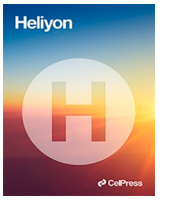
Heliyon 10 (2024) e29394

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Lectins as the prominent potential to deliver bioactive metal nanoparticles by recognizing cell surface glycans

Siva Bala Subramaniyan, Anbazhagan Veerappan *

Department of Chemistry, School of Chemical and Biotechnology, SASTRA Deemed University, Thanjavur, 613 401, Tamil Nadu, India

ARTICLE INFO

Keywords:
Lectins
Metal nanoparticles
Anticancer
Antimicrobial
Drug delivery

ABSTRACT

Lectins are renowned for recognizing specific carbohydrates, but there is evidence that they can bind to other endogenous ligands. Therefore, lectin can be used as a carrier to recognize glycoconjugates on the cell surface. The anticancer, antibacterial, and immunomodulatory properties of some lectins are established. Metal nanoparticles (MNPs) have been used in various fields recently, but their documented toxicity has raised questions about their suitability for biomedical uses. The advantages of MNPs can be realized if we deliver the NPs to the site of action; as a result, NPs may achieve greater therapeutic efficiency at lower doses with less toxicity. The use of carbohydrate specificity by lectin MNPs conjugates for diagnostics and therapeutics was addressed. The review summarised the multidimensional application of lectins and described their potential for delivery of MNPs in future drug development.

1. Introduction

The introduction of the first sustained-release formulation of Dexedrine in 1950 accelerated the research on modern drug delivery methods. Drug delivery systems (DDS) have made a great impact on secure transport and maintaining desired therapeutic levels of a drug at a specific biological location [1]. For example, siRNA formulated with lipid nanoparticles were successfully delivered to liver [1]. The existing DDS are liposomes, niosomes, polymersomes, microencapsulation, implants, nanoparticles (NPs), and transdermal drug delivery. Liposomal doxorubicin (Doxil®) and liposomal amphotericin B (Ambisome®) are well-known examples of FDA-approved medications based on liposome technology [2]. Excellent reviews have been published from time to time about the development of drug delivery methods, which emphasizes that an ideal DDS would deliver the drug only to the target biological site [3]. In this context, lectin, a carbohydrate-binding protein, was proposed as a drug carrier since 1988 to target specific glycans on the cell surface [4]. In the last three decades, there has been a wealth of information about different types of lectin, structure, carbohydrate specificity, and lectin binding other than carbohydrates, and the applications were documented [5,6]. Lectins like as jacalin, concanavalin A, and pea lectin have been shown to bind to porphyrin and other ligands besides sugar [5]. A galactose specific lectin isolated from *Erythrina cristagalli* is used to negatively select NK cells. Galactose-specific lectins, such as jacalin and *Ricinus communis* agglutinin, are useful in glycoprotein profiles of hematopoietic cell lines, particularly megakaryocytes [6]. This review intends to describe the possible implication of lectins for therapeutics, especially as a carrier for metal nanoparticles (MNPs), which have not been the main focus of any review.

The thesis presented by Doctor Hermann Stillmark, University of Dorpat, in 1888 described the agglutinating property of partially

* Corresponding author.
E-mail address: anbazhagan@scbt.sastra.edu (A. Veerappan).

https://doi.org/10.1016/j.heliyon.2024.e29394
Received 28 January 2024; Accepted 8 April 2024
Available online 11 April 2024

purified ricin from castor seeds, which was considered the beginning of lectin research [7]. Agglutinin was widely used until 1950 to describe substances and extracts that caused erythrocytes and other cells to agglutinate. The name "lectin" was coined in 1954, which defines plant-derived substances that detect and differentiate blood group components based on sugar specificity [8]. Lectins are carbohydrate-binding or glycoprotein that binds reversibly with specific carbohydrates found in glycoprotein and glycolipids. The field of lectin gained more attention after the seminal paper by Sharon and Lis in 1972 [9]. They found lectins with high selectivity for distinct cell types, as well as lectins that agglutinate red blood cells. Later, many lectins were isolated from different sources, including plants, animals, fungi, and bacteria, and now it is realized that lectin is omnipresent [10]. Lectins are involved in cell-to-cell interactions, cell migration, embryogenesis, immune defence, sugar transport and storage, host protection, organ formation, and inflammation. Various lectins exhibit varying specificity to carbohydrates, including fucose, mannose, galactose, sialic acid, *N*-acetylglucosamine, *N*-acetylgalactosamine, complex glycans, and glycoproteins [10]. Despite their ability to recognize and bind to carbohydrates, lectins differ largely in their tertiary structure, function and application [11]. Thus, lectins therapeutic applications emerged from their specificity and selectivity to cell surface glycans. This feature offers a huge potential for inhibiting microbes or target cells (Table 1).

2. Lectins as inhibitors

The viruses like HIV-1, coronaviruses, and influenza A have high-mannose-type *N*-glycans on their surface. The banana lectin (BanLec) from *Musa acuminata* binds to viral glycan and displays antiviral activity at an IC_{50} value of 9.72 nM. Similarly, snowdrop lectin and griffithsin display anti-HIV activity at nanomolar range [12]. *In silico* study showed that jacalin from jackfruit seeds binds to the glycosylated region of the receptor-binding domain (RBD) of SARS-CoV2 and alters its conformation. The conformation change in RBD affects their binding to human angiotensin-converting enzyme 2, suggesting the inhibitory potential of jacalin [13]. The water-soluble lectin from *Moringa oleifera* seeds (WSMoL) alters the membrane permeability to exhibit growth inhibition activity (5.2–167 μg/mL) against *Bacillus* sp., *Bacillus. pumillus*, *Bacillus megaterium*, *P fluorescens*, and *Serratia marcescens* [14]. A chitin-specific lectin isolated from the leaves of *Lantana camara* exhibits bactericidal activity at 10 μg against *E. coli*, *P. aeruginosa*, and *Klebsiella pneumoniae*, reaching better activity than the standard antibiotic ampicillin, as evidenced by the zone of inhibition (ZOI) method [15]. The antibacterial activity of *Andrias davidianus* lectin (ADL) isolated from the skin of the salamander *Andrias davidianus* was tested by agar disc diffusion method (10 μg per Petri dish). The findings showed ZOI against *B. subtilis*, *S. aureus*, *E. coli*, *C. perfringens* and *Shewanella* sp. ADL affects bacterial glucose degradation pathways and inhibited cellular respiration, resulting in cell death [16]. Biofilm acts as a hide-out for bacteria and represents a key mechanism of bacterial resistance. It is known that certain lectins suppress biofilms. *Bauhinia variegata* (BVL–I) lectin prevents the attachment of *Streptococcus sanguinis and Streptococcus mutans* to the oral cavity. BVL-I binds to the carbohydrates on the surface of bacterial cells at 200 μg/mL and inhibits the adherence of microorganisms [17]. *Calliandra surinamensis* leaves contain a lectin (CasuL), which showed growth inhibitory and antibiofilm activity (6.25–800 μg/mL) against non-resistant *S. aureus*, methicillin-resistant *S. aureus* (MRSA), and *S. saprophyticus* with comparable activity to the control drug, tetracycline [18].

The binding of lectins to fungal carbohydrates may impede the bioprocess of the fungus and produce inhibitory activity. Jackin isolated from the seeds of *Artocarpus integrifolia* inhibited the growth activity of *Fusarium moniliforme* and *Saccharomyces cerevisiae*. Fluorescence spectroscopy study suggests that the chitin binding protein, Jackin interacts with chitin through hydrophobic interactions mediated by tryphtophan side chain and glucosamine rings. Thus, jackin may recognize the fungal surface through hydrophobic interaction, and inhibit the germination of *F. moniliforme* at concentarion of 2.25 mg/mL. Jackin impair the normal growth of hyphae by stopping mycelium from forming spores. Similar activity was recorded with the lectin frutackin isolated from the seeds of *Artocarpus incise* [19]. CasuL exhibited antifungal activity against *Candida krusei* with minimum fungicide concentrations (MFC) of 250 μg/mL. CasuL induced dramatic cell morphological alterations, including cell rupture and release of cytoplasmic content [18]. The

Table 1
Representative lectin sugar specificity and their bioactivity.

Lectin	Abbrev.	Specificity	Bioactivity	Ref.
Banana lectin	BanLec	Mannose/glucose	HIV-1 inhibitor	[12]
Jacalin	Jacalin	Galactose	SARS-CoV2 inhibitor	[13]
Moringa oleifera seeds	WSMoL	Fructose and porcine thyroglobulin	Antibacterial	[14]
Lantana camara lectin	LCL	Asialo mucin, melibiose, chitin, methyl α,D galactopyranoside	Antibacterial, antifungal	[15]
Andrias davidianus lectin	ADL	Porcine submaxillary glycoprotein (PSM), asialo-PSM	Antibacterial	[16]
Bauhinia variegata lectin	BVL–I	Lactose, galactose and D-GalNAc	Antibiofilm	[17]
Calliandra surinamensis leaves lectin	CasuL	ovalbumin, fetuin and bovine serum albumin	Antibacteria, antibiofilm, antifungal, cytotoxic	[18]
Jackin	Jackin	Chitin	Antifungal	[19]
Frutackin	Frutackin	Chtiin	Antifungal	[19]
Chondrilla caribensis lectin	CCL	Lactose	Antibiofilm, antiprotozoal	[20]
Concanavalin A	ConA	Glucosides, mannosides	Antiprotozoal	[21]
Polygonatum odoratum lectin	POL	Mannose	Antitumor	[22]
Haliotis discus discus lectin	HddSBL	Sialic acid	Anticancer	[23]
Polygonatum cyrtonema lectin	PCL	Mannose	Cytotoxicity and apoptosis	[24]

antiprotozoal activity was documented from *Chondrilla caribensis* lectin (CCL) extracted from a marine sponge. CCL causes direct structural damage to promastigote with an IC_{50} value of 1.2 μM. CCL binds to the *L. infantum* surface glycans, lipophosphoglycan (LPG) and glycoinositol phospholipid (GIP) and induces reactive oxygen species (ROS) production to kill the parasite [20]. ConA extracted from *Canavalia ensiformis* displays antiprotozoal activity at 0.39 μM against *L. amazonensis*. The ConA treatment eliminated promastigotes in a post-infection period and increased the expressions of cytokines such as IFN-γ, IL-6, TNF- α, IL-4, IL-2, and IL-10 to overcome *L. amazonensis* infection [21]. These findings suggest that inhibitors may be developed for infectious diseases using lectins that may bind to specific cell surface glycans.

The change in glycosylation pattern was considered a hallmark of oncogenic transformation. Lectins capable of recognizing these changes can inhibit cancer progression. The specific binding of *Polygonatum odoratum* lectin (POL) to the mannose inhibits signs of apoptosis at an IC_{50} value of 23 μg/mL in A549 lung cancer cells without disturbing healthy lung cells [22]. Recombinant adenovirus gene encoding *Haliotis discus discus* lectin (HddSBL) with specificity to sialic acid inhibits the proliferation of hepatocellular carcinoma cell line (Hep3B), colorectal cancer cell line (SW480), and lung cancer cell lines (A549 and H1299). The mechanism of action of HddSBL was attributed to the downregulation of anti-apoptosis factor Bcl-2 without caspase activation [23]. *Polygonatum cyrtonema* lectin (PCL) induces autophagy and apoptosis in cancer by interacting with the carbohydrate-containing receptors on the cancer cell surface. A375 – a human melanoma cell line treated with 15 μg/mL PCL induces both autophagic and apoptosis pathways simultaneously via enhanced production of mitochondria ROS and activating the p38-p53 pathway [24].

3. Lectins for targeting and their application

The extent of glycosylation differs significantly in pathological conditions. Owing to carbohydrate specificity, lectins are useful in diagnosis via glycan recognition (Table 2). The glycosylation of cancer antigen 15-3 (CA15-3) was affected by breast cancer. Wheat germ agglutinin (WGA) and macrophage galactose-type lectin (MGL) functionalized onto europium (III)-doped nanoparticles (Eu^{+3}-NPs) recognize glyco variants of CA15-3, thereby distinguishing metastatic conditions from healthy subjects [25]. *Bandeiraea simplicifolia* (BS-1) lectin recognizes the over-expression of galactosylated glycans in the saliva of breast cancer patients [26]. Lectins are also useful in pathogen detection. The binding of WGA to the cell wall carbohydrates of bacteria was used to detect bacterial pathogens, *E. coli* and *S. aureus*, in 5 min up to a concentration of 10^6 cells/mL [27].

The unique glycan binding properties of lectins are an attractive option for carrying drugs to deliver precisely to diseased cells and tissues [Table 2]. In 1988, Woodely and Naisbett demonstrated the bioadhesion of tomato lectin (TL) to the luminal surface of the small intestine [4]. Later, researchers confirmed that TL binds to intestinal mucus. The bioadhesion nature of lectin allows the drug to retain longer in tissues. *Aleuria aurantia* lectin (AAL) extracted from the edible orange cup mushroom mediates antigen delivery to M cells (M stands for microfold or membranous) found in the intestinal epithelium [28]. BanLec binds with the immune system to induce a strong IgG4 immune response and is regarded as a potential carrier for oral antihapten immunization [29]. *Maackia amurensis* lectin (MAA/MAL I) isolated from *Maackia amurensis* seeds enhances the cytotoxicity activity of the chemotherapy medication paclitaxel. The MAA/MAL I reduces the dosage requirement of paclitaxel, indicating their chemo-adjuvant potential [30]. *Bauhinia purpurea* agglutinin (BPA) with specificity to galactose distinguishes human prostate cancer and normal prostate. BPA-PEG-modified liposomes are a useful anticancer drug carrier to treat prostate cancer [31].

NPs coated with WGA interacted more effectively with lectin receptors on the alveolar epithelium. Researchers employed respirable aerosols made of lectin-functionalized poly (lactide-*co*-glycolide) to establish high antibiotic levels in the lungs to treat *Mycobacterium tuberculosis* H37Rv [32]. *Dioclea violacea* lectin (DVL) has no antibacterial activity. Still, it has some specificity to mannose, and galactose allows DVL to enhance the antibacterial activity of gentamicin against multidrug-resistant *S. aureus* and *E. coli*. When DVL and gentamicin were combined, the MIC of gentamicin reduced from 50.8 to 10.1 μg/mL against *S. aureus* and from 32 to 12.7 μg/mL against *E. coli* [33]. A similar observation was reported with *Vatairea macrocarpa* lectin (VML). The VML potentiates the antibacterial action of gentamicin, norfloxacin, and penicillin against *S. aureus*, resulting in MIC reductions of 512 to 128 μg/mL, 40.3 to 32 μg/mL, and 512 to 406.4 μg/mL, respectively [34]. Artocarpin extracted from the heartwood of *A. heterophyllus* showed antibacterial activity. The MIC of artocarpin against MRSA and *E. coli* was 62.5 μg/mL, and the MIC against *P. aeruginosa* was 250 μg/mL.

Table 2
Representative lectins for targeting.

Lectin	Abbrev.	Specificity	Target	Ref.
Wheat germ agglutinin	WGA	NeuNAc and GlcNAc	Metastatic conditions	[25]
Macrophage galactose-type lectin	MGL	Galactose and N-acetylgalactosamine	Metastatic conditions	[25]
Bandeiraea simplicifolia lectin	BS-1	α-Gal, α-GalNAc, Galα-1,3Gal, Galα-1,6Glc	Breast cancer	[26]
Tomato lectin	TL	Poly N-acetyllactosamine	Intestinal mucus	[4]
Aleuria aurantia lectin	AAL	Sialylic, α-1-fucose	M cells in intestinal epithelium	[28]
Banana lectin	BanLec	Mannose/glucose	Immune system	[29]
Maackia amurensis lectin	MAA/MAL I	Sialic acid	Transmembrane mucin receptor protein podoplanin	[30]
Bauhinia purpurea agglutinin	BPA	Galactose	Prostate cancer	[31]
Wheat germ agglutinin	WGA	NeuNAc and GlcNAc	Alveolar epithelium	[32]
Dioclea violacea lectin	DVL	Mannose, and galactose	Glycans in bacteria	[33]
Vatairea macrocarpa lectin	VML	Lactose	Glycans in bacteria	[34]
Artocarpin	Artocarpin	Mannose	Glycans in bacteria	[35]
Parkia platycephala lectin	PPL	Glucose/mannose	Glycans in bacteria	[36]

When artocarpin combined with norfloxacin against *S. aureus*, *P. aeruginosa,* and *E. coli* showed synergistic activity [35]. The effectiveness of antibiotics against specific strains is affected differently by different lectins. For example, *Parkia platycephala* lectin (PPL) reduces the MIC of gentamicin against the MDR *S. aureus* and *E. coli* by 61 % and 36.9 %, respectively [36]. At the same time, PPL cannot potentiate the action of gentamicin against *P. aeruginosa* because the extracellular polysaccharides produced by *P. aeruginosa* may prevent the drug entry. These reports suggest that lectins could be helpful as an adjuvant in the development of innovative antibiotic-synergistic therapies to combat MDR strains.

4. Bioactive metal nanoparticles

The particles with a size less than 100 nm were considered as nanoparticles (NPs). The physicochemical properties of NPs differ significantly from their bulk counterparts. Among many nanoparticles, the ease of synthesis allowed the development of metal NPs (MNPs) applications in diverse biology, chemistry, and physics areas. In the subsequent section, we briefly illustrate the recent development in bioscience with selected MNPs. Silver NPs (AgNPs) with a size of 10 nm and a concentration of 1 μg/mL were shown inhibited SARS-CoV-2 viral replication than the large NPs and improve the cell proliferation of SARS-CoV-2 infected Vero E6 cells [37]. The antigen (recombinant trimeric HA from influenza A/Aichi/2/68 (H3N2)) and adjuvant (FliC) dual conjugated with 18 nm AuNPs act as a potential carriers and display strong cellular and humoral immune response against influenza upon intranasal administration [38]. Ghaffari et al. (2019) demonstrated that 75 μg/mL zinc oxide NPs (ZnO NPs) reduce H1N1 influenza viral load in the infected host cells by blocking hemagglutinin and neuraminidase glycopeptides [39]. Selenium nanoparticles functionalized with an antiviral drug, oseltamivir (Se@OTV), exhibit enhanced antiviral activity through synergy against the H1N1 influenza virus [40]. The MIC of Se alone is 1 mM, whereas the MIC of Se@OTV reduced to125 μM. MNPs are demonstrated to work against multi-drug-resistant bacteria and other chronic bacterial diseases. AgNPs conjugated with thiosemicarbazide and ciprofloxacin synergistically inhibit ciprofloxacin-resistant *P. aeruginosa*. These AgNPs at concentration of 32 μg/mL synergistically inhibit bacterial growth and replication by inhibiting mexA and B efflux gene expression [41]. Palladium nanocrystals incorporated with hexagonal pores of MCM-41 (Mobil composition Matter No 41) coated with ZnO NPs (Zn/Pd-MCM-41) exhibit photodynamic activity against multi-drug resistant *E. coli*, *P. aeruginosa* at MIC of 30 μg/mL and *S. aureus* at MIC of 20 μg/mL [42]. ZnO NPs (0.002–5 mg/mL) inhibited fungi such as *A. alternata* and *F. verticillioides* by releasing Zn^{2+} ions [43]. SeNPs synthesized using lactic acid bacteria *Lacticaseibacillus paracasei* (isolated from human breast milk) effectively inhibit the Candida and Fusarium species at the concentration of 15 μg/mL as compared to 15 μg/mL selenium precursor. These SeNPs adhere to the pathogen surface and penetrate successfully to damage the fungi [44]. An antifungal drug, Amphotericin B in deoxycholate buffer (Ampd), in complex with AuNPs lysed 27 % of human RBC, whereas Ampd showed higher toxicity lysed 97 % hRBC. Ampd-AuNPs (0.25 mg/kg of Amphotericin B) effectively clear *C. neoformans* infection in mice brain tissue [45]. Several MNPs are reported with anticancer activity [46]. Zinc oxide nanorods prepared through the precipitation method induce cytotoxicity against human liver cancer (HepG2) cells via ROS generation, depolarization of mitochondrial membrane potential and also induces apoptotic gene markers [47]. Palladium nanoparticles (PdNPs) biosynthesized using *Saudi propolis* exhibited anticancer activity against MCF-7 ductal carcinoma with an IC_{50} of 104.79 μg/mL [48]. PVP-stabilized PdNPs significantly decreased the viability of MCF-7 cells by disturbing mitochondrial membrane potential, damaging nuclear DNA and inducing Caspase3/7 activity [49].

5. Toxicity of nanoparticles

Many research papers describe the biological application of MNPs, but the limited knowledge and lack of standard procedures to assess nanotoxicity restrict their use in biomedical science. Titanium oxide (TiO_2) NPs are generally considered non-toxic, and their production reaches approximately ten thousand tons per year to meet demands in various industries. The post-disposal of TiO_2 NPs was shown to affect the regular biochemical process. During exposure to 42 μg/mL of TiO_2 NPs, Caco-2 cell lines accumulate TiO_2 NPs and potentiate the production of pro-inflammatory cytokines [50]. It affects the intestinal epithelium and reduces the cell viability significantly compared to the control. Rats treated with the potassium octatitanate fibers (0.25 mg) showed pulmonary toxicity, suggesting that the respirable fiber may induce carcinogenicity [51]. AgNPs and AuNPs are popular in basic nanotechnology and have shown huge potential as antimicrobial and anticancer agents. Rats consuming AgNPs water showed dose-dependent accumulation of NPs in various tissues, including the liver [52]. Prolonged exposure to 300 mg/kg AgNPs affects the blood cells and induces fatty degeneration in the liver and kidneys [53]. The MRC-5 cells exposed to an excess dose (>10 ppm) of AuNPs up-regulated the pro-inflammatory genes and tumour necrosis factor expression [54]. Rats exposed to AuNPs showed accumulation of NPs on hematopoietic bone tissue and resulting bone marrow toxicity [55]. A dose-dependent toxicity effect of zinc oxide (ZnO) NPs was observed in rats exposed to 100 mg/kg animal body weight. ZnO NPs exposed rats showed pathological changes in the liver and kidneys [56]. The dissolution and biodistribution of metal ions from the NPs are important for nanotoxicity. The copper ions released from copper oxide (CuO) NPs affect the immune system by depleting the lymphoid cells in the thymus and spleen organs [57]. The results from several toxicology investigations with MNPs shows that the dose of NPs required to treat diseased conditions should be lower than that of normal cell lines. The following section provides an overview of the potential of lectins to cargo MNPs for effective use in biomedical applications.

6. Lectin conjugated metal nanoparticles

6.1. Lectin-MNPs as biosensors

Fe_3O_4 nanocomposites (FeNC) prepared with graphene quantum dots and ConA through physical mixing showed an electrochemical response in identifying malignant HeLa cells over normal endothelium cells. The ConA guided the cancer cell detection by recognizing the modified glycans (α-D-mannosyl and α-D-glucosyl residues) in the cancer cell surface. Due to the specificity, the FeNC in complexes with doxorubicin (DOX) showed external magnetic fields induced control drug release against malignant cells [58]. The glycocode of normal, fibroadenoma, and invasive ductal carcinoma in human breast tissues were distinguished by Caramoll lectin conjugated Cadmium telluride (CdTe) nanocrystals. By fluorescence microscopy, CdTe lectin conjugates differentiate the glycan profile in normal and transformed tissue [59]. ConA conjugated with carboxyl functionalized AuNPs was used to detect prostate cancer by recognizing prostate-specific membrane antigens, and the linear detection range is 10 pM–100 nM [60]. AuNPs conjugated *Lens culinaris* lectin (LcA) detects liver cancer biomarker AFP-L3 glycoprotein [61]. Peanut lectin-immobilized fluorescent nanospheres were able to detect human colorectal adenocarcinoma cell lines over-expressing Thomsen-Friedenreich antigen, and the imaging agent attached to cancer cells on the mucosal surface with high affinity and specificity [62]. The conjugation of Soybean lectin, wheat germ lectin and ConA lectin to the magnetite NPs and their interaction with the human epidermoid carcinoma A431 cell line were analyzed using Magnetic Particle Quantification based cytometry (MPQ-cytometry) method. The results suggested that Soybean lectin conjugated magnetite NPs showed a promising binding with A431 cell line up to 4.2 pg/cell [63]. AuNPs fabricated with different lectins (WGA, LcA, and ConA) were used to evaluate the glycan expression of carcinoembryonic antigen (CEA) by chronoamperometry. These lectin-based biosensor recognize the N-glycan of CEA and distinguish CEA between healthy and cancer patients serum samples [64]. Jacalin, a lectin isolated from jackfruit seeds, binds to cadmium sulphide quantum dots (CdS QDs) with an association constant of 10^{-4} M^{-1}, comparable to lectin-carbohydrate interactions. Thermodynamic parameters associated with the binding suggest that the interaction is spontaneous and governed by an enthalpy-driven process. Hemagglutination inhibition assays popularly used in lectins suggest that the binding site for CdS QDs on the jacalin surface is distinctly different from the carbohydrate-binding site. Jacalin's

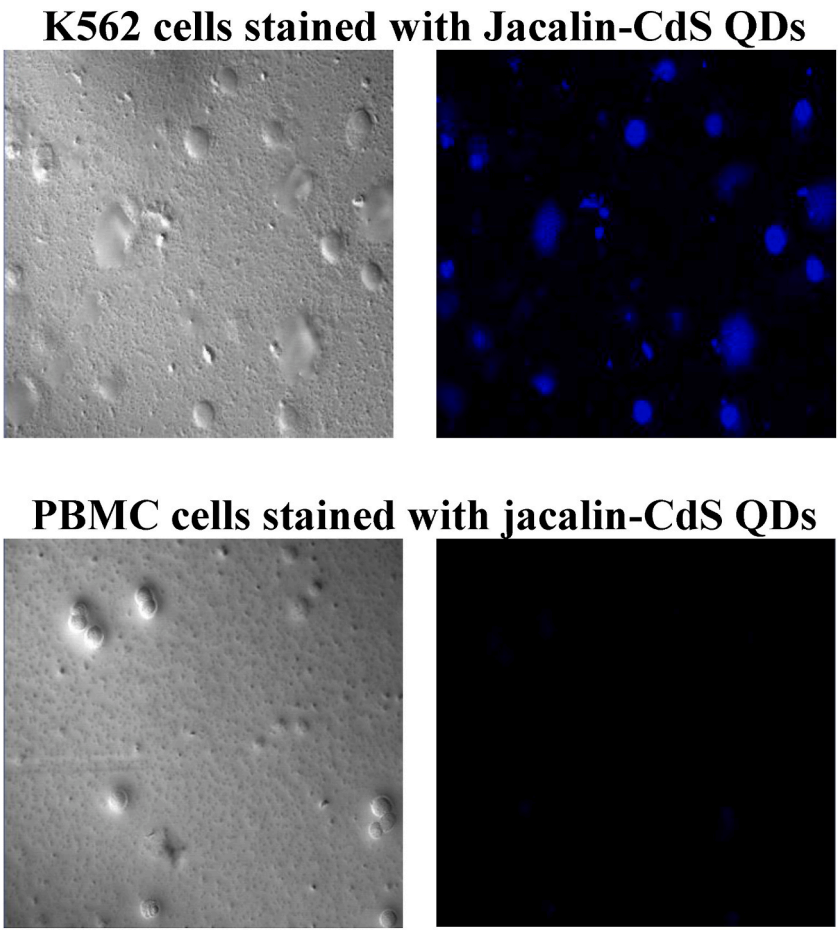


Fig. 1. Selective imaging of cancer cells using Jacalin-CdS QDs. Reproduced from Khan Bhelol et al., 2017, with permission from Elsevier.

ability to recognize the T-antigen of cancer cells was demonstrated through imaging human chronic myeloid leukaemia (K562) cells using Jacalin-CdS QDs [65]. Marangoni et al. reported that AuNPs-jacalin-FITC nanoconjugates bound more strongly to K562 than normal mononuclear blood cells [66]. While exposing Jacalin-CdS QDs to healthy human peripheral lymphocytes (PBMC) and K562 cells, the QDs selectively stain the cancer cells and show blue fluorescence cells. The results from this study suggest that the lectin-QDs selectively recognize the cancer cells without staining the healthy PBMC cells (Fig. 1). The recent findings strongly suggest that lectin can form a complex with NPs and be useful in biosensing (Table 3).

6.2. Lectin-MNPs for anticancer applications

Lectins can be used to effectively target MNPs to recognize modified glycans prevalent in cancer cells (Table 4). Pimentel et al. reported that AgNPs encapsulated in Soybean agglutinin showed decreased cytotoxicity against non-cancerous cells but maintained strong anticancer cytotoxicity against breast cancerous (MDA-MB-231and MCF7) cells [67]. Besides MNPs, letin fortified with other NPs are used targeting cancer cells. For example, ConA with DOX-loaded mesoporous silica nanoparticles (MSN) was built for the targeted treatment of bone cancer. The lectin grafting increases greatly cancer cell selectivity of the NPs while sparing healthy bone cells [68].

Obaid et al. used jacalin to target the Thomsen Friedenreich disaccharide (T antigen), which is over-expressed in over 90 % of primary human carcinomas. Jacalin-conjugated C11Pc-PEG-AuNPs showed better internalization into HT-29 colon cancer cells and 95–98 % cell death post-photodynamic treatment. (PDT) The unconjugated C11Pc-PEG-AuNPs showed only 8 % cell death post-PDT [69]. Ayaz Ahmed et al. (2016) showed that the anticancer activity of phytomolecules, acetylshikonin (AS) and beta, beta-dimethylacrylshikonin (BDS) was enhanced when loaded into jacalin capped silver nanoparticles (JAgNPs). The pure AS/BDS display cytotoxicity effect on K562 cells at 500 nM, whereas AS/BDS loaded into JAgNPs induce cytotoxicity at lower concentration (100 nM). Fluorescence microscopy studies confirmed that cancerous K562 cells prefer the uptake of JAgNPs-AS/BDS over the non-tumorigenic HepG2 cells. The internalization of JAgNPs-AS/BDS causes the excess generation of ROS, increases tumour necrosis factor (TNF-α) secretion, inhibits interleukin-10 (IL-10) production, affects mitochondrial membrane potential, damages DNA, and activates apoptosis (Fig. 2) [70].

6.3. Lectin-MNPs against microbes

Microbes resistant to existing antimicrobials are difficult to treat. Hence, medical science demands new drugs or novel strategies to combat drug-resistant microbes. The antimicrobial activity of MNPs and lectin is evident from the existing literature, but there haven't been many investigations on the antimicrobial activity of lectin-MNPs complexes (Table 5). Khan et al., showed that dextran-capped AuNPs-methylene blue-ConA complexes (0.25 mg/mL) possess excellent photo-inactivation activity against multi-drug resistant *K. pneumonia*. The complex exhibited bactericidal action by inhibiting the efflux pump, producing excess ROS, and inducing photo-toxicity to DNA [71]. AgNPs functionalized with *Portunus pelagicus* lectin isolated from the haemolymph of blue swimmer crab showed significant antimicrobial activity when compared to lectin and silver nitrate tested alone. *Portunus pelagicus* lectin coated AgNPs at 100 μg/mL inhibited the growth of human pathogenic Gram-negative *Proteus vulgaris*, *Pseudomonas aeruginosa* and Gram-positive *Enterococcus faecalis* and *Bacillus pumilus* [72]. Jacalin-capped PtNPs (JPtNPs) showed broad-spectrum antimicrobial activity at 31.25 μM against human pathogenic Gram-positive and Gram-negative bacteria. JPtNPs are biocompatible with human RBC but damage bacterial membranes and induce irreversible morphological changes to kill the bacteria. In vivo studies showed that 50 μM JPtNPs rescues zebrafish infected with fish specific pathogen *A. hydrophila*. JPtNPs can rescue fish with a single injection, whereas unfunctionalized PtNPs require three treatments to rescue infected fish. The findings suggest that jacalin aids NPs in recognizing the pathogen and overcoming any biological barriers that may be present. JPtNPs promote an adaptive immune response against the infectious pathogen through modulating pro-inflammatory cytokines and promote bacteria-specific antibody production to survive repetitive infection without needing treatment [73]. *N*-lauryl tyramine-capped CuS NPs and jacalin form a complex with an association constant of $1.91 \times 10^4\ M^{-1}$. The MIC of CuS NPs reduced from 12.5 μM to 0.78 μM when functionalized with jacalin. The lectin-NPs complex effectively affects the bacterial membrane integrity. It produces excess ROS at a 16-fold lower concentration than the CuS NPs

Table 3
Representative lectins-metal nanoparticles conjugate for biosensing.

Lectin	Nanoparticles	Method	Biosensing	Ref.
ConA	Fe_3O_4 -graphene quantum dots	Electrochemical	Malignant HeLa cells	[58]
Caramoll lectin	Cadmium telluride nanocrystals	Fluorescence microscopy	Invasive ductal carcinoma	[59]
ConA	AuNPs	Localized surface plasmon resonances	Bacteria, Prostate cancer	[60]
Lens culinaris lectin	AuNPs	Surface plasmon resonances	Liver cancer biomarker AFP-L3 glycoprotein	[61]
Peanut lectin	Fluorescent nanospheres	Fluorescence imaging	colorectal cancer	[62]
Soybean lectin	Magnetite NPs	Magnetic Particle Quantification based cytometry	Human epidermoid carcinoma	[63]
WGA, LcA, ConA	AuNPs	Chronoamperometry	carcinoembryonic antigen	[64]
Jacalin	cadmium sulphide quantum dots	Fluorescence microscopy	Human chronic myeloid leukaemia	[65]

Table 4
Representative lectin-MNPs conjugate for anticancer applications.

Lectin	Nanoparticles	Cell line	Ref.
Soybean agglutinin	AgNPs	Breast cancer, MDA-MB-231, MCF7	[67]
ConA	DOX-loaded mesoporous silica nanoparticles	Human osteosarcoma, CRL-1543	[68]
Jacalin	PEG phthalocyanine gold nanoparticles	HT-29 colon cancer	[69]
Jacalin	Shikonin-AgNPs	Leukaemia, K562	[70]

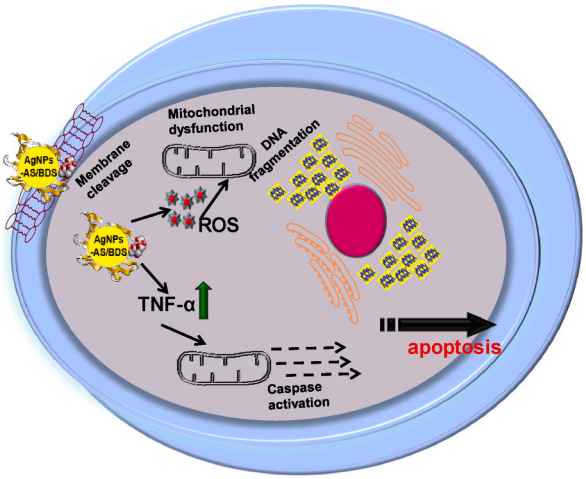


Fig. 2. Anticancer mechanism induced by JAgNPs-AS/BDS. Reproduced from Khan Bhelol et al., 2016, with permission from the Royal Chemical Society.

Table 5
Representative lectin-MNPs conjugate for antimicrobial applications.

Lectin	Nanoparticles	Microorganism	Ref.
ConA	Dextran capped AuNPs	Photo-inactivation of multi-drug resistant *K. pneumonia*	[71]
Portunus pelagicus lectin	AgNPs	*P. vulgaris, P. aeruginosa, E. faecalis, B. pumilus, C. albicans*	[72]
Jacalin	Jacalin capped PtNPs	Gram positive and Gram negative bacteria	[73]
Jacalin	*N*-lauryltyramine capped CuS NPs	*S. aureus*, MRSA, *B. subtilis*, *E. coli*, *A. hydrophila*	[74]
Jacalin	*N*-lauryltyramine capped CuS NPs	Fluconazole-resistant *C. albicans* and *C. glabrata*	[75]
Jacalin	*N*-myristoyltaurine capped CuS NPs	*S. aureus*, MRSA	[77]
Butea monosperma seed lectin	Citrate capped AgNPs	Uropathogenic *E. coli*	[79]

[74]. Jayasankari et al. (2021) demonstrated the antibiofilm activity of jacalin-functionalized CuS NPs (6.25 μM) against MRSA biofilms. The lectin-NPs complex showed a preservative effect by inhibiting young biofilm formation and disturbing biofilms formed on poultry meat samples [75]. Besides antibacterial, jacalin functionalized CuS NPs (0.5 μM) eradicate the single and mixed species biofilms formed by fluconazole-resistant *C. albicans* and *C. glabrata* isolated from Vulvovaginal Candidiasis patients [76].

N-myristoyl-taurine-capped AgNPs functionalized with jacalin kill *S. aureus* in 30 min by inducing oxidative stress and membrane damage. The MIC of the AgNPs decreases four-fold from 250 μM to 62.5 μM when complex with jacalin. The jacalin-AgNPs (31.25 μM) are highly effective compared to AgNPs in preventing colony formation and inhibiting biofilm formation by affecting the exopolysaccharide synthesis [77]. MNPs administered into the biological system may suffer from the influence of biological fluids, especially protein corona formation. Subramaniyan et al. (2019) showed that protein corona formation affected pectin-capped CuS NPs antimicrobial activity. When complexed with serum protein, a protein corona forms on the pectin-capped CuS NPs surface, raising the MIC from 12.5 μM to 50 μM. But, jacalin functionalization overcomes the interference from the protein corona and restores the efficacy of the NPs and showed MIC of 0.78 μM against *E. coli*, *P. aeruginosa*, *S. aureus*, and *B. Subtilis* [78]. The lectin from the seeds of *Butea monosperma* (BMSL) forms non-covalent complexes with AgNPs (BAgNPs) even in the presence of galactose, suggesting the BMSL sugar-binding site is distinct. Chemical modification of the serine amino acids located near the sugar-binding site affects the glycan recognition activity of BMSL. BMSL-FITC labelled uropathogenic *E. coli* (UPEC) showed green fluorescent cells, whereas modified BMSL-FITC conjugates could not label UPEC due to the modification of the sugar-binding site (Fig. 3A). 37.5 μM BAgNPs successfully eradicated the mature biofilm formed on the catheter surface, but modified BMSL-AgNPs complex (mBAgNPs) failed to disturb the biofilm (Fig. 3B). BAgNPs (18.75 μM) display superior antibacterial activity than AgNPs (75 μM)and mBAgNPs (75 μM) through affecting membrane integrity, and induce ROS/GSH imbalance to kill the bacteria. The poor activity from mBAgNPs was attributed to a

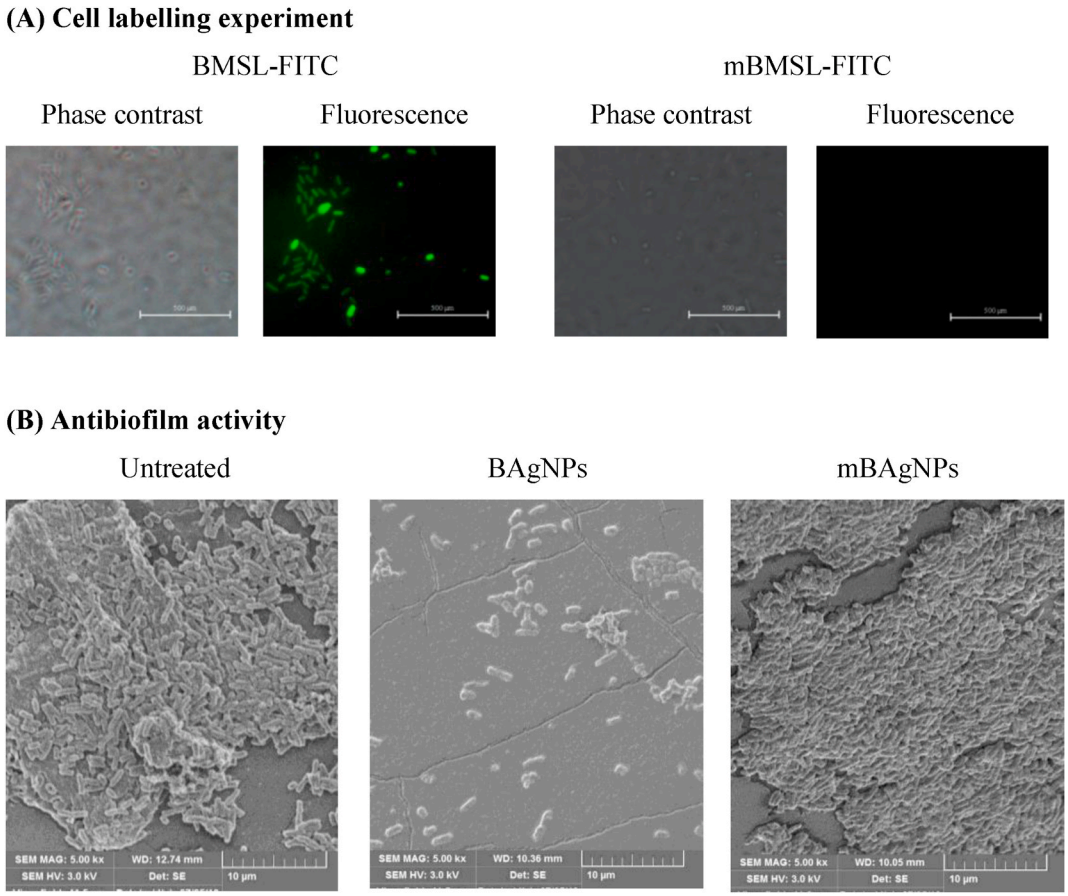


Fig. 3. (A) BMSL recognizing cell surface glycan. Fluorescence microscopy imaging showed that only BMSL-FITC recognize UPEC and fluoresce green, whereas mBMSL-FITC could not label the cells and showed cells without fluorescence. (A) Scanning electron microscopy image showed BAgNPs eradicate the biofilm from the catheter surface, and mBAgNPs showed poor antibiofilm activity. Reproduced from Siva et al., 2019, with permission from the American Chemical Society. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

lack of glycan recognition sites. Since lectins are proteins, they can be degraded by microbial proteases, affecting MNPs activity and necessitating further study. However, the results concluded that the judicial uses of lectin could enhance the activity of metal nanoparticles [79].

7. Conclusion and future perspectives

Due to carbohydrate specificity, lectins display applications in various fields, including glycobiology, immunohistochemical analysis, diagnosis, therapeutics, drug delivery, etc. Indeed, multiple lectins showed anticancer and antimicrobial activity [80,81]. The human erythrocytes agglutinating property has been considered a serious concern in developing lectin-based therapy. Kitao and Hattori (1977) showed that tumour-bearing mice injected intraperitoneally with ConA-daunomycin conjugate survived without showing the adverse effect of agglutination, suggesting lectins circumvent the negative effect *in vivo* [82]. In this regard, the judicious use of lectin conjugates will enhance the drug efficacy, particularly by utilizing the specific bioadhesive properties. This concept can greatly expand to using lectin for accurate and reliable cellular identification and targeting metal nanoparticles to exert desired therapeutic activity with low or negligible toxicity. For example, jacalin-PEG phthalocyanine AuNPs target T antigen, which is over-expressed in over 90 % of primary human carcinomas. BMSL-AgNPs rescue infected zebrafish, and *in vitro* studies showed that the nanoconjugates kill uropathogens by membrane damage and producing excess ROS. Using lectins with MNPs is a fielding subject that will surely grow in the coming years to target various pandemic and epidemic diseases such as COVID-19, Zika virus, metastatic cancers, and drug-resistant pathogens. Despite the promise, a lot of plant lectins are unexplored. Moreover, biotechnology techniques to produce an active fragment of lectins remain rudimentary. Similar to lectins, protein toxins like Shiga toxins (Stxs), Shiga-like toxins (SLT) or verotoxins (VT) [83] could be coupled with MNPs or bioactive lectins to develop efficient therapeutic molecules. Future research aspects of developing a lectin library with sugar specificity and affinity analysis beyond carbohydrates, *in vitro* and *in vivo* toxic studies are warranted to develop lectin-based therapeutics.

CRediT authorship contribution statement

Siva Bala Subramaniyan: Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Anbazhagan Veerappan:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgements

SBS acknowledges SASTRA University for teaching assistantship. The authors acknowledge SASTRA University for its infrastructure. This work was supported by grants (67/7/2022-DDI/BMS) from the Indian Council of Medical Research, India.

References

[1] J. Gao, J.M. Karp, R. Langer, N. Joshi, The future of drug delivery, Chem. Mater. 35 (2) (2023) 359–363, https://doi.org/10.1021/acs.chemmater.2c03003.
[2] U. Bulbake, S. Doppalapudi, N. Kommineni, W. Khan, Liposomal formulations in clinical use: an updated review, Pharmaceutics 9 (2017) 12, https://doi.org/10.3390/pharmaceutics9020012.
[3] T. Sahu, Y.K. Ratre, S. Chauhan, L.V.K.S. Bhaskar, M.P. Nair, H.K. Verma, Nanotechnology based drug delivery system: current strategies and emerging therapeutic potential for medical science, J. Drug Delivery Sci. Technol. 63 (2021) 102487, https://doi.org/10.1016/j.jddst.2021.102487.
[4] B. Naisbett, J. Woodley, The potential use of tomato lectin for oral drug delivery: 3. Bioadhesion in vivo, Int. J. Pharm. 114 (2) (1995) 227–236, https://doi.org/10.1016/0378-5173(94)00242-W.
[5] S.S. Komath, M. Kavitha, M.J. Swamy, Beyond carbohydrate binding: new directions in plant lectin research, Org. Biomol. Chem. 4 (6) (2006) 973–988, https://doi.org/10.1039/B515446D.
[6] B.C.M. Bomfim, J. Azevedo-Silva, G. Caminha, J.P.R. Santos, M. Pelajo-Machado, J. de Paula Ayres-Silva, Lectin-based carbohydrate profile of megakaryocytes in murine fetal liver during development, Sci. Rep. 13 (2023) 6729, https://doi.org/10.1038/s41598-023-32863-3.
[7] L. Polito, M. Bortolotti, M.G. Battelli, G. Calafato, A. Bolognesi, Ricin: an ancient story for a timeless plant toxin, Toxins 11 (6) (2019) 324, https://doi.org/10.3390/toxins11060324.
[8] E. Boyd Wc Fau - Shapleigh, E. Shapleigh, Specific precipitating activity of plant agglutinins (lectins), Science 119 (3091) (1954) 419, https://doi.org/10.1126/science.119.3091.419.
[9] H. Sharon, N. Fau - Lis, H. Lis, Lectins: cell-agglutinating and sugar-specific proteins, Science 177 (4053) (1972) 949–959, https://doi.org/10.1126/science.177.4053.949.
[10] M. Tsaneva, E.J.M. Van Damme, 130 years of plant lectin research, Glycoconjugate J 37 (5) (2020) 533–551, https://doi.org/10.1007/s10719-020-09942-y.
[11] C.D. Raposo, A.B. Canelas, M.T. Barros, Human lectins, their carbohydrate affinities and where to find them, Biomolecules 11 (2) (2021) 188, https://doi.org/10.3390/biom11020188.
[12] M.D. Swanson, H.C. Winter, I.J. Goldstein, D.M. Markovitz, A lectin isolated from bananas is a potent inhibitor of HIV replication, J. Biol. Chem. 285 (12) (2010) 8646–8655, https://doi.org/10.1074/jbc.M109.034926.
[13] S. Rajendaran, A. Jothi, V. Anbazhagan, Targeting the glycan of receptor binding domain with jacalin as a novel approach to develop a treatment against COVID-19, R. Soc. Open Sci. 7 (9) (2021) 200844, https://doi.org/10.1098/rsos.200844.
[14] M.C. Moura, T.H. Napoleão, M.C. Coriolano, P.M. Paiva, R.C. Figueiredo, L.C. Coelho, Water-soluble Moringa oleifera lectin interferes with growth, survival and cell permeability of corrosive and pathogenic bacteria, J. Appl. Microbiol. 119 (3) (2015) 666–676, https://doi.org/10.1111/jam.12882.
[15] K.Y. Hiremath, N. Jagadeesh, S. Belur, S.S. Kulkarni, S.R. Inamdar, A lectin with anti-microbial and anti proliferative activities from Lantana camara, a medicinal plant, Protein Expr. Purif. 170 (2020) 105574, https://doi.org/10.1016/j.pep.2020.105574.
[16] M. Qu, C. Tong, L. Kong, X. Yan, O.V. Chernikov, P.A. Lukyanov, Q. Jin, W. Li, Purification of a secreted lectin from Andrias davidianus skin and its antibacterial activity, Comp. Biochem. Physiol. C Toxicol. Pharmacol. 167 (2015) 140–146, https://doi.org/10.1016/j.cbpc.2014.08.008.
[17] G.B. Klafke, G.M.S.G. Moreira, J.L. Pereira, P.D. Oliveira, F.R. Conceição, R.G. Lund, A.A. Grassmann, O.A. Dellagostin, L. da Silva Pinto, Lectin I from Bauhinia variegata (BVL-I) expressed by Pichia pastoris inhibits initial adhesion of oral bacteria in vitro, Int. J. Biol. Macromol. 93 (2016) 913–918, https://doi.org/10.1016/j.ijbiomac.2016.09.062.
[18] T.F. Procópio, L.L. de Siqueira Patriota, M.C. de Moura, P.M. da Silva, A.P.S. de Oliveira, L.V. do Nascimento Carvalho, T. de Albuquerque Lima, T. Soares, T. D. da Silva, L.C. Breitenbach Barroso Coelho, M.G. da Rocha Pitta, M.J.B. de Melo Rêgo, R.C. Bressan Queiroz de Figueiredo, P.M. Guedes Paiva, T.H. Napoleão, CasuL: a new lectin isolated from Calliandra surinamensis leaf pinnulae with cytotoxicity to cancer cells, antimicrobial activity and antibiofilm effect, Int. J. Biol. Macromol. 98 (2017) 419–429, https://doi.org/10.1016/j.ijbiomac.2017.02.019.
[19] M.B. Trindade, J.L.S. Lopes, A. Soares-Costa, A.C. Monteiro-Moreira, R.A. Moreira, M.L.V. Oliva, L.M. Beltramini, Structural characterization of novel chitin-binding lectins from the genus Artocarpus and their antifungal activity, Biochim. Biophys. Acta, Proteins Proteomics 1764 (1) (2006) 146–152, https://doi.org/10.1016/j.bbapap.2005.09.011.
[20] A.R.d.O. Sousa, F.R.N. Andrade, R.P. Chaves, B.L.d. Sousa, D.B.d. Lima, R.O.d.S. Souza, C.G.L. da Silva, C.S. Teixeira, A.H. Sampaio, C.S. Nagano, R.F. Carneiro, Structural characterization of a galectin isolated from the marine sponge Chondrilla caribensis with leishmanicidal potential, Biochim. Biophys. Acta, Gen. Subj. 1865 (12) (2021) 129992, https://doi.org/10.1016/j.bbagen.2021.129992.
[21] A. Thomazelli, F. Tomiotto-Pellissier, M.M. Miranda-Sapla, S.S. da Silva, D.S. Alvarenga, C. Panis, A.H.D. Cataneo, J. Bordignon, G.F. Silveira, L.M. Yamauchi, J. de Sá, I. Felipe, W.R. Pavanelli, I. Conchon-Costa, Concanavalin-A displays leishmanicidal activity by inducing ROS production in human peripheral blood mononuclear cells, Immunopharmacol. Immunotoxicol. 40 (5) (2018) 387–392, https://doi.org/10.1080/08923973.2018.1510960.
[22] C. Li, J. Chen, B. Lu, Z. Shi, H. Wang, B. Zhang, K. Zhao, W. Qi, J. Bao, Y. Wang, Molecular switch role of Akt in Polygonatum odoratum lectin-induced apoptosis and autophagy in human non-small cell lung cancer A549 cells, PLoS One 9 (7) (2014) e101526, https://doi.org/10.1371/journal.pone.0101526.
[23] X. Yang, L. Wu, X. Duan, L. Cui, J. Luo, G. Li, Adenovirus carrying gene encoding Haliotis discus discus sialic acid binding lectin induces cancer cell apoptosis, Mar. Drugs 12 (7) (2014) 3994–4004, https://doi.org/10.3390/md12073994.
[24] B. Liu, Y. Cheng, B. Zhang, H.J. Bian, J.K. Bao, Polygonatum cyrtonema lectin induces apoptosis and autophagy in human melanoma A375 cells through a mitochondria-mediated ROS-p38-p53 pathway, Cancer Lett. 275 (1) (2009) 54–60, https://doi.org/10.1016/j.canlet.2008.09.042.
[25] J. Terävä, L. Tiainen, U. Lamminmäki, P.L. Kellokumpu-Lehtinen, K. Pettersson, K. Gidwani, Lectin nanoparticle assays for detecting breast cancer-associated glycovariants of cancer antigen 15-3 (CA15-3) in human plasma, PLoS One 14 (7) (2019) e0219480.
[26] J. Yang, X. Liu, J. Shu, Y. Hou, M. Chen, H. Yu, T. Ma, H. Du, J. Zhang, Y. Qiao, J. He, L. Niu, F. Yang, Z. Li, Abnormal galactosylated–glycans recognized by Bandeiraea simplicifolia lectin I in saliva of patients with breast cancer, Glycoconj. J. 37 (3) (2020) 373–394, https://doi.org/10.1371/journal.pone.0219480.

[27] O.D. Hendrickson, V.D. Nikitushkin, A.V. Zherdev, B.B. Dzantiev, Lectin-based detection of Escherichia coli and Staphylococcus aureus by flow cytometry, Arch. Microbiol. 201 (3) (2019) 313–324, https://doi.org/10.1007/s00203-018-1613-0.
[28] F. Roth-Walter, I. Schöll, E. Untersmayr, R. Fuchs, G. Boltz-Nitulescu, A. Weissenböck, O. Scheiner, F. Gabor, E. Jensen-Jarolim, M cell targeting with Aleuria aurantia lectin as a novel approach for oral allergen immunotherapy, J. Allergy Clin. Immunol. 114 (6) (2004) 1362–1368, https://doi.org/10.1016/j.jaci.2004.08.010.
[29] V.L. Koshte, M. Aalbers, P.G. Calkhoven, R.C. Aalberse, The potent IgG4-inducing antigen in banana is a mannose-binding lectin, BanLec-I, Int. Arch. Allergy Immunol. 97 (1) (1992) 17–24, https://doi.org/10.1159/000236090.
[30] R. Chhetra Lalli, K. Kaur, S. Dadsena, A. Chakraborti, R. Srinivasan, S. Ghosh, Maackia amurensis agglutinin enhances paclitaxel induced cytotoxicity in cultured non-small cell lung cancer cells, Biochimie 115 (2015) 93–107, https://doi.org/10.1016/j.biochi.2015.05.002.
[31] K. Ikemoto, K. Shimizu, K. Ohashi, Y. Takeuchi, M. Shimizu, N. Oku, Bauhinia purprea agglutinin-modified liposomes for human prostate cancer treatment, Cancer Sci. 107 (1) (2016) 53–59, https://doi.org/10.1111/cas.12839.
[32] A. Sharma, S. Sharma, G.K. Khuller, Lectin-functionalized poly (lactide-co-glycolide) nanoparticles as oral/aerosolized antitubercular drug carriers for treatment of tuberculosis, J. Antimicrob. Chemother. 54 (4) (2004) 761–766, https://doi.org/10.1093/jac/dkh411.
[33] V.F. Santos, A.C.J. Araújo, A.L.F. Silva, D.V. Almeida, P.R. Freitas, A.L.E. Santos, B.A.M. Rocha, W. Garcia, A.M. Leme, E. Bondan, F.T. Borges, B.S. Cutrim, L.C. N. Silva, H.D.M. Coutinho, C.S. Teixeira, Dioclea violacea lectin modulates the gentamicin activity against multi-resistant strains and induces nefroprotection during antibiotic exposure, Int. J. Biol. Macromol. 146 (2020) 841–852, https://doi.org/10.1016/j.ijbiomac.2019.09.207.
[34] V.F. Santos, M.S. Costa, F.F. Campina, R.R. Rodrigues, A.L.E. Santos, F.M. Pereira, K.L.R. Batista, R.C. Silva, R.O. Pereira, B.A.M. Rocha, H.D.M. Coutinho, C. S. Teixeira, The galactose-binding lectin isolated from Vatairea macrocarpa seeds enhances the effect of antibiotics against Staphylococcus aureus-resistant strain, Probiotics Antimicrob Proteins 12 (1) (2020) 82–90, https://doi.org/10.1007/s12602-019-9526-z.
[35] A.W. Septama, P. Panichayupakaranant, Synergistic effect of artocarpin on antibacterial activity of some antibiotics against methicillin-resistant Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli, Pharm. Biol. 54 (4) (2016) 686–691, https://doi.org/10.3109/13880209.2015.1072566.
[36] R.R.S. Silva, C.R. Silva, V.F. Santos, C.R.S. Barbosa, D.F. Muniz, A.L.E. Santos, M.H.C. Santos, B.A.M. Rocha, K.L.R. Batista, L.M. Costa-Júnior, H.D.M. Coutinho, C.S. Teixeira, Parkia platycephala lectin enhances the antibiotic activity against multi-resistant bacterial strains and inhibits the development of Haemonchus contortus, Microb. Pathog. 135 (2019) 103629, https://doi.org/10.1016/j.micpath.2019.103629.
[37] Q. He, J. Lu, N. Liu, W. Lu, Y. Li, C. Shang, X. Li, L. Hu, G. Jiang, Antiviral properties of silver nanoparticles against SARS-CoV-2: effects of surface coating and particle size, Nanomaterials 12 (6) (2022) 990, https://doi.org/10.3390/nano12060990.
[38] C. Wang, W. Zhu, B.Z. Wang, Dual-linker gold nanoparticles as adjuvanting carriers for multivalent display of recombinant influenza hemagglutinin trimers and flagellin improve the immunological responses in vivo and in vitro, Int. J. Nanomed. 12 (2017) 4747–4762, https://doi.org/10.2147/IJN.S137222.
[39] H. Ghaffari, A. Tavakoli, A. Moradi, A. Tabarraei, F. Bokharaei-Salim, M. Zahmatkeshan, M. Farahmand, D. Javanmard, S.J. Kiani, M. Esghaei, V. Pirhajati-Mahabadi, S.H. Monavari, A. Ataei-Pirkooh, Inhibition of H1N1 influenza virus infection by zinc oxide nanoparticles: another emerging application of nanomedicine, J. Biomed. Sci. 26 (1) (2019) 70, https://doi.org/10.1186/s12929-019-0563-4.
[40] Y. Li, Z. Lin, M. Guo, Y. Xia, M. Zhao, C. Wang, T. Xu, T. Chen, B. Zhu, Inhibitory activity of selenium nanoparticles functionalized with oseltamivir on H1N1 influenza virus, Int. J. Nanomed. 12 (2017) 5733–5743, https://doi.org/10.2147/IJN.S140939.
[41] M. Abdolhosseini, H. Zamani, A. Salehzadeh, Synergistic antimicrobial potential of ciprofloxacin with silver nanoparticles conjugated to thiosemicarbazide against ciprofloxacin resistant Pseudomonas aeruginosa by attenuation of MexA-B efflux pump genes, Biologia 74 (2019) 1191–1196, https://doi.org/10.2478/s11756-019-00269-0.
[42] S. Nazir, K. Tahir, R. Irshad, Q.U. Khan, S. Khan, I.U. Khan, A. Nawaz, F. Rehman, Photo-assisted inactivation of highly drug resistant bacteria and DPPH scavenging activities of zinc oxide graphted Pd-MCM-41 synthesized by new hydrothermal method, Photodiagnosis Photodyn. Ther. 33 (2021) 102162, https://doi.org/10.1016/j.pdpdt.2020.102162.
[43] K.G. Akpomie, S. Ghosh, M. Gryzenhout, J. Conradie, One-pot synthesis of zinc oxide nanoparticles via chemical precipitation for bromophenol blue adsorption and the antifungal activity against filamentous fungi, Sci. Rep. 11 (1) (2021) 8305, https://doi.org/10.1038/s41598-021-87819-2.
[44] M.T. El-Saadony, A.M. Saad, T.F. Taha, A.A. Najjar, N.M. Zabermawi, M.M. Nader, S.F. AbuQamar, K.A. El-Tarabily, A. Salama, Selenium nanoparticles from Lactobacillus paracasei HM1 capable of antagonizing animal pathogenic fungi as a new source from human breast milk, Saudi J. Biol. Sci. 28 (12) (2021) 6782–6794, https://doi.org/10.1016/j.sjbs.2021.07.059.
[45] K.R. Chintalacharuvu, Z.A. Matolek, B. Pacheco, E.M. Carriera, D.O. Beenhouwer, Complexing amphotericin B with gold nanoparticles improves fungal clearance from the brains of mice infected with Cryptococcal neoformans, Med. Mycol. 59 (11) (2021) 1085–1091, https://doi.org/10.1093/mmy/myab042.
[46] D.N. Păduraru, D. Ion, A.G. Niculescu, F. Muşat, O. Andronic, A.M. Grumezescu, A. Bolocan, Recent developments in metallic nanomaterials for cancer therapy, diagnosing and imaging applications, Pharmaceutics 14 (2) (2022) 435, https://doi.org/10.3390/pharmaceutics14020435.
[47] J. Ahmad, R. Wahab, M.J. Akhtar, M. Ahamed, Cytotoxicity and apoptosis response of hexagonal zinc oxide nanorods against human hepatocellular liver carcinoma cell line, J. King Saud Univ. Sci. 33 (2021) 101658, https://doi.org/10.1016/j.jksus.2021.101658.
[48] M.S. Al-Fakeh, S.O.M. Osman, M. Gassoumi, M. Rabhi, M. Omer, Characterization, antimicrobial and anticancer properties of palladium nanoparticles biosynthesized optimally using Saudi propolis, Nanomaterials 11 (10) (2021) 2666, https://doi.org/10.3390/nano11102666.
[49] V. Ramalingam, S. Raja, M. Harshavardhan, In situ one-step synthesis of polymer-functionalized palladium nanoparticles: an efficient anticancer agent against breast cancer, Dalton Trans. 49 (11) (2020) 3510–3518, https://doi.org/10.1039/c9dt04576g.
[50] P. Pedata, G. Ricci, L. Malorni, A. Venezia, M. Cammarota, M.G. Volpe, N. Iannaccone, V. Guida, C. Schiraldi, M. Romano, G. Iacomino, In vitro intestinal epithelium responses to titanium dioxide nanoparticles, Food Res. Int. 119 (2019) 634–642, https://doi.org/10.1016/j.foodres.2018.10.041.
[51] M. Abdelgied, A.M. El-Gazzar, W.T. Alexander, T. Numano, M. Iigou, A. Naiki-Ito, H. Takase, A. Hirose, Y. Taquahashi, J. Kanno, M. Abdelhamid, K.A. Abdou, S. Takahashi, D.B. Alexander, H. Tsuda, Carcinogenic effect of potassium octatitanate (POT) fibers in the lung and pleura of male Fischer 344 rats after intrapulmonary administration, Part. Fibre Toxicol. 16 (1) (2019) 34, https://doi.org/10.1186/s12989-019-0316-2.
[52] Y.S. Kim, J.S. Kim, H.S. Cho, D.S. Rha, J.M. Kim, J.D. Park, B.S. Choi, R. Lim, H.K. Chang, Y.H. Chung, I.H. Kwon, J. Jeong, B.S. Han, I.J. Yu, Twenty-eight-day oral toxicity, genotoxicity, and gender-related tissue distribution of silver nanoparticles in sprague-dawley rats, Inhal. Toxicol. 20 (6) (2008) 575–583, https://doi.org/10.1080/08958370701874663.
[53] S.W.P. Wijnhoven, W.J.G.M. Peijnenburg, C.A. Herberts, W.I. Hagens, A.G. Oomen, E.H.W. Heugens, B. Roszek, J. Bisschops, I. Gosens, D. Van De Meent, S. Dekkers, W.H. De Jong, M. van Zijverden, A.J.A.M. Sips, R.E. Geertsma, Nano-silver – a review of available data and knowledge gaps in human and environmental risk assessment, Nanotoxicology 3 (2) (2009) 109–138, https://doi.org/10.1080/17435390902725914.
[54] H.J. Yen, S.H. Hsu, C.L. Tsai, Cytotoxicity and immunological response of gold and silver nanoparticles of different sizes, Small 5 (13) (2009) 1553–1561, https://doi.org/10.1002/smll.200900126.
[55] O.B. Adewale, H. Davids, L. Cairncross, S. Roux, Toxicological behavior of gold nanoparticles on various models: influence of physicochemical properties and other factors, Int. J. Toxicol. 38 (5) (2019) 357–384, https://doi.org/10.1177/1091581819863130.
[56] V. Sharma, D. Anderson, A. Dhawan, Zinc oxide nanoparticles induce oxidative DNA damage and ROS-triggered mitochondria mediated apoptosis in human liver cells (HepG2), Apoptosis 17 (8) (2012) 852–870, https://doi.org/10.1007/s10495-012-0705-6.
[57] W.H. De Jong, E. De Rijk, A. Bonetto, W. Wohlleben, V. Stone, A. Brunelli, E. Badetti, A. Marcomini, I. Gosens, F.R. Cassee, Toxicity of copper oxide and basic copper carbonate nanoparticles after short-term oral exposure in rats, Nanotoxicology 13 (1) (2019) 50–72, https://doi.org/10.1080/17435390.2018.1530390.
[58] A. Dutta Chowdhury, A.B. Ganganboina, Y.-c. Tsai, H.-c. Chiu, R.-a. Doong, Multifunctional GQDs-Concanavalin A@Fe3O4 nanocomposites for cancer cells detection and targeted drug delivery, Anal. Chim. Acta 1027 (2018) 109–120, https://doi.org/10.1016/j.aca.2018.04.029.
[59] M.E.T. Carvalho, W.F. Oliveira, C.R.A. Cunha, L. Coelho, M.V. Silva, L.B. Carvalho Junior, B.S. Santos, P.E. Cabral Filho, A. Fontes, M.T.S. Correia, Evaluating the glycophenotype on breast cancer tissues with quantum dots-Cramoll lectin conjugates, Int. J. Biol. Macromol. 138 (2019) 302–308, https://doi.org/10.1016/j.ijbiomac.2019.07.088.

[60] I.G. Subramani, R.M. Ayub, S.C.B. Gopinath, V. Perumal, M.F.M. Fathil, M.K. Md Arshad, J. Taiwan Inst. Chimistry E. 120 (2021) 9–16, https://doi.org/10.1016/j.jtice.2021.03.004.
[61] M. Kalita, M.M. Payne, S.H. Bossmann, Glyco-nanotechnology: a biomedical perspective, Nanomedicine 42 (2022) 102542. https://doi:10.1016/j.nano.2022.102542.
[62] S. Sakuma, M. Kataoka, H. Higashino, T. Yano, Y. Masaoka, S. Yamashita, K. Hiwatari, H. Tachikawa, R. Kimura, K. Nakamura, H. Kumagai, J.C. Gore, W. Pham, A potential of peanut agglutinin-immobilized fluorescent nanospheres as a safe candidate of diagnostic drugs for colonoscopy, Eur J Pharm Sci 42 (4) (2011) 340–347, https://doi.org/10.1016/j.ejps.2010.12.011.
[63] V.O. Shipunova, M.P. Nikitin, M.M. Belova, S.M. Deyev, Label-free methods of multiparametric surface plasmon resonance and MPQ-cytometry for quantitative real-time measurements of targeted magnetic nanoparticles complexation with living cancer cells, Mater. Today Commun. 29 (2021) 102978, https://doi.org/10.1016/j.mtcomm.2021.102978.
[64] L. Zhao, C. Li, H. Qi, Q. Gao, C. Zhang, Electrochemical lectin-based biosensor array for detection and discrimination of carcinoembryonic antigen using dual amplification of gold nanoparticles and horseradish peroxidase Sensor, Actuator. B Chem. 235 (2016) 575–582, https://doi.org/10.1016/j.snb.2016.05.136.
[65] K.B. Ayaz Ahmed, M.R.C. Raja, S.K. Mahapatra, V. Anbazhagan, Interaction of cadmium sulfide quantum dots with jacalin for specific recognition of cancer cells, J. Lumin. 182 (2017) 283–288, https://doi.org/10.1016/j.jlumin.2016.10.045.
[66] V.S. Marangoni, I.M. Paino, V. Zucolotto, Synthesis and characterization of jacalin-gold nanoparticles conjugates as specific markers for cancer cells, Colloids Surf. B Biointerfaces 112 (2013) 380–386, https://doi.org/10.1016/j.colsurfb.2013.07.070.
[67] R.G. Casañas Pimentel, V. Robles Botero, E. San Martín Martínez, C. Gómez García, J.P. Hinestroza, Soybean agglutinin-conjugated silver nanoparticles nanocarriers in the treatment of breast cancer cells, J. Biomater. Sci. Polym. Ed. 27 (3) (2016) 218–234, https://doi.org/10.1080/09205063.2015.1116892.
[68] M. Martínez-Carmona, D. Lozano, M. Colilla, M. Vallet-Regí, Lectin-conjugated pH-responsive mesoporous silica nanoparticles for targeted bone cancer treatment, Acta Biomater. 65 (2018) 393–404, https://doi.org/10.1016/j.actbio.2017.11.007.
[69] G. Obaid, I. Chambrier, M.J. Cook, D.A. Russell, Targeting the oncofetal Thomsen-Friedenreich disaccharide using jacalin-PEG phthalocyanine gold nanoparticles for photodynamic cancer therapy, Angew. Chem., Int. Ed. Engl. 51 (25) (2012) 6158–6162, https://doi.org/10.1002/anie.201201468.
[70] K.B. Ayaz Ahmed, S.K. Mahapatra, M.R. Charan Raja, S. Subramaniam, M. Sengan, N. Rajendran, S.K. Das, K. Haldar, S. Roy, A. Sivasubramanian, V. Anbazhagan, Jacalin-capped silver nanoparticles minimize the dosage use of the anticancer drug, shikonin derivatives, against human chronic myeloid leukemia, RSC Adv. 6 (23) (2016) 18980–18989, https://doi.org/10.1039/C5RA27952F.
[71] S. Khan, S.N. Khan, R. Meena, A.M. Dar, R. Pal, A.U. Khan, Photoinactivation of multidrug resistant bacteria by monomeric methylene blue conjugated gold nanoparticles, J. Photochem. Photobiol., B 174 (2017) 150–161, https://doi.org/10.1016/j.jphotobiol.2017.07.011.
[72] S. Jayanthi, S. Shanthi, B. Vaseeharan, N. Gopi, M. Govindarajan, N.S. Alharbi, S. Kadaikunnan, J.M. Khaled, G. Benelli, Growth inhibition and antibiofilm potential of Ag nanoparticles coated with lectin, an arthropod immune molecule, J. Photochem. Photobiol., B 170 (2017) 208–216, https://doi.org/10.1016/j.jphotobiol.2017.04.011.
[73] K.B. Ayaz Ahmed, T. Raman, A. Veerappan, Jacalin capped platinum nanoparticles confer persistent immunity against multiple Aeromonas infection in zebrafish, Sci. Rep. 8 (1) (2018) 2200, https://doi.org/10.1038/s41598-018-20627-3.
[74] K.B.A. Ahmed, S.B. Subramaniyan, S.F. Banu, P. Nithyanand, A. Veerappan, Jacalin-copper sulfide nanoparticles complex enhance the antibacterial activity against drug resistant bacteria via cell surface glycan recognition, Colloids Surf. B Biointerfaces 163 (2018) 209–217, https://doi.org/10.1016/j.colsurfb.2017.12.053.
[75] S. Jayasankari, P. Vishnuvarthan, D. Rubini, S.B. Subramaniyan, V. Vadivel, V. Anbazhagan, P. Nithyanand, Jacalin hydrocolloid nanoconjugates mitigate methicillin resistant Staphylococcus aureus (MRSA) biofilms on meat products, ACS Food Sci. Technol. 1 (6) (2021) 1030–1040, https://doi.org/10.1021/acsfoodscitech.1c00052.
[76] J. Senthilganesh, S. Kuppusamy, R. Durairajan, S.B. Subramaniyan, A. Veerappan, N. Paramasivam, Phytolectin nanoconjugates in combination with standard antifungals curb multi-species biofilms and virulence of vulvovaginal candidiasis (VVC) causing Candida albicans and non-albicans Candida, Med. Mycol. 60 (2) (2022) myab083, https://doi.org/10.1093/mmy/myab083.
[77] S.B. Subramaniyan, S. Megarajan, K.S. Dharshini, A. Veerappan, Artocarpus integrifolia seed lectin enhances membrane damage, oxidative stress and biofilm inhibition activity of silver nanoparticles against Staphylococcus aureus, Colloids Surf. A Physicochem. Eng. Asp. 624 (2021) 126842, https://doi.org/10.1016/j.colsurfa.2021.126842.
[78] S.B. Subramaniyan, S. Vijayakumar, S. Megarajan, R.K. Kamlekar, V. Anbazhagan, Remarkable effect of jacalin in diminishing the protein corona interference in the antibacterial activity of pectin-capped copper sulfide nanoparticles, ACS Omega 4 (9) (2019) 14049–14056, https://doi.org/10.1021/acsomega.9b01886.
[79] S. Bala Subramaniyan, R. Senthilnathan, J. Arunachalam, V. Anbazhagan, Revealing the significance of the glycan binding property of Butea monosperma seed lectin for enhancing the antibiofilm activity of silver nanoparticles against uropathogenic Escherichia coli, Bioconjug Chem 31 (1) (2020) 139–148, https://doi.org/10.1021/acs.bioconjchem.9b00821.
[80] E.H.E. Konozy, M.E.M. Osman, Plant lectin: a promising future anti-tumor drug, Biochimie 202 (2022) 136–145, https://doi.org/10.1016/j.biochi.2022.08.002.
[81] V.J.A. Fonseca, A.L. Braga, J.R. Filho, C.S. Teixeira, G.C.A. da Hora, M.F.B. Morais-Braga, A review on the antimicrobial properties of lectins, Int. J. Biol. Macromol. 195 (2022) 163–178, https://doi.org/10.1016/j.ijbiomac.2021.11.209.
[82] T. Kitao, K. Hattori, Concanavalin A as a carrier of daunomycin, Nature 265 (5589) (1977) 81–82, https://doi.org/10.1038/265081a0.
[83] A. Robert, J. Wiels, Shiga toxins as antitumor tools, Toxins 13 (10) (2021) 690, https://doi.org/10.3390/toxins13100690.