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REVIEW

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 glycopolymer 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

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Nanoarchitectonics for Functional Particles and Materials

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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 categorised under four major classes as (i) glucose and/or mannose 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 mannose-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 nano-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).

Table 1 Classification of plant lectins based on sugar specificity with examples

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 categorised 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 CD^{4+} 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 Ca^{2+} 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 maltohexaose-β-sp1 and maltoheptaose-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 siglecs (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 CLRs in addition to scavenger receptors and toll-like receptors that attach several glycan structures on pathogenic organisms [4]. CLRs include (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 NH_2-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 galectin-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

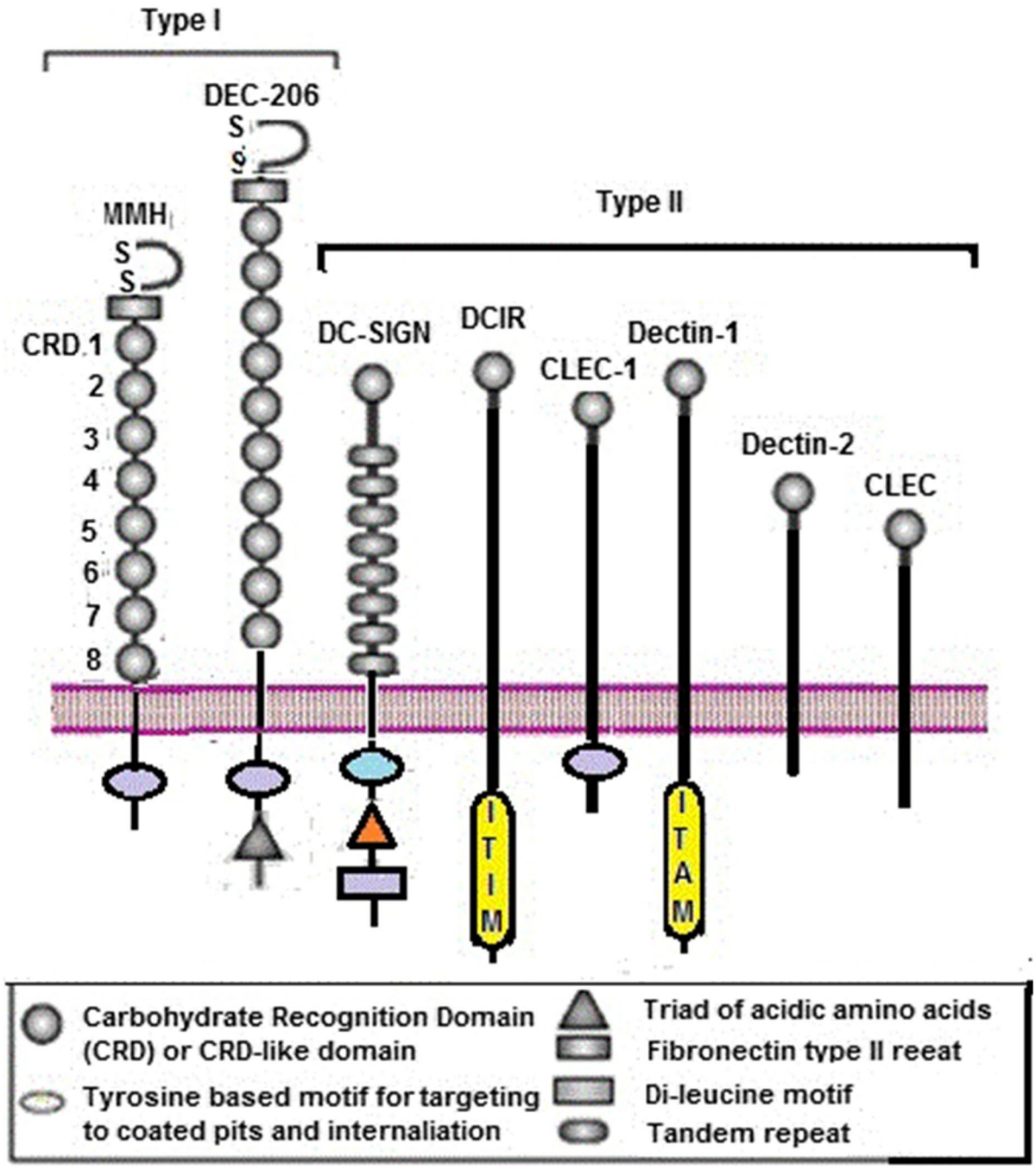

Fig. 1 C-type lectins produced by dendritic cells. Type I C-type lectins (MMR and DEC-205) have 8–10 CRDs, which bind ligand in a Ca^{2+}-dependent manner, an amino-terminal cysteine-rich repeat (S–S), a fibronectin type II repeat (FN), and a FN repeat. Type II C-type lectins have one CRD at their extracellular carboxy-terminal terminus

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 NH_2-terminal ends. Type II

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 (Manliposome) 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 artocarpin which is a D-mannose-specific agglutinin from jackfruit enhanced wound healing [65]. MBL has also been found to have a significant impact on the remodelling 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 complement 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 tuberculosis [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 reactions, reduce harmful side effects, and resolve the lack of precision of traditional chemotherapy agents. To maximize their biological half-life in the bloodstream, 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 detection, treatment, and prevention for the foreseeable future [24]. Much emphasis has been paid to glycosylated 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 glycopolymer-derived GlycoNPs [70, 71]. The synthetic techniques and multivalent interactions between glyconanoparticles and lectins have been demonstrated [72]. To achieve successful medication 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 modify the physicochemical properties of the drug carrier complex, so that it circumvents immune defence and reaches the target tissue. Micelle, NPs, polymeric conjugates, and liposomes are drug delivery methods 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-bearing NP delivery to regions of vascular restenosis, 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 oldest 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

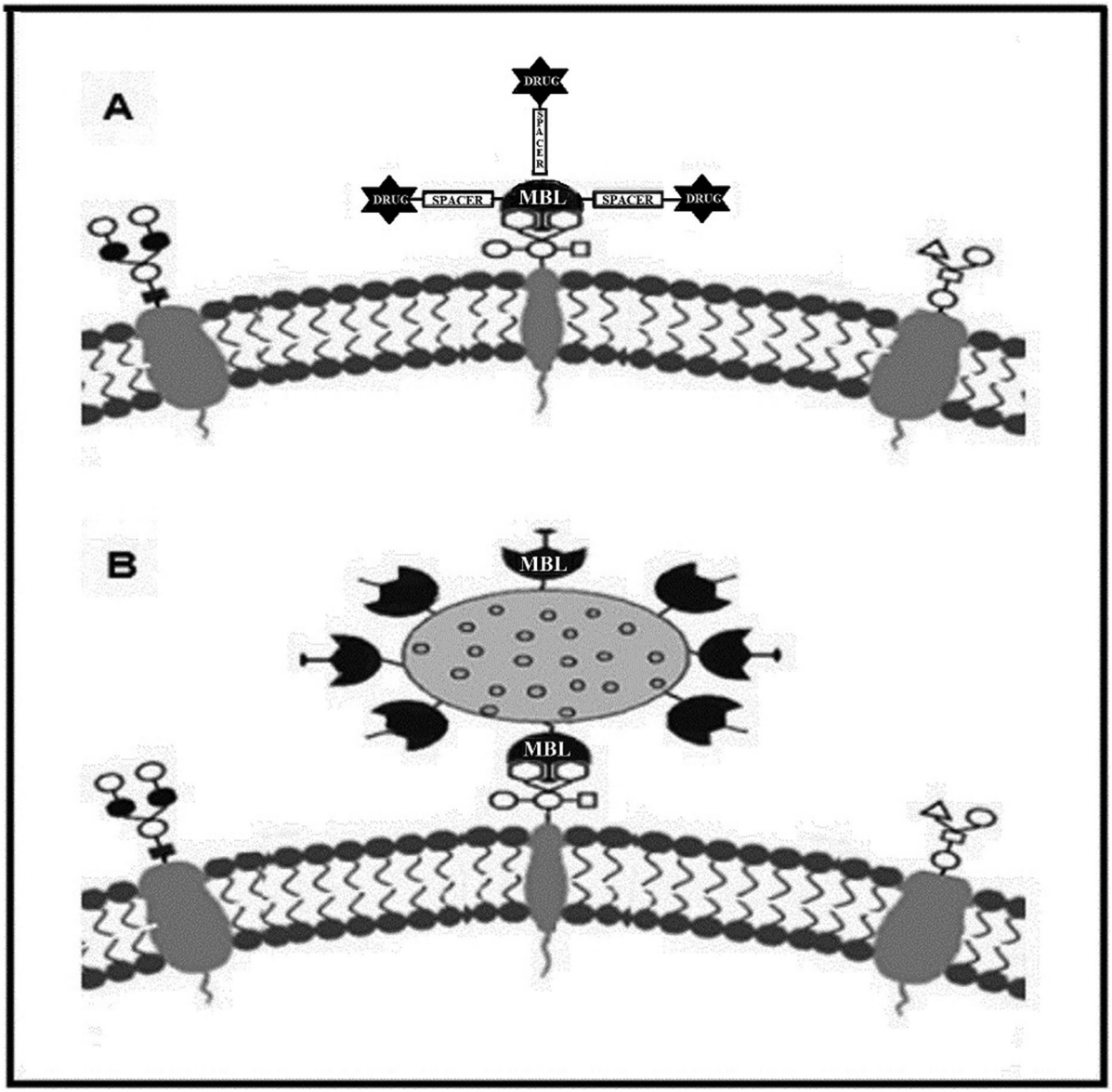

Fig. 2 Lectin-grafted formulations. **A** Lectin-grafted prodrug. **B** Lectin-grafted carrier system. Symbols ⬠ ⬭ ⬬ ▭ ▬ ▽ denote extracellular carbohydrate moieties. Symbol ⬡ denotes mannose which recognizes MBL

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

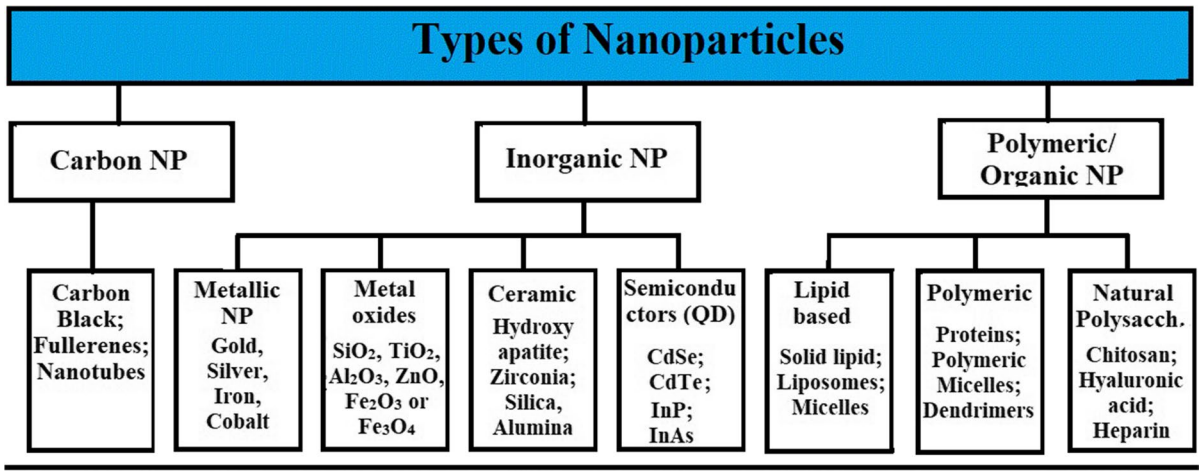

Fig. 3 Types of nanoparticles based on chemical composition: carbon-based, inorganic, and polymeric/organic. Each category includes several types of nano-formulations

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

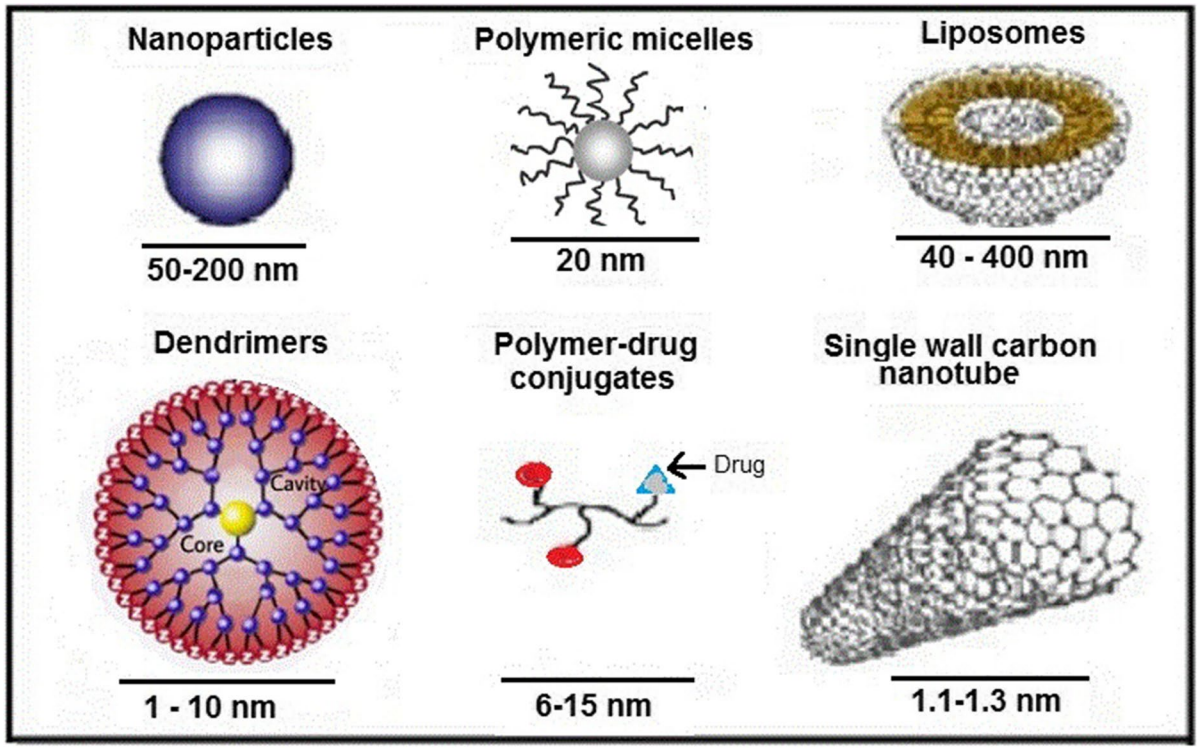

Fig. 4 Nanocarriers of several types for drug delivery. **A** Polymeric nanoparticles with conjugated medicines. **B** Polymeric micelles contain a hydrophobic core region that acts as a reservoir and a hydrophilic shell that allows hydrophobic drug to be loaded into the core. **C** Liposomes are made 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)

imaging (Fig. 4). 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 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 (SPIO) is a contrasting reagent for MRI. The most common SPIONs have a magnetite (Fe_3O_4) or maghemite (Fe_2O_3) 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 SPIO 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 (ZrO_2), silica (SiO_2), titanium oxide (TiO_2), and alumina (Al_2O_3) have been synthesised using innovative synthetic techniques to improve their physicochemical 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–arsenate (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. Bioadhesive 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 nine-fold 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 mannopyranoside 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(amidoamine) 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 mannopyranosylferrocenyl 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 mannose- 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 overexpressed in certain tumours [117].

Table 2 Applications of mannose-conjugated NP and lectin-conjugated NP in targeted drug

S. no	Nanocarrier	Cell types	Application	Reference
1	Mannose-linked PLGA NP coated with tumour-specific antigens	APCs such as dendritic cells	Cancer nano vaccines	[100]
2	MN-PEG-PE-NPs/pEGFP	Liver macrophages	Targeted gene delivery	[101]
3	Glyco-AuNP-thiolated galactomannans	Ebola virus	Blocks interaction and prevents infection	[128, 129]
4	MN-pMeOx-DOTAGd-IR800	4T1 cells	Targeting sentinel lymph nodes and tumours	[130]
5	Lectin-modified poly(ethylene-co-vinyl acetate) (PEVA)	Mucin	Drug delivery in cardiovascular diseases	[139]
6	Glycopeptide-GNPs	HepG2 and MCF7 cells	Detection and imaging of lectins	[140, 141]
7	NP HIV immunogens	Follicular DC	Nano-based vaccines	[149]
8	Mannose-anchored thiolated chitosan amphotericin B nanocarrier complexes	Macrophages	Treatment of visceral leishmaniasis	[184]
9	Mannosylated chitosan polymer encapsulated with dexamethasone	Macrophages	Inflammatory bowel disease treatment	[185, 186]
10	Mannose conjugated chitosan swine influenza A virus Ag NP	MDA-positive piglets	Anti-influenza virus	[187]
11	Mannose—Pluronic® -F127 polymer and tannic acid–based NP	Polarised macrophages	Anti-inflammation therapy	[188]
12	Scaffold composed of chitosan, poly (vinyl alcohol), FeO NPs	Diabetic patients	Wound healing scaffolds	[189]
13	Chitosan-HA NP	Cells expressing CD44	RNA delivery	[194, 195]
14	Mannose-functionalized chitosan nanocarriers	Human macrophages	Improves immune cells and efficacy	[196]
15	DOX-loaded HEP nanogels	Tumour bearing mice	Antitumor	[199]
16	Mannosylated poly(ethylene oxide)-b-poly(ε-caprolactone) diblock copolymers	Micelle's recognition using BclA lectin	Drug targeting and vaccine delivery systems	[202]
17	Konjac glucomannan and konjac glucomannan/xanthan gum	Viscous solutions	Controlled drug delivery	[203, 204]
18	Xanthan gum–konjac glucomannan blend hydrogel	Skin cells	Wound healing	[206]
19	D-Mannose coating of maghemite NP	Neural stem cells	Visualization of NSC using ex vivo MRI	[207]
20	Mannosylated PEG chains grafted on NPs	Alveolar macrophages	Phagocytosis	[208]

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, trimannoside-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 anomeric 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 glycopolymers 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 antitumour efficacy in a mouse model of leukaemia treated with i.p.-administered chemotherapy [148]. The trafficking of NP immunogens to B cell follicles is triggered by the recognition of densely stacked glycans using MBL. This concept may have potential in HIV vaccine development [149].

Mannosylated particles for cell-specific targeting

Mannosylated poly[L-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 transfect 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)-D-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-glucoamide] (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 NH_2-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 mannose-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

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 corm 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 (Fe_2O_3, γ-Fe_2O_3) 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 pharmaceutical 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.

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