManR or MMR in innate immunity is well established in several pathogens that are clinically significant, including receptors *Mycobacterium tuberculosis* and *Pneumocystis carinii*. In organising endogenous, adaptive, and immune responses, receptor plays key roles by increasing absorption and treatment of glycoconjugates released from pathogens to T cells by MHC Class II molecules [4]. The identification of carbohydrates by ManR enhances the absorption of bacteria, yeast, and parasites by macrophages, contributing to innate defence against a range of diseases. Following endosomal or phagosomal acidification, ligands are freed from the receptor, and the receptor returns to the cell surface [46–48].

ManR is an integral membrane protein of type I that has three extracellular regions: an NH₂-terminal cysteine-rich domain, a type II fibronectin-containing domain with repetitions, and eight C-type lectins (CRDs) in conjunction. The complexity of ManR’s polysaccharides is exemplified by its primary structure. The size and shape of the receptor indicate that it is a monomer with an elongated, asymmetric structure. ManR’s domain organisation represents two possible conformations for the CRD-4 monomer: extended and U-shaped. A transmembrane segment and a short cytoplasmic domain connect ManR’s extracellular domains. CRDs 4–8 are necessary for mannose/GlcNAc/fucose-terminated ligand binding and endocytosis; however, only CRD 4 possesses sugar-binding ability in isolation (Fig. 1) [48, 49]. However, in order to design a tailored vaccination, further information of ManR’s structural analysis is required [39, 50].

Lectins of dendritic cells

Members of the DC family are found in practically all organs (except the brain), where they function as tissue resident APCs, presenting antigens from the environment, bacteria, and tumours to the immune system. Specific glycan antigens are recognised by cell surface C-type lectin receptors including DC-SIGN (Fig. 1), L-SIGN, ManR, macrophage galactose-binding lectins, and lectins like galexitin-3, which may lead to coordinated Th2 adaptive responses (Fig. 1). As revealed on DC-SIGN for natural surface glycans of human pathogens, the DC-SIGN receptor [51, 52] adheres more strongly to both synthetic mannose and fucose-containing glycoconjugates which are extensively expressed on pathogens like *M. tuberculosis*, *H. pylori*, *Leishmania mexicana*, *Schistosoma mansoni*, and HIV-1 [46, 47]. Mannose-capped lipoarabinomannan in *M. tuberculosis* prevents the LPS-stimulated human DCs to release pro-inflammatory cytokine by targeting DC-SIGN.

Another DC mannose-specific receptor, DEC-205, is a type I membrane-integrated glycoprotein that internalises antigens to naive T cells for T cell–dependent immunity development. In the extracellular region of DEC-205, there are ten different CRD motifs. Anti-DEC-205 antibodies bind to the DEC-205 receptor, which allows DCs to deliver antigen to T lymphocytes. MMR binds to ligand through CRD4 and CRD5. DEC-205 and MMR are both involved in the absorption of glycosylated antigens by DC [46, 47]. DC absorption of glycosylated antigens is mediated by DEC-205 and MMR [52, 53]. The cytoplasmic domains of C-type lectins contain numerous common patterns that are critical for...
antigen uptake: a tyrosine-containing coated-pit intracellular targeting motif, a trio of acidic amino acids, and a dileucine motif. Contrary to DEC-205, another class of C-type lectins consists of polypeptides that include one CRD in their COOH-terminal ends, and numerous CRD motifs at NH2-terminal ends. Type II

Fig. 1 C-type lectins produced by dendritic cells. Type I C-type lectins (MMR and DEC-205) have 8–10 CRDs, which bind ligand in a Ca2+-dependent manner, an amino-terminal cysteine-rich repeat (S–S), a fibronectin type II repeat (FN), and a FN repeat. Type II C-type lectins have one CRD at their extracellular carboxy-terminal terminus
C lectins have additional possible signalling motifs: immunoreceptor tyrosine-based inhibitory motif, immunoreceptor tyrosine-based activation motif, proline-rich regions (P). Members of this group include the following: (i) hepatic lectin (or ASGP-R) (Fig. 1), (ii) the macrophages of galactose/N-acetylgalactosamine-specific lectin (MGL), CD23, and many receptors encoding the natural killer genes complex (CD69, CD94, Ly-49, and NKG2). DCs thus show both type I surface lectins (DEC-205 and MMR) and type II surface lectins (CD23, CD69, and DCIR, dectin-1, and dectin-2) [54, 55].

Lectins in bioadhesion

Cells and tissues can detect DDS containing carbohydrate tags, which are then internalised by endogenous lectins on the cell surface. Macrophages and other APCs, including DCs in the skin and M-cells in the colon, have cell surface receptors that recognise mammalian mannose, fucose, and galactose. ManR helps macrophages internalise a wide range of molecules and microorganisms in a pattern recognition manner. As a result, it is an appealing entry point for delivering specific drugs, genes, or antigens to macrophages and DCs. Based on this premise, macrophages, DCs, and liver cells were examined for endocytosis of delivery systems containing asialofetuin, galactose, mannose, or N-acetyl-galactosamine. Results were enhanced when carbohydrate-modified liposomes were used. Mannosylated liposomes (Man-liposome) have been shown to target macrophages in the liver and colon, as well as the mouse brain [34]. Several APC surface C-type lectin receptors, including DC-SIGN, L-SIGN, ManR, macrophage binding lectin, and other lectins that recognise specific glycans, such as collectins and galectin-3, have the potential to target antigens for improved humoral and cellular immune responses in the future [49, 52].

Carbohydrate structures present on diseased cells participate in carbohydrate–lectin interactions and help in signalling processes. The wheat germ agglutinin (WGA) was found to be the most bioadhesive of all the lectins [56]. The lectin receptor SIGN-R1 is used by DCs in the lymph node medulla to collect lymph-borne influenza virus and to activate humoral response [57]. Artocarpin, an MBL, from Artocarpus altilis heartwood extract exhibits melanogenesis inhibitory activity. Prenylated artocarpin induces human hepatocellular carcinoma cell death. In HepG2 and PLC/PRF/5 hepatoma cells, artocarpin NPs have an anticancer impact via autophagic cell killing [58]. A chitosan hydrogel patch incorporating A. altilis extract enhances the delivery of artocarpin sufficient for depigmenting the skin [59]. The lectin Eucheuma serra agglutinin (ESA), specifically binding to high-mannose N-glycans, induces apoptotic cancer cell death in vitro [60].

MBLs in enzyme replacement therapies (GM1-gangliosidosis)

GM1-gangliosidosis and Morquio B are lysosomal diseases caused by mutations in the GLB1 gene, which codes for acid-galactosidase. Currently available lysosomal enzyme replacement therapies (ERTs) in cells are based on receptor-mediated endocytosis and are ineffective in treating organs such as GM1-gangliosidosis. New enzyme delivery technologies have revolutionised the treatment of multiple lysosomal storage diseases, but their efficacy in brain and bone tissues is limited [61]. Plant lectin Ricin Toxin’s Binding subunit (RTB) is a new carrier for human lysosomal enzymes. The ricin subunit penetrates animal cells by a variety of methods, including receptor-mediated endocytosis. Human α-l-iduronidase fused with RTB is an improved enzyme for mucopolysaccharidosis type I. Fusion products preserved both lectin selectivity and enzyme activity which were effectively endocytosed and rectified the disease phenotype of mucopolysaccharidosis patient fibroblast cells in vitro. Mannose and mannose-6-phosphate receptors, which are permitted for lysosomal ERT, are not used in RTB-mediated administration. As a result, the RTB carrier may enable various in vivo pharmacodynamics, potentially addressing difficult-to-treat tissues [61, 62].

Healing applications of MBL

Deficiency of MBL has been seen to be susceptible to varied types of infections and diseases particularly during infancy and childhood. About 5–30% individuals worldwide are reported to be MBL-deficient [31, 63]. Deficiency of MBL to < 10 µg/L with a history of 15 years of chronic leg ulceration improved the healing of wounds followed by its substitution therapy [63]. MBL replacement strategy has been
used to treat radiation-induced chronic ulcer [64]. In rabbit corneal epithelium, the application of arto -
carpin which is a α-mannose-specific agglutinin from
jackfruit enhanced wound healing [65]. MBL has also
been found to have a significant impact on the remod-
elling process of bone healing. A MBL deficiency
caused by a genetic variation prevents bone healing
due to an aggregation of apoptotic cells or a reduced
scaffold of fibrin molecules [66]. MBL has also been
found to play an important function in the comple-
ment system in the pathophysiology of diabetic
nephropathy [67]. In the Han Chinese population,
MBL2 polymorphisms, haplotypes, and diplo types
have been correlated with susceptibility to tuberculo-
sis [41].

Nanotechnology and drug targeting strategies
The use of nanotechnology is a recent application
for the purification of lectins and efficient delivery
of medicinal drugs to the diseased sites [68, 69]. In
nanotechnology, nanomaterial surfaces decorated
with targeting ligands enhance their ability to direct
the drug to diseased tissues through interactions with
cell-specific receptors. Targeted treatment, however,
circumvents toxicity and offers a stronger response
compared to traditional systemic chemotherapy.
Nanotechnologies, based on NPs, can promote the
delivery of drugs to tumours, improve drug reac-
tions, reduce harmful side effects, and resolve the
lack of precision of traditional chemotherapy agents.
To maximize their biological half-life in the blood-
stream, NPs have been engineered for optimum size
and surface characteristics. The progress of NP drug
delivery is predicted to revolutionise the landscape of
the pharmaceutical industry in terms of disease detect-
tion, treatment, and prevention for the foreseeable
future [24]. Much emphasis has been paid to glyco-
sylated NPs for biomedical uses, including selective
delivery of medications. Three aspects which have
been examined include (i) glycosylated quantum
dots, (ii) glycosylated gold NPs (GlycoNPs), and (iii)
amphiphilic glycopolymers-derived GlycoNPs [70,
71]. The synthetic techniques and multivalent inter-
actions between glyconanoparticles and lectins have
been demonstrated [72]. To achieve successful medi-
cation delivery, two key characteristics must be met
while building nanocarriers. First, medications must
be able to reach their target areas with minimum loss
and activity in blood circulation. Second, medications
should exclusively destroy tumour cells while leaving
healthy tissue unaffected [70, 73]. These factors can
be achieved using two techniques: passive and active
drug targeting [71].

Passive targeting
During passive targeting, the therapeutic agent is
integrated into a NP or macromolecule that enters
the target organ passively. In this process, we mod-
ify the physicochemical properties of the drug car-
rier complex, so that it circumvents immune defence
and reaches the target tissue. Micelle, NPs, polymeric
conjugates, and liposomes are drug delivery meth-
ods being used as passive targeting carriers (Fig. 2).
Medications encapsulated in NPs or drugs linked to
macromolecules can target tumours passively via
the increased permeability and retention effect (EPR
effect).

Catheter may also be used for infusing NPs
into target tissue or organ. Localized drug-bear-
ing NP delivery to regions of vascular resteno-
sis, for example, may be beneficial for providing
sustained drug release at particular places on the
artery wall [74]. By the improved EPR, NPs are
passively forced out through leaky vascularisation,
allowing their accumulation in the tumour region.
In such situations, drugs may be released in the
extracellular matrix and then diffuse through the
tissue [71, 75]. Use of liposomes is the old-
est nanotechnology for passive targeting of drugs.
Liposomes are coated with a synthetic polymer in
advanced techniques to shield them from immune
degradation [76]. Because cancer cells have acidic
environment, pH-sensitive liposomes have been
developed to remain stable at physiological pH 7.4
but disintegrate to release therapeutic molecules at
acidic pH. Although passive targeting approaches
are used in clinical treatment, they have numerous
limitations also [77].

Active targeting
To overcome the limits of passive targeting,
ligands that attach to particular receptors on
the cell surface, such as antibodies, peptides, or
small molecules, are conjugated to the surface
of nanocarriers. The therapeutic effectiveness of medications can be improved by increasing aggregation and internalization of NPs by receptor-mediated endocytosis [78, 79]. Nanocarriers will recognise and bind to target cells through ligand-receptor interactions on the cell surface. These receptors must be widely expressed on abnormal cells, such as tumour cells, but not on normal cells, to achieve high specificity. Furthermore, the receptors do not have to be expelled into the environment. Targeting conjugates are the first to bind to their receptors; then, the ligand-receptor complex is encased by the plasma membrane to form an endosome by receptor-mediated endocytosis. The newly formed endosome is directed to certain organelles, where medicines are released.

Fig. 2 Lectin-grafted formulations. A Lectin-grafted prodrug. B Lectin-grafted carrier system. Symbols ○, □ denote extracellular carbohydrate moieties. Symbol ◆ denotes mannose which recognizes MBL.
due to acidic pH or enzymatic activity [70]. However, nanodrugs presently approved for clinical use generally lack active targeting. Furthermore, nanodrugs currently being used in clinical trials lack specific targeting [70]. Several ligands have been studied, including transferrin and antibodies with high affinity for the molecules, which are concentrated in target tissues. Lectin recognition domains are found on mannose receptors, which are widely expressed on cells like APC. Mannose constructs have been studied for cell-specific targeting of medicines or bioactive substances due to their unique identification by mannose receptors [70].

**Forms of nanoparticles (Classification)**

It has been recognised since the emergence of nanotechnology that certain materials can exhibit varied properties depending on their size and form. They can be organic or inorganic in nature. Nanomaterials are classified depending on their dimension, shape, and composition. Few models include NPs, nanotubes, and nanofilms. NPs can be formed from a single element (such as metals or carbon) or from a combination of components (like metal oxides or compounds). Metals, semiconductor materials, metal oxides (inorganic NPs), and carbon or carbon-containing compounds such as polymers can all be used to make NPs (organic NPs) [78]. NPs can be categorised in industrial applications depending on their chemical and physical properties, such as carbonic, metal oxides, semiconductors, or metals (Fig. 3).

**Artificially produced (Synthetic/Inorganic) NPs**

Many reviews focus on the emerging significance of drug nanocarriers in cancer detection and therapy [70, 73]. Modern technology has resulted in the development of novel nanoscale platforms, such as quantum dots, nanoshells, gold NPs, paramagnetic NPs, and carbon nanotubes, as well as advancements in classic, lipid-based nanoscale platforms [78]. These NPs are utilised to target malignant tumours with high affinity and specificity when combined with bio-targeting ligands such as monoclonal antibodies, peptides, or small compounds [79].

**Carbon-based NPs**

Carbon nanotubes (CNTs) and fullerenes are the two primary forms of carbon-based NPs. CNTs are single-layered or multi-layered graphene sheets wrapped into a tube which can be 100 times stronger than steel, thus are primarily employed for structural reinforcement. These days, CNTs are being studied for drug and nucleic acid delivery at targeted sites, photodynamic treatment, and photoacoustic molecular
Despite these advancements, nanotubes have the potential to activate the complement system (a key component of innate immunity), resulting in clinically severe anaphylaxis. The application of NPs as a drug delivery mechanism is being explored. To improve targeted delivery, drugs, growth factors, or other biomolecules can be conjugated to nanoparticles. This NP-assisted delivery technique allows for exact spatial and temporal management of the loaded drugs to achieve the greatest biological outcome [80, 81]. Fard et al. used fluorescent nanodiamond-lectin complexes to target glycans linked to brain diseases, including sialic acid glycans via WGA (*Triticum aestivum*), high-mannose glycans via tomato (*Lycopersicon esculentum*) lectin (TL), and core fucosylated glycans via *Aleuria aurantia* lectin (AAL) [80–82].

Metal NPs

Metal NPs made from metal precursors have high surface energy and capacity to adsorb tiny molecules. Biomolecules can be detected and visualized using these NPs. Before SEM analysis, drug is encapsulated using the gold NPs. Gold NPs have a variety of optical and chemical properties that are influenced by their size, shape, and surface modification [83]. These features enable the use of gold NPs in a variety of applications, including biochemical sensing and detection, biological imaging, diagnostics, and therapeutic applications [84].

Nanoshells are the examples of metal-based NPs with silica core and gold coating. Irradiation with a near-IR laser alters the optical absorption characteristics of these nanoshells by varying the thickness of rolled-up sheets of single-layer carbon atoms (graphene).

**Fig. 4** Nanocarriers of several types for drug delivery. A Polymeric nanoparticles with conjugated medicines. B Polymeric micelles contain a hydrophobic core region that acts as a reservoir and a hydrophilic shell that allows hydrophobic drug to be loaded into the core. C Liposomes are made of lipid bilayers that surround an aqueous volume with a membranous lipid bilayer. D Dendrimers are synthetic polymeric macromolecules made up of numerous highly branched monomers that arise radially from the central core. E Viral-based nanoparticles are multivalent, self-assembling protein cages. F Carbon nanotubes are cylindrical molecules made up of rolled-up sheets of single-layer carbon atoms (graphene).
of the gold layer. The light from an IR laser that is absorbed by nanoshells illuminates the tissue and creates a lot of heat. Nanoshells use heat to kill tumours selectively, causing no harm to healthy cells. Nanoshells with antibodies, therapeutic anticancer chemicals, and/or lectins on their surfaces can target malignant cells. The gold nanoshell antibody complex has been used to kill breast cancer cells and fast immunoassays, without any sample preparation [85]. The antibacterial efficiency of lectin-conjugated gold particles was recently demonstrated by Alnashiri et al. against the viable population of the same bacterium and/or other bacterial species [86].

**Metal oxides**

Metallic NPs are employed largely for catalysis, whereas semiconductor nanocrystals are useful in medical diagnostics due to their optical properties. Müller’s spherical, porous, anionic, molybdenum oxide-based capsule was proposed by Barboiu et al. as a useful sugar-decorated nanoplatform for multivalent lectin recognition [87].

**Superparamagnetic NP (iron oxide)**

Because of their superparamagnetic nature, iron oxide NPs are intensively probed as a passive and active targeted imaging agent. The iron oxide core of superparamagnetic iron oxide (SPION) is a contrasting reagent for MRI. The most common SPIONs have a magnetite (Fe₃O₄) or maghemite (Fe₂O₃) core. Size-dependent superparamagnetism is seen in these NPs. SPIONs have been utilised effectively as T2-weighted MRI contrast agents in cell tracking and monitoring. SPIONs have also been employed in molecular imaging applications such as apoptosis detection and gene expression analysis [83]. SPIONs also have the potential to be used as non-invasive diagnostic tools and medicine delivery vehicles. Macrophages in the liver, spleen, lymph nodes, and atherosclerotic lesions remove it. The SPION is taken up by scavenger receptors (MGL-1, SIGNR-1, and msDectin-1) but not by carbohydrate receptor recognition of dextran [88].

**Ceramic NPs**

Ceramic NPs such as hydroxyapatite (HA), zirconia (ZrO₂), silica (SiO₂), titanium oxide (TiO₂), and alumina (Al₂O₃) have been synthesised using innovative synthetic techniques to improve their physico-chemical characteristics and minimise cytotoxicity in biological systems. These NPs are extremely heat-resistant and chemically inert and have applications in photocatalysis, dye photodegradation, drug delivery, and imaging. Ceramic NPs serve as an effective medicine delivery agent by regulating some of their properties and are being employed successfully for a variety of disorders [89].

**Semiconductor NPs**

Semiconductor materials have features that fall between metals and nonmetals. Quantum dots (QDs) are NPs formed of fluorescent semiconductor materials. A semiconductor core is the basic building block of the core (e.g. cadmium–selenium (CdSe), cadmium–tellurium (CdTe), indium–phosphate (InP), or indium–arsenide (InAs)) that is overcoated with a shell, e.g. zinc sulphide (ZnS), to improve optical and physical properties and prevent toxic heavy metals from leaking out. These NPs are the most utilised in bioimaging and biosensing. This application, however, necessitates that they be conjugated to biomolecules such as proteins, peptides, or oligonucleotides (ONs), allowing them to attach to specific sites [75].

**Polymeric (Organic) NPs**

Amongst natural polymer proteins (albumin), lectins and natural polysaccharides (chitosan and heparin) have been the materials of choice to carry ONs, DNA, and proteins, as well as medicines. Besides their biocompatible and biodegradable nature, polymeric NPs provide several advantages, including regulated drug release and protection, as well as the potential to target specifically and combine therapy with imaging. They are created using block copolymers of different hydrophobicity [83, 90]. Capsules (polymeric NPs), amphiphilic core/shell (polymeric micelles), or hyperbranched macromolecules (dendrimers) are some of the possible
structures for the resultant compounds (Fig. 4). Drugs that are susceptible to environmental variables, such as stomach acid and enzymes, can be shielded by nanoparticles [91].

The next generation of NPs in cancer therapy is multifunctional and multiplex NPs [73]. The N-[2-hydroxypropyl]-methacrylamide copolymer (HPMA), polystyrene-maleic anhydride copolymer (PMA), polyethylene glycol (PEG), poly-l-glutamic acid (PGA), and poly [lactic-co-glycolic acid] (PLGA) have been employed in recent years. A paclitaxel NP formulation using serum albumin as a carrier (albumin-bound paclitaxel [Abraxane]) is utilised in metastatic breast cancer and many other malignancies, including non–small cell lung cancer [92]. The PGA was the first polymer employed for conjugate synthesis, and it was successfully evaluated for in vitro and in vivo tests. Clinical studies for Xyotax (PGA-paclitaxel) [93] and CT-2106 (PGA-camptothecin) [94] are now under clinical trials. The most extensively used nonbiodegradable synthetic polymers are HPMA and PEG [95, 96].

**Poly [lactic-co-glycolic acid] (PLGA) NPs**

PLGA is an excellent drug delivery material because of its low toxicity, biocompatibility, and ability to regulate drug release [97]. Drugs such as l-DOPA are contained inside the polymer matrix of PLGA NPs and released upon breakdown [98]. Furthermore, by conjugating PLGA with WGA, a targeted medication system is constructed to increase the delivery effectiveness of l-DOPA. WGA-conjugated PLGA NPs have also increased the intracellular transport of medicines such as paclitaxel to colon cancer cells. Biodegradable PLGA NPs with novel synthetic mannan-PEG-PE (MN-PEG-PE) have been used to obtain active targeted gene delivery system. *Solanum tuberosum* lectin-conjugated PLGA-NPs being biodegradable have the potential to serve as nose to brain DDS [99]. PLGA-based NP conjugated with tumour-specific antigens also served as cancer nanovaccines in APC-like DCs and improves the transfection activity of the targeted gene delivery [100–102].

**Polymeric micelles (amphiphilic block copolymers)**

Block-copolymer micelles are amphiphilic copolymer super-molecular assemblies that are spherical in shape. Micelles have a hydrophobic core that can hold hydrophobic medications, and a hydrophilic brush-like corona that makes the micelle water soluble that is ideal for intravenous delivery [73]. Micelles’ functional characteristics are based on amphiphilic block copolymers that combine in aqueous conditions to produce a nanoscale core/shell structure (Fig. 4). Multifunctional polymeric micelles with imaging and therapeutic compounds are now being actively developed [103] and will soon become the norm amongst numerous micellar formulation methods [73]. Reports showed that mannosylated micelles increased cell absorption in DC 2.4 cells and bone marrow–derived dendritic cells (BMDCs), suggesting that they might be used to modulate the immune system [104].

**Dendrimers**

A dendrimer is a naturally occurring nano-sized synthetic polymeric macromolecule made of amino acids, sugars, and nucleotides. It is made up of several highly branched monomers that emerge radially from the central core (Fig. 4) [105]. Due to their unique construction, dendrimers can be utilised as sensors as well as carriers for drugs and genes. In a study, doxorubicin (DOX) attached to a dendrimer was 10 times less hazardous to colon cancer cells than free DOX, and tumour absorption of DOX-dendrimers was ninefold greater than free DOX [106]. Sehad et al. used propargylated scaffolds with sugar densities that ranged from 2 to 18 for the attachment of azido mannoside derivatives by cycloaddition. Mannosylated dendrimers were shown to be highly effective as potential inhibitors of *E. coli* adhesion and biofilm development in preliminary investigations using the leguminous lectin Con A [107].

Poly(amideamine) or PAMAM is a kind of dendrimer made up of a core of alkyl-diamine and tertiary amine branches that are repeated. For carbohydrate-protein interactions, a series of PAMAM-based dendrimers with mannosylferrocenyl moieties on the surfaces were reported. Such dendrimers demonstrated a significant increase in redox sensing skills towards Con A compared to mono- and divalent equivalents [108]. To examine glycodendrimer-lectin interactions, Kikkeri et al. developed fluorescent compounds with 2, 4, 6, or 18 mannose or galactose units. The photoinduced electron transfer’s fluorescence
emission and optical behaviour provide a one-step strategy for screening a glycodendrimer library and selecting the optimal dendrimer for researching carbohydrate-lectin interactions [109].

**Lipid-based NPs and liposomes**

The discovery of liposomes changed the prospects of DDS [110]. Liposomes’ biocompatibility and biodegradability make them ideal for transfection of genetic material into cells (lipofection). Lipofection (or liposome transfection) is a procedure where a cationic lipid is used to build an aggregate with anionic genetic material (DNA). In order to increase their blood half-life and stability in vivo, liposomes are conjugated with biocompatible polymers such as polyethylene glycol [111, 112].

**Lectins as drug carrier systems**

The number of endogenous lectins found in mammals is quickly growing [3]. Some lectins have a role in innate and adaptive immunity by recognising the foreign patterns of cell surface carbohydrates on malignancy cells. Lectins have been demonstrated to alter tumour growth, adherence to the endothelial or matrix proteins, tumour vascularization, and other processes important for metastatic dissemination and growth [113]. There are mainly two techniques to drug carrier formulation (Fig. 2): The first method is to make prodrugs with lectin as the glycotargeting moiety, drug as the active component, and spacer as a link (Fig. 2A). Reverse lectin targeting refers to the incorporation of lectins into NPs that are directed to cell surface carbohydrates. Development of lectin-grafted carrier systems (Fig. 2B) is the second technique. Liposomes or NPs serve as the reservoir for the medication, while lectins are immobilised on the reservoir’s exterior, resulting in the formation of NPs with carbohydrate moieties directed to specific lectins (direct lectin targeting). Lectin should aid in the navigation of the drug to the absorption location, bringing the vision closer to reality. It was discovered that enterocytes and M-cells are both engaged in particulate matter transcytosis. Until now, only whole organs have been the target of drug delivery methods based on this particular interaction between carbohydrates and lectins, which might be harmful to healthy tissues [114]. Despite these drawbacks, due to their unique selectivity for glycan moieties on the tumour surface, lectins are being investigated for the development of smart carrier molecules for the administration of medicine. Table 2 lists a few applications for mannos- and lectin-conjugated NPs in targeted medication delivery.

**Proteins in drug targeting**

Due to their nontoxic, non-immunogenic, and biocompatible properties, proteins have become flexible carriers for medicines to treat cancer, diabetes, rheumatoid arthritis, and a range of other ailments. They are presently being used in the development of cancer DDS. Candidates for drug conjugation that are particularly appealing are proteins called lectins because they have good pharmacokinetics and may accumulate in specific (cancer) tissues. Proteins are also excellent carriers as target-specific delivery systems due to their design. Protein NP systems have the potential to be used in a variety of biological fields. Up to 70% of mannose bound bovine serum albumin (Man-BSA) accumulated in the liver, with endothelial cells and Kupffer cells accounting for most of it. Gliotoxin in liver cells is an apoptotic agent inducing reversion of liver fibrosis [115]. Mannosylated-gelatin NPs (Man-G-NPs) selectively delivered an anti-HIV drug, didanosine, to target organs. Intravenous administration of drug coupled to Man-G-NPs substantially increased the drug uptake by liver, lung, and lymph nodes as compared to free drug or non-coupled G-NPs. Yewale et al. studied protein-conjugated NPs using lectins, gelatin, elastin, albumin, casein, and silk proteins and reported their preclinical and clinical status with respect to cancer therapy [116]. Albumin-bound NPs (nab) transport hydrophobic compounds into the circulation through endogenous albumin pathways. A paclitaxel NP formulation with serum paclitaxel acting as a 130-nm transporter has been successfully adapted for the drug delivery vehicle. The albumin-bound paclitaxel named Abraxane is FDA-approved and used to treat metastatic breast cancer. It can also target the SPARC (secreted protein, acidic, and rich in cysteine)—an albumin-binding protein that is over-expressed in certain tumours [117].
Human ferritin protein cage NPs (HFPCNs) can be transported using two different types of monosaccharide. Study suggested that uniform and polyvalent displays of mannose or galactose on the surface of HFPCNs are achieved by using site-specific thiol-maleimide Michael-type addition. Mannose- or galactose-displaying HFPCNs recognize and tightly bind to DC-SIGN or ASGP-R lectins on the surface of the mammalian cells, DCEK, or HepG2 cells [118].

Lectins in drug targeting

Oral drug delivery techniques have employed lectins such as peanut agglutinin (PNA), TL, WGA, and MBL [119–122]. In the use of lectins for glycotargeting, a DDS is coated with lectins of specific carbohydrate specificity so that it may interact with glycosylated surfaces. WGA is a prospective transporter for oral medicines due to its biochemical traits.
and nontoxic properties. Lectins can aid in the breakdown of the cell membrane barrier. The interaction of lectins with carbohydrates during drug delivery facilitates cytoadhesion and cytoinvasion, which is of a significant advantage for drug transfer to the small intestine [123]. Non-pathogenic strains of some bacteria can also be utilized through this approach. In addition to mannan-binding plant lectins, trimannose-recognizing peptide sequences have been identified in T7 phage. These phage sequences PSVGLFTH and SVGLGLGFSTVNCF must be investigated for the creation of inhibitors or DDS targeting polysaccharides [124].

Lectin-grafted carrier systems

The addition of lectins to a drug carrier system will enrich the drug’s distribution on glycosylated gastrointestinal surfaces. TL has applications in both drug delivery and oral vaccination. TL also acts as an adjuvant, preparing immune responses in the systemic and mucosal tissues [114]. The lectins coupled to NPs increased the rate of transcytosis much higher than that of lectin-free NPs. Drug administration via various biological barriers, such as the nasal mucosa, buccal cavity, lungs, eye, and blood–brain barrier, might be based on the idea of lectin-mediated bioadhesion. This technique is expected to boost absorption and possible bioavailability of poorly absorbable medications, peptides, and proteins, as well as therapeutic DNA, as proven by lectin-grafted prodrug and carrier systems [96, 114].

At first glance, plant lectins with intricate glycosyl side chains looked to be better at targeting the gut. They bind firmly and reversibly to M-cells on the villous and crypt epithelia resulting in elevated levels of endocytosis and transcytosis [125]. In contrast to Phaseolus vulgaris agglutinin and Robinia pseudoacacia lectin, other mannose-specific lectins like snowdrop lectin showed comparatively weak attachment to jejunal epithelial cells and mild affinity to M-cells [126, 127].

Bipartite drug delivery system

The capacity of multifunctional NPs to deliver one or more therapeutic compounds via conjugated antibodies or other recognition agents is being investigated. These NPs may eventually be capable of detecting malignant cells (active targeting moiety), visualising their location in the body (real-time in vivo imaging), killing cancer cells without harming healthy cells through active targeting, and controlling drug release system and monitoring the treatment effect in real time. The bipartite drug delivery method makes use of (i) endogenous lectin binding to target glycosylated enzyme conjugates to certain, predefined cell types, and (ii) injection of a prodrug at the targeted site activated by the pre-delivered enzyme. The discovery of Rha-DOX, a lectin-directed enzyme-activated prodrug, and its application to minimise tumour burden in a hepatocarcinoma model demonstrated the efficacy of lectin-directed enzyme-activated prodrug therapy [121].

MBL-conjugated NPs

Carbohydrate-lectin interactions are critical in a range of biological processes and illnesses, including viral infection and cancer metastasis. The structure and function of NP receptors are currently poorly known and represented. To identify and target specific cells, endogenous lectins might be utilised. The use of galactose-binding lectins for drug delivery and cancer markers is becoming more prevalent. Gold NPs (AuNPs) combined with mannose-modified glycopeptides exhibit a selective binding and aggregation formation in the detection of lectins like Con A and RCA120 or inhibit DC-SIGN-mediated infection caused by Ebola virus [128, 129]. Mannan-based polymer carriers can be used as versatile imaging tools for the detection of malignancy in sentinel lymph nodes (Table 2) [130].

In nanomedicine, polysaccharides are combined with multifunctional polysaccharide-binding proteins such as Con A to form a functional NP coating. This coating self-assembles in a layer-by-layer manner by sequentially binding a NP with lectin or a polysaccharide such as glycogen. The coating is then self-assembled with a galactomannan targeting ligand. The mannose residues of the galactomannan backbone appear to be important for Con A binding, whereas the galactose chain residues appear to be responsible for targeting the liver-specific ASGP-R. Binding to ASGP-R induces endocytic absorption, while low endosomal pH causes coating breakup and release of the NP-entrapped molecule. Such study will demonstrate the efficacy of
MBLs like Con A in the production of functional biomaterials by broadening their applicability to sugar-mediated and organ-specific targeting [131]. Con A–conjugated poly(ethylene glycol)-poly(lactic acid) NPs (Con A-NPs) have been developed for intranasal medication delivery to cervical lymph nodes. Con A–conjugated NPs preserved their ability to bind to particular glycans and boost cellular absorption at a faster rate (Table 2) [132]. Ali et al. demonstrated the bio-conjugation of Con A to glycoenzyme horseradish peroxidase (HRP) inside single nanopores and fabricated in heavy ion tracked polymer membranes. The immobilised molecules of the HRP enzyme carry mannose groups required for Con A binding. The immobilisation of biomolecules inside the nanopore can be exploited to adjust the conductance and selectivity of the nanopores in aqueous solution [133].

**Insulin delivery systems**

A Con A–based glucose-responsive insulin delivery device has been reported [134]. Experiments using Con A conjugate and glycosyl poly(ethylene glycol) [G-PEG]-insulin combination contained in a membrane device in vitro showed the viability of a release mechanism for in vivo research on diabetic-pancreatectomized dogs. Following oral administration of peptide and protein drugs, lectin-modified solid lipid NPs [SLN] containing insulin suggested that SLN- and WGA-modified SLN promote insulin oral absorption [135].

**Con A polystyrene HIV-1 nanospheres in immunization**

Mannose moieties in polystyrene derivatives bind to ManR-carrying cell lines (DCs, macrophages) or MBP. Con A, which was linked to polystyrene NPs through a poly (ethylene oxide) linker, preserved protein structure and activity. Con A–coated particles attached to different glycoproteins preferentially and Con A–immobilised polystyrene nanospheres (Con A-NS) could efficiently trap HIV-1 [136]. In mice, vaginal anti-HIV-1 IgA antibody was generated after intranasal vaccination with inactivated HIV-1-capturing nanospheres (HIV-NS). Macaques were immunised intranasally with Con A-NS–captured nanospheres (Simian-HIV-NS) and shown partial protection [4].

PNA- and WGA-decorated drug loaded to the surface of NP demonstrated their stability and degree of bioadhesion in murine colitis models. As a result, targeted NPs linked to lectins like PNA appear to be a viable approach for treating inflammatory bowel disease [137, 138]. The systemic bioavailability of carvedilol, which is used to treat cardiovascular disorders, is 25–35%. The most effective variable was lectin-modified poly-[ethylene-co-vinyl acetate] (PEVA) [139].

Gliadin NP (GNP) conjugated with lectin is useful when treating *H. pylori* [140]. *Ulex europaeus* agglutinin I (UEA-I) and Con A lectin coupled to GNP with acetohydroxamic acid (AHA) were shown to efficiently inhibit *H. pylori* binding. Furthermore, the antibacterial activity of UEA-GNP and Con A-GNP was double that of GNP. It implies that nanomedicines might be utilised to treat a wide range of illnesses, including cancer. An effective therapeutic technique for cancer therapy uses NPs coupled with ligands of cancer-specific tumour biomarkers [141].

The specificity of a photosensitizer is critical in photodynamic treatment. The glycodendrimeric porphyrins reacted more strongly with the lectin than the sugar-free compound [142]. Similarly, the antibacterial photodynamic activity of hyperbranched polyglycerol (hPG) loaded with zinc porphyrin photosensitizers and mannose units is functionalized with around 15 molecules of photosensitizer [143]. The conjugates with higher mannose units (70–110) had more antibacterial activity than lower mannose unit conjugates (20–60), indicating a multivalency impact in photodynamic treatment [143, 144]. Romero-Ben et al. introduced a shot-gun method that enables the synthesis of mannose-coated photopolymerised glycomicelles from diacetylene-based mannopyranosyl glycolipids having varied lengths of PEG chains and the oxidation states of the anomic sulphur atom with improved affinity for the solubilisation and slow release of clinically important lipophilic drugs in prostate cancer cells [145].
Carbohydrate-Directed Targeting (Glycotargeting)

Although the utilization of mannose-targeted structures requires greater understanding of the interaction between structure and operation, the efficacy of mannosylation approaches is well established [146]. Covalently conjugated medicines have been delivered using synthetic glyco-polymers with specificity towards carbohydrate ligands. However, because active drug release is dependent on endogenous mechanisms such as lysosomal breakdown, undesirable drug release at places other than the targeted site of action is possible. The oligosaccharide moiety and the lectin are used to perform glycotargeting as part of the medication delivery mechanism [146–148]. Nanotechnology-based devices can be used to increase medicine delivery to glioblastoma [126]. Mannan-methotrexate combination shows much better anti-tumour efficacy in a mouse model of leukaemia treated with i.p.-administered chemotherapy [148].

Mannosylated particles for cell-specific targeting

Mannosylated poly[3-lysine] (ManPL)

The ManPL system promotes cellular absorption of ONs in alveolar macrophages (AMs) via ManR-mediated endocytosis. The system with a partly substituted mannose-linked polymolecular complex is associated with ONs. When recognised by macrophage ManRs, ManPL was internalised via a receptor-mediated route, co-carrying ONs. Alveolar macrophages treated with the ManPL:ON complex absorbed much more ONs than free ON-treated controls. Polylysine that had not been changed was less effective in enhancing ON uptake. ONs were predominantly found in endocytic vesicles after cellular internalisation [150]. Mannosylated liposomes have also been used to target the drug in alveolar macrophages and intratracheal administration in rats [151].

Poly-[L-lysine citramide imide]

Quinic and shikimic acids, which are commercially accessible, emerge as stable mannose bioisosteres, which could offer useful aids for targeted drug delivery [152, 153]. Internalization of the antibiotic norfloxacin, which is active against certain intracellular bacteria, was combined with a polymeric transporter, [poly-(L-lysine citramide imide)], which is biocompatible and steadily degradable under mild acidic conditions. As a result, the prodrug macromolecules successfully compete with glucose oxidase, bringing the drug up to the mannosyl receptor-bearing membranes of macrophages invaded by intracellular bacteria [154].

Man-poly-ethyleneimine (ManPEI)/ poly-propyleneimine (ManPPI) conjugates

Several ManPEI conjugates were employed to produce ManPEI/DNA transfection complexes. DCs that contain adenovirus particles transfused with a ManPEI/DNA complex are successful in stimulating transgenic T cells of the T cell receptor [155]. An evaluation study of the anti-HIV activity of lamivudine [3TC]–loaded poly[propyleneimine] (PPI) and ManPPI dendrimers found that 3TC-loaded PPI and ManPPI formulations had stronger anti-HIV activity than free medication. Thus, ManPPI carriers have a greater likelihood for antiretroviral treatment toxicity [156].

In vitro transfection of plasmid DNA was investigated using mesoporous silica NP (MSN) and ManPEI [158]. MSN is difficult to transfet into various cell types. However, ManPEI in combination with MSN (MPS) increased transfection efficiency via receptor-mediated endocytosis via ManR. As a result, MPS may be seen as a possible gene carrier for APCs [157].

Poly[Np-vinylbenzyl-O-β-mannopyranosyl-(1–4)-α-glucoamide] (PV-Mannose)

PV-Mannose contains mannose structures that form linkages with ManR-expressing cell lines. PV-Mannose binds strongly to macrophage cells and ManRs on the cell membrane facilitating their contact. A PV-Mannose glycopolymer was used to facilitate receptor-mediated gene transfer into macrophages [158].
Polymeric nanospheres with a polystyrene core and a glucosyloxyethyl methacrylate (GEMA) oligomer corona nanosphere proved to be a viable material for sugar-biomolecule identification studies, permitting the use of a multi-lectin NP array in glycoprotein mapping utilising PV-Mannose glycopolymer [159, 160]. Poly[N-p-vinylbenzyl-O-d-glucopyranosyl-(1–4)-d-glucosamide] (PV-Maltose) and PV-Mannose, which contain glucose and mannose moieties, respectively, have specific binding ability with murine haematopoietic cells. PV-Mannose and PV-Maltose have also been proposed for gene and drug transfer to haematopoietic cells in clinical situations [161].

**Mannose-capped silicon NPs**

Silicon NPs (SiNPs) are incredibly involved in diverse areas of biomedical applications. Stable SiNPs functionalized with Con A have been developed into cross-linked aggregates which indicate that Man can attack cancerous cells with functionalized SiNPs [162].

**Liposomes**

**Mannosylated liposomes**

Because mannose binds directly to cellular CLR, multivalent mannosyl-lipoconjugates pose a difficulty in glycosylation of liposomes and targeted drug delivery. Štimac et al. synthesised two kinds of O-mannosides: conjugates 1 and 2 with a COOH- and NH₂-functionalized spacer and the connection to a lysine and FmocNH-PEG-COOH. The chemicals synthesised were integrated into liposomes, and liposomal formulations were recognised by exposed mannose units. Con A has efficiently recognized these liposomes with integrated mannosyl-lipoconjugates and offers a lot of promise for tailored liposomal DDS [163, 164].

The development of a pulmonary delivery method to alveolar macrophages by inhalation of mannose-tagged liposomal carriers is of tremendous attention. However, clumping of mannose moieties on liposomal shells was found to be crucial in affecting Man-liposome MBP binding affinity [151]. In splenic macrophages, mannosylated liposomes with the intercalated-benzyl antibiotic MT81 [Bz2MT81] liposomes excluded intracellular *Leishmania donovani* amastigotes more efficiently than Bz2MT81 intercalated liposomes or free Bz2MT81. When mannosate-grafted liposomal Bz2MT81 was delivered, its toxicity was reduced to normal levels in liver and kidney function tests [165].

Stavudine-loaded Man-liposomal formulations have been investigated for targeting HIV-infected cells by using the cell receptors on the surface of mononuclear phagocyte cells, which are significant hosts for HIV. Man-liposomes have shown promising uses for site-specific and ligand-directed delivery systems with enhanced pharmacological effect, using Con A as a model system for in vitro ligand-binding capabilities [137, 166]. Surface-engineered mannosylated liposomes demonstrated a biphasic response to zidovudine [ZDV] release to improve localisation to lymphatics, especially the lymph node and spleen. In AIDS treatment, man-liposomes looked to be a potential vesicular method for improved targeting of ZDV to lymphatics [167].

**Mannosylated cationic liposomes**

One of the most effective gene delivery mechanisms is cationic liposomes (CLs) consisting of 3beta-[N- (N’, N’-dimethylaminoethane) carbamoyl] cholesterol (DC-Chol) and dioleoylphosphatidylethanolamine (DOPE) (DC-Chol/DOPE liposomes) [168]. CLs are positively charged lipid structures that are being investigated intensively for application in gene transfection. Because of their preferred interactions with negatively charged DNA and cell membranes, Man-chemical C4-Chols’ structure and physicochemical properties appeared to satisfy the conditions for transfection in macrophages by providing a cationic charge and being recognised by the mannose structure on liposomal surface therapy. CLs are commonly employed as non-viral gene delivery vectors and as conventional gene vectors, particularly for in vitro transfection [169].

Mannose-linked polylysine-DNA complex enhances gene expression in macrophages. The incorporation of cell surface receptor ligands into liposomes increased transfection efficiency in macrophages. Transferrin, immunoglobulins, and asialoglycoproteins are the macromolecular ligands that are frequently coated on liposomes [170, 171]. A galactosylated cholesterol derivative in combination with DOPE effectively transferred plasmid...
DNA into human hepatoma cells (HepG2) via an asialoglycoprotein receptor-mediated pathway. These CLs on the other hand showed no cell specificity in vivo.

In transfection studies, Kawakami and colleagues synthesised a low-molecular-weight lipid ligate containing a mannosylated cholesterol by-product and compared it to other types of liposomes made with different Man-C4-Chol molar ratios and particle sizes [170]. Predosing with Man-C4-Chol/DOPE liposome/DNA complexes dramatically inhibited gene expression in liver non-parenchymal cells. The fact that plasmid DNA complexed with Man-liposomes displayed substantial transfection activity in the liver following intraportal injection was shown by enhanced gene expression in the liver. This may be attributed to identification of ManR both in vitro and in vivo. DNA-cationic liposome complexes when injected intravenously induced gene expression in a variety of tissues, implying that ManR is involved in the absorption of Man-liposome-DNA complexes in Kupffer cells and liver sinusoidal endothelial cells. Man-liposomes follow a similar approach in liver cells as galactosylated protein, thus according with surface density of galactose residues [171]. Man-C4-Chol met the parameters for gene transfection in macrophages by supplying a cationic charge and being detected as mannose structures on the liposomal surface. Intrathecal administration of Man-liposomes to rats resulted in efficient targeting to alveolar macrophages through ManR-mediated endocytosis [143]. According to research that tested them with various ratios of mannosylated cholesterol derivatives (Man-C4-Chol), Man-liposomes absorb in vitro in a concentration-dependent manner. While Man-C4-Chol is a novel mannosylated cholesterol derivative with higher transfection activity than DC-Chol liposomes in mouse peritoneal based on a receptor-mediated mechanism, the function of serum proteins must be investigated and overcome. Although the compound itself has a positive effect, it is possible to deposit a high density of mannose residues on the liposome surface without compromising the binding potential of CLs to DNA. These properties of mannosylated cholesterol-derived liposomes are reflected in their superior transfection gene in vivo [171].

Mannan cationized with spermine was thought to provide a stable method for DNA delivery. This spermine-mannan (SM)-based macrophage transfection system required MMR for intracellular transport, indicating the potential of a new non-viral delivery vehicle for macrophage engineering [172]. A mannose-PEG-cholesterol conjugate (MPC) is a model antigen that forms a vaccine adjuvant delivery system targeting APCs anchored on liposomes trapped in lipid A [173]. These MPC/lipid A-liposomes (MLLs), up to 300 nm in size, induced an effective immune response in mice through the oral mucosal path, as evidenced by the high levels of IgG and IgA. High levels of IgG2a and IFN-γ in treated mice revealed that MLLs prompted a mixed response and developed both humoral and cellular immunity. This showed that MLLs are an efficient oral mucosal vaccine adjuvant delivery device free from the cold chain.

Bartheldyová et al. synthesised a novel aminooxy lipid for the formulation of nanoliposomes by microfluidic mixing, demonstrating selective internalisation of fluorochrome-labelled mannan-liposomes and their capacity to induce DC equivalent to lipopolysaccharide [174]. The new drug delivery platform is ideal for mannan receptor–targeted antimicrobial drugs based on in vitro studies with human and mouse DCs. A promising treatment is immunotherapy using immunostimulatory CpG DNA to tackle refractory peritoneal dissemination. Observations indicate that the (Man/CpG DNA lipoplex) mannosylated CLs/immunostimulatory CpG DNA complex is an important inhibitor for peritoneal dissemination in mice. In this method, Man/CpG DNA lipoplex can be used to tackle peritoneal dissemination for successful immunotherapy [171].

For epithelial drug administration, lectinized liposomes were reported to bind alveolar type II epithelial cells [175]. Con A recognises amphiphiles that have several mannose residues as side chains and are integrated in liposomes; the degree of polymerization and the surface density of the amphiphile in liposomes had a substantial influence on the interaction between sugar residues on the liposome and the lectin. Lectins were evaluated for binding and absorption into live human airway epithelium to develop non-viral vectors for cystic fibrosis gene therapy. Con A was internalized into the epithelium within 1 h; however, peanut lectin,
Glycine max, *Erythrina crista-galli*, and Jacalin were taken up within 4 h [175].

**Mannosylated emulsions**

Carbohydrate-grafted emulsion-based nanosystems are the most promising cell-specific targeting methods for lipophilic drugs. Following intravenous injection in mice, Man-emulsions [70:25:5] of soybean oil, EggPC, and Man-C4-Chol were significantly transported to liver non-parenchymal cells (NPC), indicating the creation of pDNA/ligand-grafted cationic liposome complexes enabling cell-specific gene delivery [168, 170]. The mannose density of Man-emulsions is critical in cellular recognition and internalisation via a ManR-mediated mechanism [170]. A promising tool for investigating the glycosylation sites on the virion envelopes is H84T BanLec, a rationally produced dimer from the banana lectin that binds high-mannose N-glycans [176]. By binding to the glycosylated viral spike protein to prevent virus entrance into cells, BanLec demonstrates strong in vitro and in vivo action against human-pathogenic coronaviruses such as SARS-CoV-2, MERS-CoV, influenza, and human herpes viruses in cells, skin, and mice [176–178].

**Natural Mannosylated Polysaccharides**

The use of natural polysaccharides is increasingly rising in the production of the nano-size DDS. This is due to excellent features of polysaccharides which include a wide variety of physicochemical properties, biocompatibility, biodegradability, low toxicity, and low cost. Although most of the research on polysaccharide NPs has focused on well-known materials such as chitosan or hyaluronic acid, dos Santos and Grenha discussed the possibilities of polysaccharides that are less well recognised or researched [179]. Mannosylated nanomaterials have significant potential in the treatment of cancer and infection due to their direct therapeutic effects on targeted cells, modulation of the tumour microenvironment, and activation of the immune response through antigen presentation [39].

Chitosan (CS), a natural polysaccharide, is a non-viral vector with high cationic potential and benefits in biocompatibility, biodegradability, and low toxicity. Chitosan has been widely employed as a protein drug carrier and gene delivery vehicle. The addition of a mannose ligand can improve the efficacy of CS transmission via mannose receptor–mediated endocytosis. For improving cell specificity and transfection performance, Kim et al. focused on galactose or mannose ligand modification of CS [180]. Using a colon targeted formulation of CS and guar gum as carriers and diltiazem hydrochloride as a medicine, it was revealed that CS as a carrier and inulin and shellac as coating materials may be utilised successfully for colon targeting for treating local and systemic diseases [181, 182]. Nucleic acids can interact with the CS-coated NPs, strengthening transfection properties [181].

A prophylactic anti-GRP DNA vaccine (pCR3.1-VS-HSP65-TP-GRP6-M2, pGRP) was condensed with mannosylated chitosan (MCS) to create MCS/pGRP NPs and utilised for vaccination. As an antigen, MCS/pGRP NPs were found to inhibit cancer development. MCS/pGRP NPs have been discovered to be connected to macrophages through CLR. MCS/pGRP is a critical targeting gene delivery carrier that can be employed in antitumor immunotherapy [182].

A CS hydrogel patch containing *A. altilis* heartwood extract improves artocarpin distribution enough to depigment the scalp. The formulated CS hydrogel patch delivers an efficient amount of integrated artocarpin depigmenting action [59, 183]. Mannose functionalised nanocarriers have also shown potential applications in the treatment of visceral leishmaniasis [184], inflammatory bowel disease [185, 186], and prevention against influenza virus (Table 2) in macrophages [187, 188]. Nanocomposites comprising CS, poly (vinyl alcohol), and phytogenic iron oxide (FeO) NPs are being employed for developing antimicrobial and wound healing dressings for diabetic patients [189].

**Hyaluronic acid**

Amongst natural polysaccharides, hyaluronic acid NPs (HANPs) have been extensively searched for biomedical and pharmaceutical applications because of...
their biocompatibility and receptor-binding properties. Rho et al. proposed that an empty HANP may itself be a treatment agent for type 2 diabetes [190]. Using hyaluronic acid (HA) and MBL to interact with CD44, Gennari et al. produced DC targeting materials (DC receptors). Because HANP is negatively charged and made by polyelectrolyte complexing (mannosylated) HA with high- or low-molecular-weight CS, CS36 is more exposed and has a sophisticated affinity for HA receptors, resulting in clusters with more receptors. With the growth of HA, appropriate ligand presentation can be exploited to boost HA-based carrier internalisation [191, 192].

Hyaluronic acids treated with glycyrrhetinic acid and L-histidine were used to make a GHH copolymer (His). For liver-targeted drug delivery and pH-sensitive drug release, DOX-loaded GHH NPs (DOX/GHH) were utilised. DOX/GHH NPs were shown to be internalised in human hepatoblastoma cells and to have a dose-dependent anticancer impact. Thus, for liver-targeted treatment, GHH NPs give a promising nano-delivery carrier for hydrophobic drugs [193].

Yoon et al. developed tumour-targeting HANPs for simultaneous photodynamic imaging and therapy as the carrier of the hydrophobic photosensitizer, chlorin e6 (Ce6). These NPs (Ce6-HANPs) are stable nanostructures in aqueous solution and may be easily assimilated by tumour cells. Ce6-HANPs rapidly breakdown hyaluronidases, which are prevalent in tumour cell cytosols and may facilitate intracellular release of Ce6 to tumour tissue. It was revealed that Ce6-HANPs might be employed to simultaneously image and treat tumours in vivo [194, 195]. Chitosan/hyaluronic acid NPs have also been utilised to deliver an RNA/DNA molecule to cells overexpressing HA receptors like CD44. Yoon et al. could deliver mRNA with CS/HANPs for the first time under these settings [195, 196].

Heparin-tailored biopolymeric NPs

Drug conjugates based on heparin are attractive options for DDS. Synthetic heparin NPs possess good biocompatible characteristics. Heparin is formed by the mast cells in all mammals. There are numerous possibilities that open the door for heparin for a range of novel applications, including improving anticoagulant activity, anticancer, and antitubercular therapy, and biosensors [116]. Heparin NPs are useful for future applications in medicine for imaging, treatment of diseases and against antibacterial activity [197]. She et al. discovered that the dendronized heparin–DOX conjugate is a drug delivery vehicle generated from a combination of dendrimer and heparin characteristics. The NPs of DOX are pH-sensitive due to faster drug release at pH 5.0 and delayed drug release at physiological pH. The dendronized heparin–DOX conjugate NPs might be used as a nanoscale DDS for the treatment of breast cancer in the future due to their strong antitumor efficacy and minimal side effects [198]. DOX loaded into HEP nanogels, in vitro, exhibited substantially redox-sensitive drug release behaviour, indicating that in vivo drug delivery effectiveness is excellent. The DOX-loaded HEP nanogels accumulated significantly in tumours after injection into tumour-bearing animals [199].

Cyclodextrin conjugates

The binding efficiency of dendritic β-cyclodextrin (βCD) and its variant forms carrying multivalent mannosyl ligands towards Con A and mammalian mannose/fucose specific cell surface MMR has been investigated. Receptor-mediated endocytosis allowed DOX-loaded NP with multivalent mannose target units to be effectively taken up by MDA-MB-231 breast cancer cells. The release of DOX, which triggers apoptosis, happens when DOX enters the cell. Using multivalent mannose as a target significantly increased the capacity of DOX-loaded NP to inhibit the development of MDA-MB-231 cancer cells in vivo with little side effects [180, 200]. According to Benito et al., a minor shift in the composition of a conjugate has a significant impact on receptor affinity [201]. McNicholas et al. proved that Lens culinaris lectin is a selective binder of hexylthio assemblies [124]. A bioeliminable, mannose residue-capped amphiphilic poly[ethylene oxide]-b-poly[ε-caprolactone] diblock copolymer demonstrated that these mannosylated colloidal structures offer a lot of potential for medication targeting and vaccine administration [202].

Xanthan gum

NPs of natural polysaccharide xanthan gum (XG) possess an inherent ability to target endothelial cells. Biodistribution studies of pEGFP-XG NP in mice indicated the expression of GFP in the vascular tissues and suggested the potential use of xanthan
gum–functionalised NPs in gene targeting of endothelial cells [203].

Konjac glucomannan

The konjac plant is a starchy root called a corn that is rich in glucomannan, a dietary fibre that is also a hemicellulose component in the cell walls of several plant species. Glucomannan is a food ingredient that thickens and emulsifies liquids. KGM (konjac glucomannan) is a non-ionic polysaccharide that is water-soluble. KGM creates thermo-reversible gels with biodegradation capabilities using xanthan gum (XG). The KGM is broken down in the colon but not in the small intestine. Assessment studies indicate that mixtures of XG and KGM forms provide the ability to build distribution mechanisms capable of retaining physical integrity and opioid release [204, 205]. Water-soluble galactomannan composed of D-galactose and D-mannose is found in Cassia pleurocarpa endosperm seeds and can be used for medicinal applications in fields such as drug delivery and tissue engineering [205, 206]. The heteropolysaccharide repeating unit reveals a backbone of D-mannopyranosyl units linked to β(1–4) to which D-galactopyranosyl units are related by α(1–6) linkages as side chains.

Other natural compounds

Some of the naturally occurring salts like D-mannose coating of maghemite (Fe₂O₃, γ-Fe₂O₃) NP have been used to track neural stem cells in mouse brain using MRI imaging after transplantation [207]. Uptake and binding of magnetite NP in alveolar macrophages got increased when treated with SP-A as compared to albumin [208].

Conclusions

Lectins have begun to play an important part as biomaterials in various medication delivery strategies due to their extraordinary accuracy for their cognate carbohydrates. Lectin-carbohydrate interactions play a role in several biological procedures. The rising interest in lectin receptors has resulted in a slew of novel therapeutic options, such as cell targeting drugs and endocytic cell vaccines. Effective methods for tagging lectins with NPs must be developed in order to fully exploit this potential. NPs have the potential to carry both tiny medicinal compounds and macromolecules like genes and proteins. Liposomes, polymeric micelles, nanosystems, nanoshells, carbon nanotubes, dendrimers, quantum dots, and other NP-based customised DDS have a lot of promise for improving patient cure rates while lowering pharmacetical toxicity, especially in cancer patients. Both new and established scientists working on lectins and glycopolymers as drug carriers would benefit from the perspectives offered in this article, which would be included in a single reference book.

Declarations

Conflict of interest  The authors declare no competing interests.

References

1. Tsaneva M, Van Damme EJM (2020) 130 years of plant lectin research. Glycoconj J 37:533–551. https://doi.org/10.1007/s10719-020-09942-y
2. Gupta A, Sandhu RS (1997) A new high molecular weight agglutinin from garlic (Allium sativum). Mol Cell Biochem 166:1–9. https://doi.org/10.1023/a:1006827921151
3. Gupta GS (2012) Animal lectins: form, function and clinical applications. Springer-Wien
4. Nizet V, Varki A, Aebi M (2017) Microbial lectins: hemagglutinins, adhesins, and toxins. In: A Varki, RD Cummings, JD Esko, (Eds) Essentials of glycobiology. 3rd ed. Cold Spring Harbor (NY), Ch 37.
5. Peumans WJ, Damme V (1995) EJM. Lectins as plant defence proteins. Plant Physiol 109:347–352. https://doi.org/10.1104/pp.109.2.347
6. Gupta A (2020) Emerging applications of lectins in cancer detection and biomedicine. Mater Today: Proc 31:651–661. https://doi.org/10.1016/j.matpr.2020.05.810
7. Muramoto K (2017) Lectins as bioactive proteins in foods and feeds. Food Sci Technol Res 23:487–494. https://doi.org/10.3136/fstr.23.487
8. Gupta A, Sandhu RS (1998) Effect of garlic agglutinin and garlic extracts on the rat jejunum. Nutr Res 18:841–850. https://doi.org/10.1016/s0271-5317(98)00069-4
9. Gupta A, Sandhu RS (1997) In vivo binding of mannose specific lectin from garlic to intestinal epithelium. Nutr Res 17:703–711. https://doi.org/10.1016/S0271-5317(97)00040-7
10. von Itzstein M (2008) Disease-associated carbohydrate-recognising proteins and structure-based inhibitor design. Curr Opin Struct Biol 18:558–566. https://doi.org/10.1016/j.sbi.2008.07.006
11. Lagarda-Diaz I, Guzman-Partida AM, Vazquez-Moreno L (2017) Legume lectins: proteins with diverse applications. Int J Mol Sci 18:1242–1260. https://doi.org/10.3390/ijms18061242
12. Katroch R, Tripathi A (2021) Research advances and prospects of legume lectins. J Biosci 46(4):104. https://doi.org/10.1007/s12038-021-00225-8
13. Dias Rde O, Machado Ldos S et al (2015) Insights into animal and plant lectins with antimicrobial activities. Molecules 20:519–541. https://doi.org/10.3390/molecules20010519
14. Czedyński M, Świerczko AS (2020) Components of the lectin pathway of complement in haematologic malignancies. Cancers 12:1792–1810. https://doi.org/10.3390/cancers12071792
15. Sampaolesi S, Nicotra F, Russo L (2019) Glycans in nanomedicine, impact and perspectives. Future Med Chem 11:43–60. https://doi.org/10.4155/fmc-2018-0368
16. Hatton NE, Baumann CG, Faschine MA (2021) Developments in mannose-based treatments for uropathogenic Escherichia coli-induced urinary tract infections. ChemBioChem 22:613–629. https://doi.org/10.1002/cbic.202000406
17. Ofek I, Beachey EH (1978) Mannose binding and epithelial cell adherence of Escherichia coli. Infect Immun 22:247–254. https://doi.org/10.1128/iai.22.1.247-254.1978
18. Ohlsen K, Oelschlaeger TA, Hacker J et al (2009) Carbohydrate receptors of bacterial adhesion: implications and reflections. Top Curr Chem 288:3895–3904. https://doi.org/10.1007/s0338-4
19. Hynes SO, Hirmo S, Wadstrom T et al (1999) Differentiation of Helicobacter pylori isolates based on lectin binding of cell extracts in an agglutination assay. J Clin Microbiol 37:1994–1998. https://doi.org/10.1128/JCM.37.6.1994-1998.1999
20. Botos I, Wlodawer A (2005) Proteins that bind high-mannose sugars of the HIV envelope. Prog Biophys Mol Biol 88:233–282. https://doi.org/10.1016/j.pbiomolbio.2004.05.001
21. Tchesnokova V, Aprikian P, Kisiela D et al (2011) Type 1 fimbrial adhesin FimH elicits an immune response that enhances cell adhesion of Escherichia coli. Infect Immun 79:3895–3904. https://doi.org/10.1128/IAI.05169-11
22. Cuinet S, Bouvrée A, Bouchara JP (2017) Nanoscale mapping of multiple lectins on cell surfaces by single-molecule force spectroscopy. Adv Biosys 1:1700050. https://doi.org/10.1002/adbi.201700050
23. Gupta A, Gupta RK, Gupta GS (2009) Targeting cells for drug and gene delivery: emerging applications of mannan and mannan binding lectins. J Sci Indus Res 68:465–483
24. Barre A, Bourne Y, Van Damme EJM et al (2001) Mannose-binding plant lectins: different structural scaffolds for a common sugar-recognition process. Biochimie 83:645–651. https://doi.org/10.1016/s0300-9084(01)01315-3
25. Barre A, Simplicien M, Benoist H et al (2019) Mannose-specific lectins from marine algae: diverse structural scaffolds associated to common virucidal and anti-cancer properties. Mar Drugs 17:440. https://doi.org/10.3390/md17080440
26. Hwang HJ, Han JW, Jeon H et al (2020) Characterization of a novel mannose-lectin with antiviral activities from red alga Grateloupia chiangii. Biomolecules 10:333. https://doi.org/10.3390/biom10020333
27. Nabi-Aljadi M, Heydari M, Zalpoor H et al (2022) Lectins and lectobodies: potential promising antiviral agents. Cell Mol Biol Lett 27:37. https://doi.org/10.1186/s11658-022-00338-4
28. Martinez D, Amaral D, Markovitz D et al (2021) The use of lectins as tools to combat SARS-CoV-2. Curr Pharm Des 27(41):4212–4222. https://doi.org/10.2174/1381232766610830094743
29. Gupta A (2012) Collectins: mannan-binding protein as a model lectin. In: Gupta GS (ed) Animal lectins: form, function and clinical applications. Springer-Wien, pp 483–499
30. Stravalaci M, De Blasio D, Orsini V et al (2016) A new surface plasmon resonance assay for in vitro screening of mannos-binding lectin inhibitors. Biomol Screen 21:749–757. https://doi.org/10.1177/1087057116637563
31. Dorflinger GH, Holt CB, Thiel S et al (2017) Effect of optimization of glycaemic control on mannan-binding lectin in type 1 Diabetes. J Diabetes Res 2017:1249729. https://doi.org/10.1155/2017/1249729
32. De Blasio D, Fumagalli S, Longhi L et al (2017) Pharmacological inhibition of mannos-binding lectin ameliorates neurobehavioral dysfunction following experimental traumatic brain injury. J Cereb Blood Flow Metab 37:938–950. https://doi.org/10.1177/0271678X16647397
33. Meier M, Bider MD, Malashkevich VN et al (2000) Crystal structure of the carbohydrate recognition domain of the H1 subunit of the asialoglycoprotein receptor. J Mol Biol 300:857–865. https://doi.org/10.1006/jmbi.2000.3853
34. Wu J, Nantz MH, Zern MA (2002) Targeting hepatocytes for drug and gene delivery: emerging novel approaches and applications. Front Biosci 7:d717-725. https://doi.org/10.2741/A806
35. Hu J, Wei P, Seeberger PH, Yin J (2018) Mannose-functionalized nanoscaffolds for targeted delivery in biomedical applications. Chem Asian J 13:3448–3459. https://doi.org/10.1002/asia.201801088
36. Ip WK, Chan KH, Law HK et al (2005) Mannose-binding lectin in severe acute respiratory syndrome coronavirus infection. J Infect Dis 191:1697–1704. https://doi.org/10.1086/429631
37. Świerżko AS, Czedyński M (2020) The influence of the lectin pathway of complement activation on infections of the respiratory system. Front Immunol 11:585243. https://doi.org/10.3389/fimmu.2020.585243
38. Medetalibeyoglu A, Bahat G, Senkal N et al (2021) Mannose-binding lectin gene 2 (rs1800450) missense variant may contribute to development and severity of COVID-19 infection. Infect Genet Evol 89:104717. https://doi.org/10.1016/j.meegid.2021.104717
39. Gupta A, Gupta GS (2021) Status of mannose-binding lectin (MBL) and complement system in COVID-19 patients and therapeutic applications of antiviral plant
MBLs. Mol Cell Biochem 21:1–26. https://doi.org/10.1007/s11010-021-04107-3
40. Ambrosio AR, De Messias-Reason IJ (2005) Leishmaniasis (Viannia) braziliensis: interaction of mannose-binding lectin with surface glycoconjugates and complement activation. An antibody-independent defence mechanism. Parasite Immunol 27:333–340. https://doi.org/10.1111/j.1365-3042.2005.00782.x
41. Zhang JX, Gong WP, Zhu DL et al (2020) Mannose-binding lectin 2 gene polymorphisms and their association with tuberculosis in a Chinese population. Infect Dis Poverty 9:46. https://doi.org/10.1186/s40249-020-00664-9
42. Ramos-Soriano J, Reina JJ, Illescas BM et al (2019) Synthesis of highly efficient multivalent disaccharide-[60] fullerene nanoballs for emergent viruses. J Am Chem Soc 141:15403–15412. https://doi.org/10.1021/jacs.9b08003
43. Bhute VJ, Harte J, Houghton JW et al (2020) Mannose binding lectin is hydroxylated by collagen prolyl-4-hydroxylase and inhibited by some PHD inhibitors. KIDNEY360. 1:447–457. https://doi.org/10.34067/KID.0000092020
44. Gupta RK, Gupta GS (2012) Mannose receptor family: R-type lectins. In: Gupta GS (ed) Animal lectins: form, function and clinical applications. Springer-Wien, pp 331–347
45. Boskovic J, Arnold JN, Stilion R et al (2006) Structural model for the mannose receptor family uncovered by electron microscopy of Endo180 and the mannose receptor. J Biol Chem 28:8780–8787. https://doi.org/10.1074/jbc.M513277200
46. Gupta RK, Gupta GS (2012) Dectin-1 receptor family. In: Gupta GS (ed) Animal lectins: form, function and clinical applications. Springer-Wien, pp 725–747
47. Gupta RK, Gupta GS (2012) Dendritic cell lectin receptors (dectin-2 receptors family). In: Gupta GS (ed) Animal lectins: form, function and clinical applications. Springer-Wien, pp 749–771
48. Huang X, Jain PK, El-Sayed IH et al (2007) Gold NPs: interesting optical properties and recent applications in cancer diagnostics and therapy. Nanomedicine 2:681–693. https://doi.org/10.2217/17435889.2.5.681
49. Napper CE, Dyson MH, Taylor ME (2001) An extended conformation of the macrophage mannose receptor. J Biol Chem 276:14759–14766. https://doi.org/10.1074/jbc.M100425200
50. Sedaghat B, Stephenson R, Toth I (2014) Targeting the mannose receptor with mannosylated subunit vaccines. Curr Med Chem 21:3405–3418. https://doi.org/10.2174/092986731666140826115552
51. Feinberg H, Mitchell DA, Drickamer K et al (2001) Structural basis for selective recognition of oligosaccharides by DC-SIGN and DC-SIGNR. Science 294:2163–2166. https://doi.org/10.1126/science.1066371
52. Gupta RK, Gupta GS (2012) DC-SIGN family of receptors. In: Gupta GS (ed) Animal lectins: form, function and clinical applications. Springer-Wien, pp 773–798
53. Gupta RK, Gupta A (2012) Endogenous lectins as drug targets. In: Gupta GS (ed) Animal lectins: form, function and clinical applications. Springer-Wien, pp 1039–1057
54. Dennehy KM, Brown GD (2007) The role of the β-glucan receptor dectin-1 in control of fungal infection. J Leuko Biol 82:253–258. https://doi.org/10.1189/jlb.1206753
55. Blattes E, Vercellone A, Eutaméne H et al (2013) Mannodendrimers prevent acute lung inflammation by inhibiting neutrophil recruitment. Proc Natl Acad Sci USA 110:8795–8800. https://doi.org/10.1073/pnas.1221708110
56. Engleder E, Demmerer E, Wang X et al (2015) Determination of the glycosylation-pattern of the middle ear mucosa in guinea pigs. Int J Pharm 484:124–130. https://doi.org/10.1016/j.ijpharm.2015.02.056
57. Gonzalez SF, Kornek VL, Kilgowski MP et al (2010) Capture of influenza by medullary dendritic cells via SIGN-R1 is essential for humoral immunity in draining lymph nodes. Nat Immunol 11:427–434. https://doi.org/10.1038/ni.1856
58. Tzeng CW, Tzeng WS, Lin LT et al (2016) Enhanced autophagic activity of artocarpin in human hepatocellular carcinoma cells through improving its solubility by a NP system. Phytomedicine 23:528–540. https://doi.org/10.1016/j.phymed.2016.02.010
59. Kwankaew J, Phimnuan P, Wanapatpathamkul S et al (2017) Formulation of chitosan patch incorporating Artocarpus altilis heartwood extract for improving hyperpigmentation. J Cosmet Sci 68:257–269
60. Omokawa Y, Miyazaki T, Walde P, Akiyama K, Sugahara T et al (2010) Hyperpigmentation. J Cosmet Sci 68:257–269
61. Gonzalez SF, Kornek VL, Kuligowski MP et al (2010) Antimonials prevent acute lung inflammation by inhibiting neutrophil recruitment. Proc Natl Acad Sci USA 110:8795–8800. https://doi.org/10.1073/pnas.1221708110
62. Acosta W, Ayala J, Dolan MC et al (2015) RTB Lectin: a novel receptor-independent delivery system for lysosomal enzyme replacement therapies. Sci Rep 5:14144. https://doi.org/10.1038/srep14144
63. Bitsch M, Laursen I, Engel AM et al (2009) Epidemiology of chronic wound patients and relation to serum levels of mannan-binding lectin. Acta Derm Venereol 89:607–611. https://doi.org/10.2340/00015555-0730
64. Maaloe CB, Laursen I et al (2011) Mannan-binding lectin and healing of a radiation-induced chronic ulcer—a case report on mannan-binding lectin replacement therapy. Plast Reconstr Aesthet 64:e146–e148. https://doi.org/10.1016/j.prs.2011.01.013
65. Chahud F, Ramalho LNZ, Ramalho FS et al (2009) The lectin KM+ induces corneal epithelial wound healing in rabbits. Int J Exp Pathol 90:166–173. https://doi.org/10.1111/j.1365-2613.2008.00626.x
66. Van EJ, Van Baardewijk LJ, Sier CF et al (2013) Bone healing and mannose-binding lectin. Int J Surg 11:296–300. https://doi.org/10.1016/j.ijsu.2013.02.022
67. Axelgaard E, Østergaard JA, Thiel S et al (2017) Diabetes is associated with increased autoreactivity of
mannose-binding lectin. J Diabetes Res 2017:6368780. https://doi.org/10.1155/2017/6368780
68. Demir EF, Atay NO, Koruyucu M et al (2018) Mannose based polymeric nanoparticles for lecin separation. Sep Sci Technol 53:1–11. https://doi.org/10.1080/01496395.2018.1452943
69. Tetala KKR, Chen B, Visser GM et al (2007) Preparation of a monolipidic capillary column with immobilized α-mannose for affinity chromatography of lectins. J Biochem Biophys Methods 70:63–69. https://doi.org/10.1016/j.jbpb.2006.09.009
70. Bamrungsap S, Zhao Z, Chen T et al (2012) A focus on NPs as a drug delivery system. Nanomedicine 7:1253–1271. https://doi.org/10.2217/nmm.12.87
71. Sinha R, Kim GJ, Nie S et al (2006) Nanotechnology in cancer therapeutics: bioconjugated NPs for drug delivery. Mol Cancer Ther 5:1909–1917. https://doi.org/10.1158/1535-7163.MCT-06-0141
72. Yilmaz G, Becer CR (2015) Glyconanoparticles and their interactions with lectins. Polym Chem 6:5503–5514. https://doi.org/10.1039/c5py00898k
73. Cho K, Wang X, Nie S et al (2008) Therapeutic NPs for drug delivery in cancer. Clin Cancer Res 14:1310–1316. https://doi.org/10.1158/1078-0432.CCR-07-1441
74. Sahoo SK, Lahbasetwar V (2005) Enhanced antiproliferative activity of transferrin-conjugated paclitaxel-loaded NPs is mediated via sustained intracellular drug retention. Mol Pharm 2:373–383. https://doi.org/10.1021/mp050032z
75. Smith AM, Duan H, Mohs AM et al (2008) Bioconjugated quantum dots for in vivo molecular and cellular imaging. Adv Drug Deliv Rev 60:1226–1240. https://doi.org/10.1016/j.addr.2008.03.015
76. Kubik T, Bogunia K, Sugisaka M (2005) Nanotechnology on duty in medical applications. Curr Pharm Biotechnol 6:17–33. https://doi.org/10.2174/138920105367248
77. Yatvin MB, Kreet W, Horwitz BA et al (1980) pH-sensitive liposomes: possible clinical implications. Science 10:1253–1255. https://doi.org/10.1126/science.7434025
78. Salata O (2004) Applications of nanoparticles in biology and medicine. J Nanobiotechnol 2:3. https://doi.org/10.1186/1477-3155-2-3
79. Khan I, Khalid S, Idrees K (2019) Nanoparticles: properties, applications and toxicities. Arab J Chem 12:908–931. https://doi.org/10.1016/j.arabjc.2017.05.011
80. Cha C, Shin SR, Annabi N et al (2013) Carbon-based nanomaterials: multi-functional materials for biomedical engineering. ACS Nano 7:2891–2897. https://doi.org/10.1021/nn401196a
81. Andersen AJ, Robinson JT, Dai H et al (2013) Single-walled carbon nanotube surface control of complement recognition and activation. ACS Nano 7:1108–1119. https://doi.org/10.1021/nn3055175
82. Fard MG, Khabir Z, Reineck P et al (2022) Targeting cell surface glycans with lectin-coated fluorescent nanodiamonds. Nanoscale Adv 4:1551–1564. https://doi.org/10.1039/d2na00036a
83. Tripathi SK, Kaur G, Khurana RK, Kapoor S, Singh B (2015) Quantum dots and their potential role in cancer theranostics. Crit Rev Ther Drug Carr Sys 32:461–502. https://doi.org/10.1615/101615702.2015012360
84. Toraskar S, Gade M, Sangabathuni S, Thulasiram HV, Kikkeri R (2017) Exploring the influence of shapes and heterogeneity of glyco-gold nanoparticles on bacterial binding for preventing infections. Chem Med Chem 12(14):1116–1124. https://doi.org/10.1002/cmdc.201700218
85. Pelicano H, Martin DS, Xu RH, Huang P (2006) Glycolysis inhibition for anticancer treatment. Oncogene 25:4633–4646. https://doi.org/10.1038/sj.onc.1209597
86. Alnashiri HM, Aldakeel FM, Binshaya AS, Alhathli NS, Ahmed M (2022) Antimicrobial analysis of biosynthesized lectin-conjugated gold nanoparticles. Adsorp Sci Technol 8187260. https://doi.org/10.1155/2022/8187260
87. Barboiu M, Mouline Z, Silion M et al (2014) Multi-valent recognition of concanavalin A by Mo132 glyco-nanocapsules—toward biomimetic hybrid multilayers. Chemistry 20:6678–6683. https://doi.org/10.1002/chem.201402187
88. Chao Y, Karmali PP, Simberg D (2012) Role of carbohydrate receptors in the macrophage uptake of dextrancoated iron oxide nanoparticles. Adv Exp Med Biol 733:115–123. https://doi.org/10.1007/978-94-007-2555-3_11
89. Thomas SC, Harshita MPK et al (2015) Ceramic nanoparticles: fabrication methods and applications in drug delivery. Curr Pharm Des 21:6165–6188
90. Rawat M, Singh D, Saraf S et al (2006) Nanocarriers: promising vehicle for bioactive drugs. Biol Pharm Bull 29:1790–1798. https://doi.org/10.1248/bpb.29.1790
91. Jores K, Mehnert W, Drechsler M et al (2004) Investigations on the structure of solid lipid nanoparticles (SLN) and oil-loaded solid lipid nanoparticles by photon correlation spectroscopy, field-flow fractionation and transmission electron microscopy. J Control Release 95:217–227. https://doi.org/10.1016/j.jconrel.2003.11.012
92. Gradishar WJ, Tjulandin S, Davidson N et al (2005) Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 23:7794–7803. https://doi.org/10.1200/JCO.2005.04.937
93. Sabbatini P, Aghajanian C, Dizon D et al (2004) Phase II study of CT-2103 in patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. J Clin Oncol 22:4523–4531. https://doi.org/10.1200/JCO.2004.12.043
94. Bhatt R, de Vries P, Tulinsky J et al (2003) Synthesis and in vivo antitumor activity of poly(l-glutamic acid) conjugates of 20S-camptothecin. J Med Chem 46:190–193. https://doi.org/10.1021/jm020022r
95. Duncan R (2003) The dawn of era of polymer therapeutics. Nat Rev Drug Discov 2:347–360. https://doi.org/10.1038/nrd1088
96. Chen Y, Liu L (2012) Modern methods for delivery of drugs across the blood-brain barrier. Adv Drug Deliv Rev 64:640–665. https://doi.org/10.1016/j.addr.2011.11.010
97. Mohamed F, van der Walle CF (2008) Engineering biodegradable polyester particles with specific drug
targeting and drug release properties. J Pharm Sci 97:71–87. https://doi.org/10.1002/jps.21082

98. Pillay S, Pillay V, Choonara YE et al (2009) Design, biometric simulation and optimization of a nano-enabled scaffold device for enhanced delivery of dopamine to the brain. Int J Pharm 382:277–290. https://doi.org/10.1016/j.ijpharm.2009.08.021

99. Chen J, Zhang C, Liu Q et al (2012) Solanum tuberosum lectin-conjugated PLGA nanoparticles for nose-to-brain delivery: in vivo and in vitro evaluations. J Drug Target 20:174–184. https://doi.org/10.3109/1061186X.2011.622396

100. Yang R, Xu J, Xu L et al (2018) Cancer cell membrane-coated adjuvant nanoparticles with mannose modification for effective anticancer vaccination. ACS Nano 26:5121–5129. https://doi.org/10.1021/acsnano.7b09041

101. Wu G, Zhou F, Ge L et al (2012) Novel mannan-PEG modified bio adhesive PLGA nanoparticles for targeted gene delivery. J Nanomaterials 2012:981670. https://doi.org/10.1155/2012/981670

102. El-Hammadi MM, Arias JL (2022) Recent advances in the surface functionalization of PLGA-based nanomedicines. Nanomaterials 12:354. https://doi.org/10.3390/nano12030354

103. Nasongkla N, Bey E, Ren J, Ai H et al (2006) Multifunctional polymeric micelles as cancer-targeted MRI-ultrasensitive drug delivery systems. Nano Lett 6:2427–2430. https://doi.org/10.1021/nl061412u

104. Heller P, Mohr N, Birke A et al (2015) Directared interactions of block copolypept(o)ides with mannose-binding receptors: PeptoMicelles targeted to cells of the innate immune system. Macromol Biosci 15:63–73. https://doi.org/10.1002/mabi.201400417

105. Svensson S, Tomalia DA (2005) Dendrimers in biomedical applications—reflections on the field. Adv Drug Deliv Rev 57:2106–2129. https://doi.org/10.1016/j.addr.2005.09.018

106. Lee CC, Gillies ER, Fox ME et al (2006) A single dose of doxorubicin-functionalized bow-tie dendrimer cures mice bearing C-26 colon carcinomas. Proc Natl Acad Sci USA 103:16649–16654. https://doi.org/10.1073/pnas.0607705103

107. Sehad C, Shiao TC, Sallam LM et al (2018) Effect of dendrimer generation and aglyconic linkers on the binding properties of mannosylated dendrimers prepared by a combined convergent and onion peel approach. Molecules 23(8):1890. https://doi.org/10.3390/molecules23081890

108. Martos-Maldonado MC, Casas-Solvas JM, Quesada-Soriano I et al (2013) Poly(amiido amine)-based mannos-glycodendrimers as multielectron redox probes for improving lectin sensing. Langmuir 29:1318–1326. https://doi.org/10.1021/la304107a

109. Kikkeri R, Grünstein D, Seeberger PH (2010) Lectin biosensing using digital analysis of Ru(II)-glycodendrimers. J Am Chem Soc 132:10230–10232

110. Giddam AK, Zaman M, Skwarczynski M et al (2012) Liposome-based delivery system for vaccine candidates: constructing an effective formulation. Nanomedicine 7:1877–1893. https://doi.org/10.2217/nmm.12.157

111. Jain KK (2005) Nanotechnology in clinical laboratory diagnostics. Clin Chim Acta 358:37–54. https://doi.org/10.1016/j.cca.2005.03.014

112. Nisini R, Poerio N, Mariotti S et al (2018) The multirole of liposomes in therapy and prevention of infectious diseases. Front Immunol. https://doi.org/10.3389/fimmu.2018.00155

113. Gorelik E, Galili U, Raz A (2001) On the role of cell surface carbohydrates and their binding proteins (lectins) in tumor metastasis. Cancer Metastasis Rev 20:245–277. https://doi.org/10.1023/a:1015535427597

114. Gabor F, Bogner E, Weissenoebck A et al (2004) The lectin-cell interaction and its implications to intestinal lectin-mediated drug delivery. Adv Drug Deliv Rev 56:459–480. https://doi.org/10.1016/j.addr.2003.10.015

115. Dekel R, Zviel I, Brill S et al (2003) Gliotoxin ameliorates development of fibrosis and cirrhosis in a thioacetamide rat model. Dig Dis Sci 48:1642–1647. https://doi.org/10.1023/a:102479259601

116. Yewale C, Baradia D, Vhora I et al (2013) Proteins: emerging carrier for delivery of cancer therapeutics. Expert Opin Drug Deliv 10:1429–1448. https://doi.org/10.1517/17425247.2013.805200

117. Gradishar WJ, Tjulandin S, Davidson N et al (2005) Phase III trial of NP albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 23:7794–7803. https://doi.org/10.1200/JCO.2005.04.937

118. Kang YJ, Yang HJ, Jeon S et al (2014) Polyvalent display of monosaccharides on ferritin protein cage NPs for the recognition and binding of cell-surface lectins. Macromol Biosci 14:619–625. https://doi.org/10.1002/mabi.201300528

119. Hussain N, Jani PU, Florence AT (1997) Enhanced oral uptake of tomato lectin-conjugated nanoparticles in the Rat. Pharm Res 14:613–618. https://doi.org/10.1023/a:1012153011884

120. Kasuya T, Jung K, Kadoya H et al (2008) In vivo delivery of bionanocapsules displaying Phaseolus vulgaris agglutinin-L4 isoelectin to malignant tumors overexpressing N-acetylglucosaminyl transferase V. Hum Gene Ther 19:887–895. https://doi.org/10.1089/hum.2008.037

121. Robinson MA, Charlton ST, Garnier P et al (2004) LEAPT: lectin-directed enzyme-activated prodrug therapy. Proc Natl Acad Sci USA 101:14527–14532. https://doi.org/10.1073/pnas.0303574101

122. Gao X, Chen J, Tao W et al (2007) UEA I-bearing NPs for brain delivery following intranasal administration. Int J Pharm 340:207–215. https://doi.org/10.1016/j.ijpharm.2007.03.039

123. Bies V, Lehr CM, Woodley JF (2004) Lectin-mediated drug targeting: history and applications. Adv Drug Deliv Rev 56:425–435. https://doi.org/10.1016/j.addr.2003.10.030

124. Nishiyama K, Takakusagi Y, Kusayanagi T et al (2009) Identification of trimannoside-recognizing peptide sequences from a T7 phage display screen using a QCM device. Bioorg Med Chem 17:195–202. https://doi.org/10.1016/j.bmc.2008.11.004

125. McNicholas S, Rencurosi A, Lay L et al (2007) Amphiphilic N-glycosyl-thiocarbamoyl cyclodextrins:
synthesis, self-assembly, and fluorimetry of recognition by Lens culinaris lectin. Biomacromol 8:1851–1857. 
https://doi.org/10.1021/bm070055u

126. PusztaI A, Grant G, Spencer RJ et al (1993) Kidney bean lectin-induced Escherichia coli overgrowth in the small intestine is blocked by GNA, a mannose-specific lectin. J Appl Bacteriol 75:360–368. https://doi.org/10.1111/j.1365-2672.1993.tb02788.x

127. Branderhorst HM, Ruitienbeek R, Liskamp RMJ et al (2008) Multivalent carbohydrate recognition on a glyco-dendrimer-functionalized flow-through chip. ChemBioChem 9:1836–1844. https://doi.org/10.1002/cbic.20080195

128. Kong JE, Kahkeshani S, Pushkarsky I et al (2014) Research highlights: micro-engineered therapies. Lab Chip 14:4585–4589. https://doi.org/10.1039/c4lc0107j

129. Budhadev D, Poole E, Nelhmeier I et al (2020) Glycan-gold nanoparticles as multifunctional probes for multivalent lectin–carbohydrate binding: implications for blocking virus infection and nanoparticle assembly. J Am Chem Soc 142:18022–18034. https://doi.org/10.1021/jacs.0c06793

130. Jirátková M, Gálišová A, Rabyk M et al (2020) Mannan-based nanodiagnostic agents for targeting sentinel lymph nodes and tumors. Molecules 26:146. https://doi.org/10.3390/molecules2610146

131. Zhang C, Qu X, Li J et al (2015) Biofabricated NP coating for liver-cell targeting. Adv Healthc Mater 4:1972–1981. https://doi.org/10.1002/adhm.201500202

132. Shao X, Liu Q, Zhang C et al (2013) Concanavalin A-conjugated poly(ethylene glycol)-poly(lactic acid) NPs for intranasal drug delivery to the cervical lymph nodes. J Microencapsul 30:780–786. https://doi.org/10.3109/02652048.2013.788086

133. Ali M, Ramirez P, Tahir MN et al (2011) Biomolecular conjugation inside synthetic polymer nanoparticles via glycoprotein-lectin interactions. Nanoscale 3:1894–1903. https://doi.org/10.1039/c1nr0003a

134. Zhang N, Ping QN, Huang GH et al (2005) Investigation of lectin-modified insulin liposomes as carriers for oral administration. Int J Pharm 295:247–259. https://doi.org/10.1016/j.ijpharm.2005.01.018

135. Zhang N, Ping QN, Huang GH et al (2006) Lectin-modified solid lipid nanoparticles as carriers for oral administration of insulin. Int J Pharm 327:153–159. https://doi.org/10.1016/j.ijpharm.2006.07.026

136. Miyake A, Akagi T, Enose Y et al (2004) Induction of HIV-specific antibody response and protection against vaginal transmission by intranasal immunization with inactivated -capturing nanospheres in macaques. J Med Virol 73:368–377. https://doi.org/10.1002/jmv.20100

137. Moulari B, Béduneau V, Lampricht A (2014) Lectin-decorated NPs enhance binding to the inflamed tissue in experimental colitis. Control Release 188:9–17. https://doi.org/10.1016/j.jconrel.2014.05.045

138. Ulbrich W, Lampricht A (2010) Targeted drug-delivery approaches by nanoparticulate carriers in the therapy of inflammatory diseases. J R Soc Interface 7:S55–S66. https://doi.org/10.1098/rsif.2009.0285.focus

139. Varshosaz J, Moazen E (2014) Novel lectin-modified poly[ethylene-co-vinyl acetate] mucosalhesive NPs of carvedilol: preparation and in vitro optimization using a two-level factorial design. Pharm Dev Technol 19:605–617. https://doi.org/10.3109/10837450.2013.819011

140. Umamaheshwari RB, Jain NK (2003) Receptor mediated targeting of lectin conjugated gliadin NPs in the treatment of Helicobacter pylori. J Drug Target 11:415–423. https://doi.org/10.1080/10618603.2001647771

141. Bahrami B, Hojjat-Farsangi M, Mohammadi H et al (2017) NPs and targeted drug delivery in cancer therapy. Immunol Lett 190:64–83. https://doi.org/10.1016/j.imlet.2020.01193

142. Makky A, Michel JP, Kasselouri A et al (2010) Evaluation of the specific interactions between glycodendrimeric porphyrins, free or incorporated into liposomes, and concanavalin A by fluorescence spectroscopy, surface pressure and QCM-D measurements. Langmuir 26:12761–12768. https://doi.org/10.1021/la101260t

143. Staegemann MH, Gitter B, Dernede J et al (2017) Man- nose-functionalized hyperbranched polyglycerol loaded with zinc porphyrin: investigation of the multivalency effect in antibacterial photodynamic therapy. Chemistry 23:3918–3930. https://doi.org/10.1002/chem.201605236

144. Vosson L, Asenjo BD, Gutiérrez-Corbo C et al (2020) Mannose-decorated dendritic polyglycerol nanocarriers drive antiparasitic drugs to Leishmania infantum-infected macrophages. Pharmaceutics 24:915. https://doi.org/10.3390/pharmaceutics12010015

145. Ben ER, Barragán TM, de Dionisio EG et al (2019) Mannose-coated polydiacetylene (PDA)-based nanomicelles: synthesis, interaction with concanavalin A and application in the water solubilization and delivery of hydrophobic molecules. J Mater Chem B 7:5930–5946. https://doi.org/10.1039/C9TB01218D

146. Irache JM, Salman HH, Gamazo C et al (2008) Mannose-targeted systems for the delivery of therapeutics. Expert Opin Drug Deliv 5:703–724. https://doi.org/10.1517/17425247.5.6.703

147. Cuenca AG, Jiang H, Hochwald SN et al (2006) Emerging implications of nanotechnology on cancer diagnostics and therapeutics. Cancer 107:459–466. https://doi.org/10.1002/cncr.22035

148. Budzynska R, Nevozhay D, Kanska U et al (2007) Antitumor activity of mannathetrose conjugate in vitro and in vivo. Oncol Res 16:415–421. https://doi.org/10.3727/000000007783980837

149. Tokatlian T, Read BJ, Jones CA et al (2019) Innate immune recognition of glycans targets HIV nanoparticles immunogens to germinal centres. Science 363:649–654. https://doi.org/10.1126/science.aat9120

150. Liang WW, Shi X, Deshpande D et al (1996) Oligonucleotide targeting to alveolar macrophages by mannose-receptor-mediated endocytosis. Biochim Biophys Acta 1279:227–234. https://doi.org/10.1016/0005-2736(95)00237-5

151. Wijagkamanal W, Kawakami S, Takenaga M et al (2008) Efficient targeting to alveolar macrophages by intratracheal administration of mannosylated liposomes in rats. J Control Release 125:121–130. https://doi.org/10.1016/j.jconrel.2007.10.011

152. Grandjean C, Angyalosi G, Loing E et al (2001) Novel hyperbranched glycomimetics recognized by the human
mannose receptor: quinic or shikimic acid derivatives as mannosine biosossteres. ChemBioChem 2:747–757. https://doi.org/10.1002/1439-7633(20011001)2:10%3c747::AID-CBIC74%3e3.0.CO;2-O

153. Choi M, Choi SJ, Jang S et al (2019) Shikimic acid, a mannosine biososster, promotes hair growth with the induction of anagen hair cycle. Sci Rep 9:17008. https://doi.org/10.1038/s41598-019-53612-5

154. Gac S, Coudane J, Bouhatta M et al (2000) Synthesis, characterisation and in vivo behaviour of a norfl oxacin-poly-L-lysine citramide imide] conjugate bearing mannosyl residues. J Drug Target 7:393–406

155. Diebold SS, Kursa M, Wagner E et al (1999) Mannose polyethyleneimine conjugates for targeted DNA delivery into dendritic cells. J Biol Chem 274:19087–19094. https://doi.org/10.1074/jbc.274.27.19087

156. Dutta T, Jain NK (2007) Targeting potential and anti-HIV activity of lamivudine loaded mannosylated poly [propyleneimine] dendrimer. Biochim Biophys Acta 1770:681–686. https://doi.org/10.1016/j.bbagen.2006.12.007

157. Park YJ, Kim YI, Yoo MK et al (2008) Mannosylated polyethyleneimine coupled mesoporous silica NPs for receptor-mediated gene delivery. Int J Pharm 359:280–287. https://doi.org/10.1016/j.ijpharm.2008.04.010

158. Park KH, Sung WJ, Kim S et al (2005) Specific interaction of mannosylated glycolipomers with macrophage cells mediated by mannos receptor. J Biosci Bioeng 99:285–289. https://doi.org/10.1263/jbb.99.285

159. Fromell K, Andersson M, Elihn K et al (2005) NP decorated surfaces with potential use in glycosylation analysis. Colloids Surf B Biointerfaces 46:84–91. https://doi.org/10.1016/j.colsurfb.2005.06.017

160. Serizawa T, Yasunaga S, Akashi M (2001) Synthesis and lectin recognition of polystyrene core-glycopolymers corona nanospheres. Biomacromol 2:469–475. https://doi.org/10.1021/bm000131s

161. Lee YS, Park KH, Kim TS et al (2008) Interaction of glycopomers with human hematopoietic cells from cord blood and peripheral blood. J Biomed Mater Res A 86:1069–1076. https://doi.org/10.1002/jbm.a.31743

162. Ahire JH, Chambrier I, Mueller A et al (2013) Synthesis of D-mannose capped silicon NPs and their interactions with MCF-7 human breast cancerous cells. ACS Appl Mater Interfaces 5:7384–7391. https://doi.org/10.1021/am4017126

163. Štimac A, Cvitaš VL, Frikance L et al (2016) Design, and syntheses of mono and multivalent mannosyl- lipoconjugates for targeted liposomal drug delivery. Int J Pharm 511:44–56. https://doi.org/10.1016/j.ijpharm.2016.06.123

164. Witonsaridsilp W, Paeratakul V, Panyarachun B et al (2012) Development of mannosylated liposomes using synthesized N-octadecyl-D-mannopyranosylamine to enhance gastrointestinal permeability for protein delivery. AAPS Pharm Sci Tech 13:699–706. https://doi.org/10.1208/s12249-012-9788-1

165. Mitra M, Mandal AK, Chatterjee TK et al (2005) Targeting of mannosylated liposome incorporated benzyl derivative of Penicillium nigricans derived compound MT81 to reticuloendothelial systems for the treatment of visceral leishmaniasis. J Drug Target 13:285–293. https://doi.org/10.1080/10611860500233306

166. Garg M, Ashana A, Agashe HB et al (2006) Stavudine-loaded mannosylated liposomes: in-vitro anti-HIV-I activity, tissue distribution and pharmacokinetics. J Pharm Pharmacol 58:605–616. https://doi.org/10.1211/jpp.58.5.0005

167. Kaur CD, Nahar M, Jain NK (2009) Lymphatic targeting of zidovudine using surface-engineered liposomes. J Drug Target 16:798–805. https://doi.org/10.1080/10616180802475688

168. Zhang Y, Li H, Sun J et al (2010) C-Chol/DOPE cati- onic liposomes: a comparative study of the influence factors on plasmid pDNA and siRNA gene delivery. Int J Pharm 390:198–207. https://doi.org/10.1016/j.ijpharm.2010.01.035

169. Ozapolat B, Sood AK, Lopez-Berestein G (2014) Liposomal siRNA nanocarriers for cancer therapy. Adv Drug Deliv Rev 66:110–116. https://doi.org/10.1016/j.addr.2013.12.008

170. Yeepraw W, Kawasaki S, Yamashita F et al (2006) Effect of mannosine density on mannos receptor-mediated cellular uptake of mannosylated O/W emulsions by macrophages. J Control Release 114:193–201. https://doi.org/10.1016/j.jconrel.2006.04.010

171. Kuramoto Y, Kawasaki S, Zhou S et al (2008) Use of mannosylated cationic liposomes/ immunostimulatory CpG DNA complex for effective inhibition of peritoneal dissemination in mice. J Gene Med 10:392–399. https://doi.org/10.1002/jgm.1162

172. Ruan GX, Chen YZ, Yao XL et al (2014) Macrophage mannos receptor-specific gene delivery vehicle for macrophage engineering. Acta Biomater 10:1847–1855. https://doi.org/10.1016/j.actbio.2014.01.012

173. Wang N, Wang T, Zhang M et al (2014) Mannose derivative and lipid A dually decorated cationic liposomes as an effective cold chain free oral mucosal vaccine adjuvant-delivery system. Eur J Pharm Biopharm 88:194–206. https://doi.org/10.1016/j.ejpb.2014.04.007

174. Bartheldyová E, Knotigová PT, Zachová K et al (2019) 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 207:521–532. https://doi.org/10.1016/j.carbpol.2018.10.121

175. Bručk A, Abu-Dahab R, Borchard G et al (2001) Lecture-functionalized liposomes for pulmonary drug delivery: interaction with human alveolar epithelial cells. J Drug Target 9:241–251. https://doi.org/10.3109/10611860108997933

176. Lloyd MG, Liu D, Legendre M et al (2022) H84T Ban-Lec has broad spectrum antiviral activity against human herpesviruses in cells, skin, and mice. Sci Rep 12:1641. https://doi.org/10.1038/s41598-022-05580-6

177. Covés-Datson EM, King SR, Legendre M et al (2021) Targeted disruption of pi-pi stacking in Malaysian banana lectin reduces mitogenicity while preserving antiviral activity. Sci Rep 11:656. https://doi.org/10.1038/s41598-020-80577-7
178. Christodoulou I, Rahnama-Ravich R et al. (2021) Glyceroprotein targeted CAR-NK cells for the treatment of SARS-CoV-2 infection. Front Immunol 12:763460. https://doi.org/10.3389/fimmu.2021.763460

179. dos Santos MA, Grena H (2015) Polyacrylchide NPs for protein and peptide delivery: exploring less-known materials. Adv Protein Chem Struct Biol 98:223–261. https://doi.org/10.1016/b.apscb.2014.11.003

180. Ye Z, Zhang Q, Wang S et al. (2016) Tumor-targeted drug delivery with mannose-functionalized nanoparticles self-assembled from amphiphilic b-cyclodextrins. Chem Eur 22:15216–15221. https://doi.org/10.1002/chem.201603294

181. Lemarchanda C, Gref R, Couvreura P (2004) Polyacrylchide-decorated NPs. Eur J Pharma Biopharma 58:327–341. https://doi.org/10.1016/j.ephb.2004.02.016

182. Yao W, Peng Y, Du M et al. (2013) Preventative vaccine-loaded mannosylated chitosan NPs intended for nasal mucosal delivery enhance immune responses and potent tumor immunity. Mol Pharm 10:2904–2914. https://doi.org/10.1021/acs.molpharmaceut.7b00278

183. Yasin U, Bilal M, Bashir H et al. (2020) Preparation and nanoencapsulation of lectin from Lepidium sativum on chitosan-tripolyphosphate nanoparticle and their cytotoxicity against hepatocellular carcinoma cells (HepG2). BioMed Res Int 2020:7251346. https://doi.org/10.1155/2020/7251346

184. Shahnaz G, Edagwa BJ, McMillan J et al. (2017) Development of mannose-anchored thiolated amphotericin B nanocarriers for treatment of visceral leishmaniasis. Nanomedicine 12:99–115. https://doi.org/10.2217/nmm-2016-0325

185. Mukhtar M, Zeeshan M, Khan S et al. (2020) Fabrication and optimization of pH-sensitive mannose-anchored nano-vehicle as a promising approach for macropage uptake. App Nanosci 10:4013–4027

186. Liu P, Gao C, Chen H et al. (2021) Receptor-mediated target drug delivery systems for treatment of inflammatory bowel disease: opportunities and emerging strategies. Acta Pharmaceutica Sinica B 11:2798–2818. https://doi.org/10.1007/s40263-020-00353-1

187. Renu S, Feliciano-Ruiz N, Patil V et al. (2021) Immunity and protective efficacy of mannose conjugated chitosan-based influenza vaccine in maternal antibody positive pigs. Front Immunol 12:584299. https://doi.org/10.3389/fimmu.202

188. Hatami E, Mu Y, Shields DN et al. (2019) Mannose-decorated hybrid nanoparticles for enhanced macropage targeting. Biochem Biophys Rep 17:197–207. https://doi.org/10.1016/j.bbrep.2019.01.007

189. Sathiayaseelan A, Saravanakumar K, Mariadoss AVA et al. (2021) Antimicrobial and wound healing properties of FeO fabricated chitosan/PVA nanocomposite sponge. Antibiotics 10:524. https://doi.org/10.3390/antibiotics10050524

190. Rho JG, Han HS, Han JH et al. (2018) Self-assembled hyaluronic acid NPs: implications as a nanomedicine for treatment of type 2 diabetes. J Control Release 279:89–98. https://doi.org/10.1016/j.jconrel.2018.04.006

191. Gennari A, Pelliccia M, Donno R et al. (2016) Mannosylation allows for synergic (CD44/C-type lectin) uptake of hyaluronic acid NPs in dendritic cells, but only upon correct ligand presentation. Adv Healthc Mater 5:966–976. https://doi.org/10.1002/adhm.201500941

192. Spadea A, Rios de la Rosa JM et al. (2019) Evaluating the efficiency of hyaluronic acid for tumor targeting via CD44. Mol Pharm 16:2481–2493. https://doi.org/10.1021/acs.molpharmaceut.9b00083

193. Tian G, Sun X, Bai J et al. (2019) Doxorubicin-loaded dual-functional hyaluronic acid NPs: preparation, characterization, and antitumor efficacy in vitro and in vivo. Mol Med Rep 19:133–142. https://doi.org/10.3892/mmr.2018.9687

194. Lallana E, Rios de la Rosa JM et al. (2017) Chitosan/ hyaluronic acid NPs: rational design revisited for RNA delivery. Mol Pharm 14:2422–2436. https://doi.org/10.1021/acs.molpharmaceut.7b00320

195. Yoon HY, Koo H, Choi KY et al. (2012) Tumor-targeting hyaluronic acid NPs for photodynamic imaging and therapy. Biomaterials 33:3980–3989. https://doi.org/10.1016/j.biomaterials.2012.02.016

196. Nanda RK, Hajam IA, Edao BM et al. (2014) Immuno- nological evaluation of mannosylated chitosan NPs based foot and mouth disease virus DNA vaccine, pVAC FMDV VP1-OmpA in guinea pigs. Biologicals 42:153–159. https://doi.org/10.1016/j.biologicals.2014.01.002

197. Rodriguez-Torres M, Acosta-Torres LS, Diaz-Torres LA (2018) Heparin-based NPs: an overview of their applications. J Nanomaterials 2018:9780489. https://doi.org/10.1155/2018/9780489

198. She W, Li N, Luo K et al. (2013) Dendronized heparin- doxorubicin conjugate-based NP as pH-responsive drug delivery system for cancer therapy. Biomaterials 34:2252–2264. https://doi.org/10.1016/j.biomaterials.2012.07.017

199. Wu W, Yao W, Wang X et al. (2015) Bioreducible heparin-based nanogel drug delivery system. Biomaterials 39:260–268. https://doi.org/10.1016/j.biomaterials.2014.11.005

200. Imsaya WT, Tjandraiwata RR, Rachmawati H (2020) Lectins from edible mushroom Agaricus bisporus and their therapeutic potentials. Molecules 25:2368. https://doi.org/10.3390/molecules25102368

201. Benito JM, Gomez-Garcia M, Mellet CO et al. (2004) Optimizing saccharide-directed molecular delivery to biological receptors: design, synthesis, and biological evaluation of glycodendrimer-cyclodextrin conjugates. J Am Chem Soc 126:10355–10363. https://doi.org/10.1021/ja047864v

202. Rieger J, Stoffelbach F, Cui D et al. (2007) Mannosylated poly[ethylene oxide]-b-poly[epsilon-caprolactone] diblock copolymers: synthesis, characterization and interaction with a bacterial lectin. Biomacromol 8:2717–2725. https://doi.org/10.1021/bm070342y

203. Alvarez-Manceño F, Landin M, Lacik I et al. (2008) Konjac glucomanan and konjac glucomanan/xanthan gum mixtures as excipients for controlled drug delivery systems. Diffusion of small drugs. Int J Pharm 349:11–18. https://doi.org/10.1016/j.ij.pharm.2007.07.015

204. Alvarez-Manceño F, Landin M, Martinez-Pacheco R (2008) Konjac glucomanan/xanthan gum enzyme sensitive binary mixtures for colonic drug delivery. Eur J
205. Singh V, Sethi R, Tiwari A (2009) Structure elucidation and properties of a non-ionic galactomannan derived from the Cassia pleurocarpa seeds. Int J Biol Macromo 44:9–13. [https://doi.org/10.1016/j.ijbiomac.2008.09.012]

206. Alves A, Miguel SP, Araujo ARTS et al (2020) Xanthan gum–konjac glucomannan blend hydrogel for wound healing. Polymers 12:99. [https://doi.org/10.3390/polym12010099]

207. Ruge CA, Hillaireau H, Grabowski N et al (2016) Pulmonary surfactant protein A-mediated enrichment of surface-decorated polymeric nanoparticles in alveolar macrophages. Mol Pharm 13:4168–4178. [https://doi.org/10.1021/acs.molpharmaceut.6b00773]

208. Pongrac IM, Radmilović MD, Ahmed LB et al (2019) D-mannose-Coating of maghemite nanoparticles improved labeling of neural stem cells and allowed their visualization by ex vivo MRI after transplantation in the mouse brain. Cell Transplant 28:553–567. [https://doi.org/10.1177/0963689719834304]

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