Microbial polysaccharides: An emerging family of natural biomaterials for cancer therapy and diagnostics

Microbial Polysaccharides: An Emerging Class of Natural Biomaterials with Multifaceted Applications in Cancer Research

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Abstract

Microbial polysaccharides (MPs) offer immense diversity in structural and functional properties. They are extensively used in advance biomedical science owing to their superior biodegradability, hemocompatibility, and capability to imitate the natural extracellular matrix microenvironment. Ease in tailoring, inherent bio-activity, distinct mucoadhesiveness, ability to absorb hydrophobic drugs, and plentiful availability of MPs make them prolific green biomaterials to overcome the significant constraints of cancer chemotherapeutics. Many studies have demonstrated their application to obstruct tumor development and extend survival through immune activation, apoptosis induction, and cell cycle arrest by MPs. Synoptic investigations of MPs are compulsory to decode applied basics in recent inclinations towards cancer regimens. The current review focuses on the the anticancer properties of commercially available and newly explored MPs, and outline their direct and indirect mode of action. The review also highlights cutting-edge MPs-based drug delivery systems to augment the specificity and efficiency of available chemotherapeutics, as well as their emerging role in theranostics.

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1. Introduction

Cancer epitomizes a serious threat to public health, in which cancerous cells tend to proliferate in an uncontrolled manner and disseminate from one part of the body to another through blood and lymphatic systems [1]. It accounts for around 13% of all death globally. Cancer is predicted to be the foremost reason of 17 million deaths per year worldwide by 2030 [2]. The most common cancer types include breast, liver, colorectal, lung, and prostate, accounting for approximately 9.5 million deaths in 2018 [3]. The reason behind alarming mortality rate is delayed diagnosis of tumor and the unavailability of treatment methods for advanced cancer stages. Despite eliminating malignant tumors using surgery and radiation therapy, some metastasis cells always persist, leading to recurring tumors [4]. Chemotherapy and immunotherapy are current treatment methods; employ to obstruct re-initiating tumor growth, but exhibit severe toxicity over individuals' healthy cells, resulting in deaths [4]. Scientific communities focus on finding more precise biomaterials for chemotherapy and immunotherapy to accurately tune malignant cells' functionality.

In current years, a plethora of scientific reports have been acknowledged on the utility of microbial polysaccharides (MPs) in existing cancer treatment improvements because MPs are biocompitable and biodegradable biomaterials, participate in a array of cellular events, including immune reaction, infection, adhesion, and signal transduction [5, 6]. MPs provide advantages over plant- derived polymers in terms of large-scale defined and reproducible production. In addition, a diverse class of microbes such as bacteria, fungi, and microalgae offer abundant diversity in MP. A different genus of the same class produce specific biopolymers, drawing great interest in exploring the novel chemotherapeutics [7]. Some MPs possess intrinsic antitumor properties, such as glycans, a broad group of anticancer polysaccharides [8]. Antitumor potential of MPs depends on their sugar composition, molecular weight, branching rate and form, and chemical properties [5]. For instance, low molecular weight and hydrophobic glucans seem to be less efficient as compared to their contraries. Similarly, the polysaccharides having β-(1→3) bonds in the parent backbone and branching in β-(1→6) and usually show promising antitumor activity [5, 9, 10].

In addition, MPs are of great significance in intelligent drug delivery systems. Various functional groups, namely hydroxyl (OH), amino (–NH2), carboxylic (–COOH), and aldehyde make them perfect for optimizing all aspects of theranostics [11]. Chemical modification of polysaccharides by conjugating different entities, such as carboxy-methyl, glycol, and PEGylation results in more ideal substances for self-reorganized nanostructures, fabricating self-assembled micelles, surface decorating polymeric microspheres, and getting better drug delivery in cancer sites [12]. In last few decades, to develop advanced therapeutics and overcome the drawbacks of cancer chemotherapeutics and RNA interference therapies, both therapies have been integrated or co-integrated with MPs-based nano-carriers. Commonly, RNA interference therapies face failure due to rapid degradation by endogenous nucleases, immunogenic nature, off-target site toxicity, and rapid renal clearance [13]. Similarly, poor pharmacokinetics, low bioavailability, rapid clearance by renal and macrophages, and high dose requirements of chemotherapeutics limit their potential applications [14]. MPs behave as an ideal carrier for RNAi and chemotherapeutics. They possess fundamental attributes such as efficient binding capabilities to siRNA, protection ability to the siRNA from enzymatic degradation and phagocytic system, maintain stability under physiological conditions, enhance the intracellular uptake, and sustain release of siRNA and drugs. The combine delivery of therapeutic RNAi and a anticancer agent to cancer cells is a paramount regime for cancer therapy, which can deal with superior cell killing potential and reduce the side-effects [15]. Moreover, some polysaccharides act as a ligand for cell surface receptors, frequently involves in nano-assembly designing to deliver chemotherapeutics and RNAi. For example, hyaluronic acid can target CD44 overexpressing cells while pullulan specifically binds with asialoglycoprotein receptor of hepatocytes [16]. Moreover, the surface charge is a crucial attribute of MPs, which determines the engineered nanomaterials' fate. Cationic polysaccharides evoke endocytic uptake by cancer cells, while anionic polysaccharides enhnace bio-availability and reduce secretion by the glomerular capillary wall [17]. The spatial conformation of MPs certifies their hydrophilicity and bio adhesion ability, which can be utilized in the fields of bio-

nanomaterials or pharmaceutical formulation [18]. This review summarized the inherent antitumor property and mechanistic of MPs and covers past and current attempts to discover next-generation therapies for cancer with the help of MPs. We also highlighted forefront prospects for cutting-edge developments and technological advances in cancer theranostics using MPs.

2. Characteristics and structural diversity of MPs

The microorganisms such as bacteria, fungi, and algae offer great diversity in polysaccharides's chemical structure with their unique physical characteristics. The chemical structure can vary at degree of branching and relative quantity of specific type of glycosidic links (Fig. 1). The MPs can be homopolymer and heteropolymers of neutral (hexose and pentose) and/or anionic (glucuronic acid) sugars, interchanged or not by non-sugars compounds, linear, or ramified (Table 1).

2.1. Anionic MPs

Anionic MPs comprise examples, namely alginate, pectin, xanthan gum, hyaluronic acid, and gellan gum etc. Alginates are linear anionic polysaccharides of several bacterial strains such as *Pseudomonas aeruginosa* and brown seaweeds, including *Laminaria hyperborea*, *L. japonica*, *L. digitata*, *Ascophyllum nodosum* and *Macrocystis pyrifera*. Two glycosyl subunits namely, (1→4)-α-l-glucuronic acid (G) and (1→4)-β-d-mannuronic acid (M) units arrange randomly through covent bond, and form a complex structure of alginate. The proportion and pattern of MG blocks affects the physical properties of alginate. The gel forming property of alginate increases as pH of reaction mixture decreases [19]. It is widely utilized in the controlled delivery of many cationic and low molecular weight drugs [20]. The loading effectiveness and the drug liberation rate of these alginates are influenced by the ionic interface among the drug and the alginate prevailing conditions. Moreover, alginate gel has been utilized as extracellular matrix (ECM) for three dimensional (3D) cell cultures to gain depth insights regarding cell-ECM interaction biology [21].

Gellan gum (GG) is a hydrophilic anionic MP secreted extracellularly by the bacterium, *Sphingomonas elodea*. It contains repeatative units of trisaccharidics, including β-d-glucose, β-d-glucuronate and β-l-rhamnose in the molar ratios of 1:1:2 [22]. GG is recognized as a biosafe and biodegradable microbial polymer by FDA [23]. The gel state of gellan gum formed in presence of divalent cations and it remains maintain over a broad range of pH. The physical properties of its gel differ at the ratio of acetylation of gellan gum. For instance, highly acetylated gellan gum forms soft, easily deformable gels while the low molecular weight acyl gellan forms inflexible and fragile gels [22].

Xanthan gum (XG) is a non-toxic polymer secreted by *Xanthomonas campestris* which exhibits distinct rheological properties, such as high resistance to shear degradation, good stability at a wide array of temperatures and pH, and excellent viscosity at low shear strength [24]. It is a hetero-polysaccharide comprising of various sugar components, namely d-mannose, d-glucose, pyruvic, and glucuronic acids. It contains β-(1→4) linked D-glucose residues, including a trisaccharide branches linked to alternate [25]. The chemical configuration of the major chain is indistinguishable to that of cellulose. The high molecular weight of XGs helps to form physical and chemical systems, making them appropriate to develop pharmaceutical formulations as a gelling agent, binder, drug and protein carrier, and disintegrant. Hence, the combination of XG and other polymer-based biomaterials has been extensively utilized as an excipient.

Hyaluronic acid (HA), an unsulfated linear MP related to the glycosaminoglycans, consists of repeated components of disaccharide having of β-(1→4) linked-D-glucuronic acid and β-(1→3) linked *N*-acetyl-D-glucosamine units. HA are also non-immunogenic, biocompatible, ecofriendly, and viscoelasticity polymers, utilized in cosmetics and medicine [24]. Besides, HA has the capability to identify specific receptors of tumor cells, and anticancer drugs could be targeted to the malignant cells to superior destroy them. Thus, HAs have attracted much attention as potent drug carriers [26].

2.2. Cationic MPs

Chitosan (CS) is a structural component of filamentous fungi, especially belongs to family zygomycetes. It is mainly consisted of β-(1→4)-D-glucosamine belonging to *N*-acetyl-D-glucosamine residues [27]. CS owns not only good physiochemical properties, such as biocompatible, biodegradable, and bioadhesive but also has several inherent biological properties, including antimicrobial, antidiabetic, anticancer, and wound healing [27]. CS has solubility in acidic aqueous medium. It has polycationic surface and the ability to form intermolecular and intramolecular H-bonding which regulate its exclusive properties, including sustainable drug release, transfection, mucoadhesion, in-situ gelation, efflux pump inhibition, and penetration improvement [28, 29].

2.3. Non-ionic MPs

Pullulan (PL) is a by-product of microbial fermentation of starch through *Aureobasidium pullulans*. PL is a linear exopolysaccharide complex of frequently repeating units of α-(1→4)-maltotriosyl and 3-d-glucopyranosyl attached via α-(1→6) linkages [30]. It's molecular weight depends on fermentation conditions which varies from 4.5×10^4 to 6×10^5 Da. PL is a water-soluble, biodegradable, impermeable to oxygen, non-reducing, and non-hygroscopic polymer. Owing to high solubility in water, it is not amenable to self-aggregated pullulan nanoparticles. It's solubility and pH sensitivity can be altered through replacing it's few hydroxyl groups with the hydrophobic groups [31, 32]. The hydrophobic PL derivatives can self-assemble to prepare colloidal stable nanostructures haing inner hydrophobic centre in aqueous medium. This hydrophobic centre can entrap water insoluble substances, like drugs, RNA, DNA, lipids, and proteins. It exhibits specific binding affinity for asialoglycoprotein receptor (ASGPR), a specific receptor of hepatocytes. Additionally, it's nontoxic, non-carcinogenic, non-mutagenic and non-immunogenic characteristics make it appropriate for targeted drug and gene delivery [33].

Schizophyllan, known as Sizofiran is a nonionic and hydrophilic exopolysaccharide possessing molecular weight of 10^6 Dalton. It possesses a 1→3-β-D associated chain branched with single β-(1→6)-attached dextran moieties at about each third residue. It has poor gelation property under cold conditions but when it can produce strong gel in the presence of small molecules such as borax or sorbitol [34]. Similar to Sizofira, Scleroglucan is a non-ionic neutral branched homoglucan formed by fungi belonging to the genus *sclerotium*. It is composed of a major straight chain of *β*-1→3-D-glucopyranosyl components branched with a *β*-1→6-D-glucopyranosyl entity. Schizophyllan effortlessly dissolves in both types of water (cold and hot) and its aqueous solution remain constant in excess of a wide range of pH, like 2.5–12 [35].

Dextran, a α-glucan is composed of forked α-D-glucans by imitating anhydro-d-glucopyranose components as their key molecular series. Dextran's rheological properties such as viscosity depends on the attachment of glucose moieties to the key series through α-1,2-, α-1,3-, and α-1,4-glycosidic attachements [24]. The mean molecular weight of dextran veers from 9×10^6 to 5×10^8 depending upon the producing microorganism's culture conditions. It is obtained by sucrose fermentation applying a specific lactic-acid producing bacteria that belong to genera *Leuconostoc*, *Lactobacillus*, and *Streptococcu*s. It is a bio-safe, biocompatible, biodegradable, antithrombotic agent and eliminated completely by kidney [36].

Curdlan is a linear 1-3-β-glucans obtained as a by-product of fermentation process through a bacterial strain, *Alcaligenes faecalis* [37]. It can soluble in dimethyl sulfoxide (DMSO), diluted bases (250 mM NaOH), and formic acid but it is insoluble in organic solvents and water [38]. It has distinct gelling properties in the ability to cast either a thermo-irreversible gel or a thermo-reversible gel. Curdlan is found to be exist as a single helix, triple helix, or single chain depending mainly on heating temperature, degree of hydration, and solvent conditions. It is documented for anti-tumor, anti-HIV, anti-coagulation, and anti-virus activities [39].

On the basis of type of O-glycosidic bond, polysachharide are categorized into two groups namely, alpha-glucan and β-glucans. Alphan-glucans includes pullalan and dextrans while β-glucans are

xanthan gum, alginate, lentinan, chitosan, zymosan and many others. β-glucans, are comprehensively explored class of MPs which encompass a straight parent backbone of β-(1→3)-attached D-glucose moieties with β-(1→6) flank chains of uneven lengths happening at diverse positions. There are numerous elucidated configurations of β-glucan attachements, including β-(1→3), β-(1→4), and β-(1→6) [24].

3. Antitumor property of MPs and their mechanisms

As rich sources of novel antitumor agents, the potential of MPs for use in the development of alternative medicines is clear. MPs have promising preventive and therapeutic potentials against a wide range of cancers. Therefore, it is predictable that there has been significant curiosity from the medicine field in anticancer MPs, demonstrated by the growing body of related literature.

A number of exopolysaccharides and intra-polysaccharides of microorganism has been documented for antineoplastic activity against different cancer model systems (Fig. 2; Table 2). Bacterial exopolysaccharide EPS-1 derived from an endophytic bacterum, *Paenibacillus polymyxa* EJS-3 showed antiproliferative action on human gastric cancer BGC-823 cells. Moreover, modification of EPS-1 by acetylation, phosphorylation, and benzylation increased electron-donating efficacy, leading to improve the antiproliferative activity of EPS-1 derivatives, compared to natural EPS-1 against BCG-823 cells [40]. *Rhizobium* sp. N613 exopolysaccharide (REPS) showed antitumor activity in mice bearing Ehrlich ascites carcinoma tumor, sarcoma 180, and hepatoma 22 without causing toxic effect at the concentration of 120 mg/kg [41]. Microwave degradation of REPS in H_2O_2 with lower molecular weight (10.352 kDa) showed enhanced-anticancer activity as compared to normal *Rhizobium* sp. 613 REPS (Wei et al., 2011). Low molecular weight exopolysaccharide Levan from *Microbacterium laevaniformans* also exhibited remarkable anticancer activity against HepG2 and SNU-1 cells [42]. Antiproliferative activity of polysaccharide of *G. lucidum* has been performed against mouse melanoma B16F10 cells [43]. Likewise, antiproliferative activity of selenium-containing polysaccharide from *G. lucidum* was

reported against different cancer cell lines, including human erythroid chronic myeloid leukemia K562 cells, human malignant breast carcinoma MCF-7 cells, human cervical cancer HeLa cells, human hepatocarcinoma HepG2 and 7721 cells, and human ovarian cancer SKOV4 cells [44]. MPs combat tumor formation by interfering in different tumor progressive signalling pathways which are discussed below.

3.1 Direct anticancer actions

3.1.1 Apoptotic cell death

Apoptosis, an orchestrated cell death process is an ordinary phenomenon to maintain healthy cell turnover, hormone-dependent atrophy, embryonic development, and the immune system's proper functioning. Majorly two pathways are included in apoptosis induction: i) the extrinsic, a death receptor mediated program and ii) the intrinsic, a mitochondrial mediated program [45-47]. An additional caspase-independent way to induce apoptosis has been reported, which was mediated through T-cell facilitated cytotoxicity and perforin/granzyme reliant cell death [48]. The extrinsic pathway is triggered through the binding of ligands, namely TNF, FasL, and TRAIL to extracellular membrane-bound receptors which causes receptor clustering and forms a death-inducing signalling complex (DISC). Next, DISC adopts and activates membrane-proximal caspases, such as caspase-8/3 results in apoptosis induction. The intrinsic pathway is not regulated by a receptor; intracellularly produced stimuli signal directly target within the cell and are mitochondrial-initiated events. Stimuli change the inner mitochondrial membrane potential (MMP) to liberate cytochrome c and calcium into the cytosole of cells. Cytosolic cytochrome c combines with Apaf-1 and triggers membrane-proximal caspases. The activated caspase-3 further arbitrates attenuation of caspase-activated DNase and cleave the substrate protein, poly-(ADP-ribose) polymerase (PARP) to induce cell dysfunction, DNA destruction, and removal of tumor cells [49].

Several microbial polysaccharides are reported for their anticancer efficacy by inducing apoptotic pathway. A homogenous polysaccharide (LEP1) extracted from *Lentinus endodes* was examined

for anticancer activity against cervical carcinoma HeLa cells. The possible mechanism of LEP1 is to trigger apoptotic pathway by liberating cytochrome c, inhibiting MMP, activating caspases-9/3, and inducing cleaved PARP expression [50]. Five different polysaccharides, including JLNT1, JLNT2, JLNT3, SLNT1, and SLNT2 were extracted from *L. endodes* and tested their antitumor activity in H22-tumor bearing mice. JLNT1 and SLNT1 induced apoptotic cell death and serum TNF-α and IL-2 production [51]. Further, mechanistic studies conclude that SLNT, a water-soluble Lentinan, exhibits anticancer activity through activation of ROS-mediated intrinsic apoptotic and TNF-α dependent pathways [52]. Recently, water-extracted polysaccharide (WEP1) isolated from *L. edodes* was examined for antitumor activity in H-22 tumor bearing mice. Results showed that WEP1 inhibits H22 cells' proliferation and induces ROS-mediated cell death and G2/M phase cell capture through inhibition of tubulin polymerization [53]. A sulfated polysaccharide isolated from *G. frondosa* that triggers apoptosis in HepG2 cells via Notch1/NF-κB/p65-mediated caspase pathway [54]. A different chemically sulfated and peptide bound polysaccharide from *G. frondosa* exhibited anticancer activity by apoptotic inducing pathway [55]. Sizophyllan was reported for the apoptosis-inducing property, which led to G0/G1phase cell arrest in CNS-1glioma cells [56]. Levan isolated from *Halomonas smyrnensis* AAD6 that inhibited proliferative of breast cancer cells by inducing oxidative stress-mediated apoptotic cell death [57]. Aldehyde-activated levan derivative exhibited strong a wide spectrum anticancer activity by activating the caspase-3/7 in human lung adenocarcinoma A549 cells, human gastric adenocarcinoma AGS cells, human breast adenocarcinoma MCF-7 cells, and human hepatocellular carcinoma HepG2/C3A cells [58]. A levan derivative, SL-1, showed anticancer activity in HepG2 cell lines through the initiation of nuclear genetic material condensation and fragmentation, and depolarization of MMP, leading to cytochrome C release, and subsequent activates caspases-3/9 to induce apoptotic pathway [58]. Low-molecular-weight chitosan (LMWC) cease the proliferation of oral squamous cell Ca9-22 through inducing the caspase-dependent apoptosis pathway and arresting the cells at G1/S cell cycle arrest while it was less cytotoxic to HaCaT [59]. A hydrophilic and sulfated polysaccharide

of *G. lucidum* showed inhition of cancer cells growth and triggered apoptotic pathway by harmonizing the anti-apoptotic/pro-apoptotic gene expression and arresting the G2/M phase in sarcoma-180 induced tumor-bearing BALB/c mice [60]. A "F3" polymer-rich fraction prepared from *G. lucidum* that not only induced the death receptor ligands, but also modulated expression of adaptor proteins and caspase cascade, leading to apoptosis induction and cell shrinkage in human monocytic leukemia cells [61]. Moreover, a unique selenium comprising glucopolymer SeGLP-2B-1 has been extracted from *G. lucidum* and inhibited the development of breast cancer through disruption of MMP and sub-G1 cell arrest [62].

3.1.2 Anti-angiogenic

Tumor cells receive angiogenic switch by overexpressing proangiogenic factors, viz. vascular endothelial growth factors to recruit new blood vessels, which enhances the higher blood supply to fulfilling the desire of oxygen and nutrients of invasive tumor growth and metastasis cells. Excessive angiogenesis in tumors facilitates metastasis by providing a principle passage for the distribution of tumor cells from the main tumor site to another cells and tissues of the body. Antiangiogenic therapy, therefore, is an excellent approach to prevent tumor formation and malignancy. Few MPs have been explored for antiangiogenic mediated-tumor preventive therapy. For instance, lentinan exhibited antiangiogenic property in murine CT26 colorectal and LAP0297 lung tumor models by upregulating the expression of angiostatic factor, IFN-γ [63]. Genistein-combined polysaccharide isolated from *G. lucidum* cultured with soybean extract containing isoflavone glycosides displayed significant antiangiogenic effect by inhibiting new blood vessel formation on chorioallantoic membrane in colon carcinoma cells [64], xenogeneic athymic mice [65] and prostate cancer cells [66].

3.1.3 Anti-metastasis

MPs are known to increase bioavailability and targeted delivery of drugs. *L. edodes* is recongnized as a lentinan polysaccharide producer and permitted as a potential anticancer agent in Japan as well as in China. Selenium-was conjugated with lentinan (Se-Lentinan) which inhibits endothelial to mesenchymal transition transformation, tumor formation, and metastasis in colon cancer cells, namely B16-BL-6 and HCT-8. Se-Lentinan also displayed less toxic than sodium selenite [67]. The sulfated hetero-polysaccharide of *G. frondosa* suppressed tube formation and migration of endothelial cells [68]. Numerous studies have been demonstrated that the treatement of D-fraction (DF) of *G. frondosa* to BALBc mice inhibits the risk of cancer carcinogenesis, inhibit tumor invasiveness, decrease angiogenesis, and enhance generally survival [69, 70]. DF reduced viability, metastatics of mammary tumor cells, creating a fewer hostile cell behaviour. Administration of DF decreased tumor load and quantity of metastatic lung cancer, examined in a mouse model of mammary cancer [71]. Besides, DF inhibited tumor metastasis by activation of NK cells and antigen presenting cells and suppressed intercellular adhesion molecule (ICAM)-1 suppression, triggering the inhibition of the cancer cell adherence to endothelium [72]. Anti-metastatic activity of O-sulfated polymer isolated from *E. coli* K5 (K5PS) has been reported in mice model system and in-vitro. K5PS inhibited the fastening of B16-BL6 cells to P-selectin and ICAM-1 to repress tumor cell adhesion [73]. SPG, a beta-glucan reduced tumor volume, lung metastasis and lung nodule formation in tumor-bearing mice [74].

3.2 Indirect anticancer actions

3.2.1 Immunomodulation

MPs can shape the tumor microenvironment's immune system (TEM) consisting of a tumor, stroma, and infiltrating immune cells [75]. The component of TME collectively produces interleukin (IL)-10 and IL-35 as immunosuppressive factors for the production of hypoxia-

inducible factor (HIF), transforming growth factor-beta (TGF-β), and adenosine to promote tumor burden [76]. The remodelling of TME by MPs can boost the target site's antitumor response and can be utilized after chemo-radiotherapy [77]. Several studies have been reported the enhancing host's defense system by MPs in cancerous model systems. For instance, *G. lucidum* polysaccharide-rich fractions boosted advanced-stage cancer's immunity by increasing the action of natural killer (NK) cells, PBL mitotic response to PHA, and generation of IL-2 and interferon gamma (IFN-γ) and by suppresing the TNF-α expression [78]. Likewise, *Grifola frondosa's* polysaccharides displayed significant anticancer activity by modulating immune response and inducing cell death program [79]. *G. frondosa,* commonly known as Maitake in Japan, is widely used as a edible mushroom that flourishes under the shade of oaks. It has been extensively explored for different medicinal properties [79]. Fraction-1 of *G. frondosa* (GF-1) polysaccharide isolated from *G. frondosa's* fruiting body that reveals a promising anticancer activity in mice. Although, a tumor preventive potential was noticed, when GF-1 was given intraperitoneally, intravenously, and intratumorally, but no effect was noticed during oral administration [80]. Moreover, GF-1 has not shown direct anticancer activity, but indirectly it enhanced the immune system to produce a humoral-mediated immune response, leading to an antitumor activity [81]. Another polysaccharide extracted from from *G. frondosa,* grifolan NMF-5N, a β-(1→3)-glucan that exhibited antitumor activity by activating T-cells and macrophages [82]. A (1→3)-branched β-1,6-glucan Maitake Z, a novel heteropolysaccharide obtained from *G. frondosa* that exhibited strong anticancer activity in MM-46 carcinoma and IMC-carcinoma mice. This ramification was associated with the stimulation of NK-cells, T-cells and macrophages, and also enhancement of the levels of lymphokines and IL-1, an activator of T-cells [83]. Masuda and colleagues demonstrated that Maitake Z induces the growth of splenocytes and peritoneal macrophages. Simultaneously, it also upregulated the transcript expression of IL-12, IL-2, and IFN-γ assisting in Th1-mediated response against the tumor development [84]. Further in-depth study

illustrated that Maitake Z induces antigen-specific T-cell reaction through IL-12 production by dendritic cells against murine colon cancer [85].

Triggering of cellular receptors by external stimuli is necessary to transfer the signal for activation of immunological response. In recent years, different types of receptors, including complement receptor 3 (CR3), dendritic cell-associated C-type lectin (Dectin-1), and toll-like receptor 4 (TLR-4), have been explored, which can be recognized and docked by MPs. A homogenous polysaccharide, GFPBW2 has been purified from *G. frondosa* fruiting body, revealed potential to bind with the dectin-1 receptor, which led to further activation of macrophage secretion [86]. Similarly, treatment of GFPBW1 triggered the Dectin-1/Syk/NF-κB pathway and inhibited splenocyte proliferation in Sarcoma-180 induced allograft ICR mice model [87]. A water-soluble polysaccharide GP11 of *G. frondosa* enhanced the relative spleen and thymus weights as well as the magnitute of TNF-α and IL-2 in the serum of tumor-bearing ICR mice. These antitumor effects of GP11 might be due to enhanced immune response through increase the levels of NO and TNF-α levels by TLR-4 [88]. Mao and co-workers carried out a study to characterize immunomodulatory and anti-cancer activities of a Se-containing polysaccharide of *G. frondosa* named Se-GP11. Treatment of Se-GP11 did not show an anti-cancer action against hepatic cancer cells, but it showed inhibitory effect on Heps tumor growth in-vivo due higher expression of TNF-α and NO [89]. Also, a hot water extract of *G. frondosa* mycelium, mostly contained of polysaccharide induced expression of CD11b on the surface of polymorphonuclear neutrophils, indicating that complementary receptor 3 may be involved in augmentation of host immunological reaction against tumor and enhancement of the phagocytic activity of neutrophils [90]. A D-fraction containing of (1→3)-β glucan linked to β-(1→6)-glucoside resudues in combination with few unidentified protein components has been extracted from *G. frondosa* that exhibited a promising anticancer activity. The fraction was observed to be most effective in inducing the immune system, either oral treatment or intravenous administration [91]. D-fraction mechanism to enhance immune response is umpired through NO production and delayed-type hypersensitivity associated with tumor growth

[92]. Moreover, D-fraction activated macrophages, NK cells and T-cells in tumor-bearing mice. In a study, immune boosting potential of D-fraction has been examined in C3H/Hej mice that was due to NK cell activation through IL-12 secreted by dendritic cells and macrophages [93]. A clinical study has confirmed that the D-fraction primly triggers NK cells to hinder metastasis in various tumor-bearing cancer patients, including lung, liver, and breast [94]. D-fraction also differentiated Th-1 or Th-2 cells in colon tumor-bearing BALB/c mice by enhancing IFN-γ and IL-12p70 [95]. Curdlan is a natural agonist of dectin-1, which is recognized on the outer layer of immune cells i.e. dendritic and macrophages cells. It increased the phosphorylation of the downstream targets of dectin-1, such as MAPKs, Syk, Akt, Raf-1, NF-κB p65, and IKK in dendritic cells. The study concluded that curdlan triggers dendritic cells via dectin-1 and TLR4 which powerfully hamper tumor growth in mice [96]. β-glucans comprising β-(1,6) units isolated from *L. edodes* that showed S-180 tumor-inhibiting potential without toxic effect when given through intragastric, intraperitoneal, and intratumoral injections. It has also been observed that β-glucans increased the level of $CD4^+$ T cells in lymphoid organs which reduces the tumor-burden, demonstrating endorsement of immunomodulation [97]. MPSSS, a polysaccharide from *L. edodes,* exhibits anticancer activity against prostate cancer by interfering in cancer-associated fibroblasts-mediated T-cell inhibition through the TLR4-NF-κB pathway [98]. XG isolated from plant-pathogenic bacteria *Xanthomonas campestris pv.* that prolonged survival rate of B16Kb melanoma cells induced tumor-bearing mice. The results also showed that XG activates immune response through generation of TNF-α, IL-12, and activation of macrophages through myd-88 dependent TLR-4 signalling [99].

3.2.2 Modulation of gut dysbiosis

Gut dysbiosis represents the compositional and functional alterations of the gut microbiome, which now is considered as a new risk factor for cancer progression [100]. For instance, the infection of *Helicobacter pylori* evokes carcinogenesis by trggering the β-catenin signaling pathway [101]. Similarly, colon cancer is associated with specific microbes, including *Porphyromonas*

asaccharolytica, *Bacteroides fragilis*, *Alistipes finegoldii*, *Thermanaerovibrio acidaminovoran, Fusobacterium nucleatum*, *Parvimonas micra*, and *Prevotella intermedia* [101]. Therefore, tumor-associated bacteria are used as diagnostic or prognostic markers for cancer in preclinical and clinical studies. Cancer can be associated with any abnormality in a single strain. As the number of pathogenic bacteria and their by-products is increased, endotoxemia is occurred which further results in portal hypertension and hepatocyte damage, leading to the development of hepatocellular carcinoma (HCC). Thus, the gut microbiota influences oncogenesis and tumor progression, both locally and systemically. MPs prevent cancer progression by shaping gut health [102]. Previous studies demonstrated that the extraneous polysaccharides remain indigestible until they reach to the gastrointestinal track. Gut microbes ferment them and utilize them for their growth; thereby, polysaccharides influence the gut microbe's diversity [102]. *G. lucidum* polysaccharide fraction (GLPs) significantly alleviated colorectal cancer in CRC mice by reducing the plentitude of cecal *Oscillospira* along with an unidentified genus of Desulfovibrionaceae and by down-regulating the four tumor-associated genes, namely Acaa1b, Mgll, Fabp4, and Scd1 [103]. Similarly, the polysaccharides from *G. lucidum* and *G. sinense* modulated the gut microbiota in a BALB/C mice model bearing 4T1 induced breast carcinoma in a similar trend. Both polysaccharides recovered a strain, *Alistipes,* a significant producer of short-chain fatty acid [104]. Tretment of anticancer drugs could harm the mucosal epithelium, thus increasing bacterial translocation. Therefore, the polysaccharide derived from *G. lucidum* spore (SGP) was used as adjuvant agents with paclitaxel (PTX) to control tumor progression in a murine 4T1-breast tumor model effectively. The obtained findings discribed that the cancer-related genera, namely *Odoribacter* and *Desulfovibrio*, significantly decreased in combined treatment of SGP and PTX, while PTX alone induces gut dysbiosis. The combinational treatment suppressed the tumor metabolism by downregulating the expression of pyruvate dehydrogenase (*Pd*), lactate dehydrogenase A (*Ldha*), and glucose transporter 3 (*Glut3*) genes [105].

4. MPs act as synergistic agents for cancer chemotherapeutics

Combining the MPs with cancer chemotherapeutics provides a multifunctional therapeutic platform for cancer therapy due to synergism. It also reduces side effects and enhances the bioefficacy of chemotherapeutics. In this context, lentinan obtained by *Lentinus edodes* is examined with oxaliplatin in a combination against HCC, obtained results concluded that to inhibit HCC through mitochondrial pathway and inhibition of NF-κB, stat3 and survivin signaling, and also reduces side effects which were induced by oxaliplatin [106]. Similarly, Harada and colleagues investigated the combinational effect of lentinan with fluoropyrimidine (S-1) in both in-vivo and in-vitro systems of squamous cell carcinoma [107]. Moreover, a combination of chemically-sulfated polysaccharide of *G. frondosa* and 5-fluorouracil notably prevented the growth of gastric carcinoma SGC-7901 cells compared to chemically sulfated polysaccharide alone [108]. Schizophyllan (SPG), a β-D glucan, exhibited synergy with tamoxifen against breast cancer in Swiss albino mice by inducing apoptosis, PCNA cell proliferation marker, and tumor volume [109]. Numerous studies demonstrated that vitamin C reduces chemotherapy's adverse effect on cancer patients [110]. The synergistic effect of vitamin C with polysaccharides D-fraction of *G. frondosa* was also confirmed against HCC in vitro [111]. Antitumour polysaccharide sizofiran (APS), an cultured extract of *Schizophyllum commune* Fries combined with mitomycin C synergistically has enhanced the survival rate of patients those are surffering from gastric cancer due to its immune modulating effects [112]. Besides, APS with multiple chemotherapeutic drugs, namely cisplatin, adriamycin, and cyclophosphamide improved the ovarian cancer stage's postoperative survivability in non-serious adenocarcinomas patients [113]. APS prevented chromosomal damage in murine bone marrow cells caused by chemotherapeutic drugs, including mitomycin C, adriamycin, and cyclophosphamide as well as X-radiation when used in combination [114]. APS with pion irradiation and X-rays improved mice's overall survival rate induced with B-16 melanoma [115, 116]. The study also pointed out that APS exhibits an adjuvant effect when a restricted tumor cells remain after pion irradiation [116]. Later on, Inomata and colleagues

concluded that radiation therapy could increase macrophage and T-lymphocytes' penetration in the local tumor and lung nodules [74]. However, there is no significant synergistic effect observed in tumor formation when treated with APS and pion as well as X-rays in lung cancer cells-transplanted C57BL/6 mice.

5. MPs as micro/nanocarriers for cancer chemotherapeutics

MPs are promising class of biomaterials with a remarkable application in nano-based drug delivery. MPs can undergo a variety of enzymatic and chemical alterations to yield diverse materials; they are biodegradable, and biocompatible in nature. Ionic polysaccharides could be utilized to design stimuli responsive drug delivery systems. They could be applied with bio-macromolecules, such as proteins, petides, lipid, and carbohyrades to prepare as conjugates or complexes and they can easily form gel. These characteristics make MPs as exceptional biomaterials for smart drug delivery purposes [117, 118]. Various functional groups of MPs, such as OH, -NH_2, and -COOH can be altered by adding hydrophobic groups to obtain amphiphilic polysaccharides that could be self-assembled in the nano form in aqueous media. Optimizing the conditions to load a higher extent of drug and confer target specificity and higher MPs-based nano-carriers' stability is highly innovative. Ligands incorporation to nano therapeutics, facilitate the enternalization of nanomaterials to cancer cells through receptor mediated-endocytosis, thereby release their drug payloads to proliferative cells (Table 3).

Paclitaxel (PTX)-loaded chitosan nanoparticles (NPs) modified with polyethylene glycol (PEG) and conjugated with transferrin (Tf) to deliver the drug site specifically. PTX-NPs-PEG-Tf displayed improved antiproliferative activity against human non-small lung cancer HOP-62 cells, superior entry of NPs particularly in nuclei and showed low hemolytic action as compared to PTX, NPs and Tf alone [119]. Pullulan is often grafted with different hydrophobic moieties, namely cholesterol, acetate, and poly(DL-lactide-co-glycolide) to get amphiphilic materials possessing the ability to convert into nanosphere-like structures for the efficient delivery of drugs [120]. Ichinose

et al. designed a liposome in a function specific manner. In which adriamycin (ADM) was first entrapped in core-shell of cholesterol pullulan (CHP) to augment its prolong stability of the drug, followed by prepared liposome were wrapped by 1-aminolactose (1-AL), a tumor recognition molecule [121]. 1-AL/CHP-coated liposomal ADM superiorly arrested the tumor malignancy as compared to non-targated CHP-coated liposomal ADM in AH66 hepatoma transplanted nude mice, indicating that 1-AL/CHP liposome appears to be a versatile drug vehicle for targeting of cancer cells. Hydrophobic core of cholesteryl-containing pullulan nano-spheroids efficiently entraped mitoxantrone and passively delivered mitoxantrone to bladder cancer cells. The drug-loaded nano-spheroids significantly enhanced the release of therapeutic agent in acid media [122]. Epirubicin (EPI) was fabricated to the hydrophobic core of folate-conjugated pullulan acetate NPs to enhance its cellular uptake into KB cells over-expressing folate receptors. EPI-loaded NPs exhibited greater extent of cytoxicity with an IC_{50} value of 1.12 mg/L, compared to free EPI (IC_{50}=3.92 mg/L) due to enhanced delivery of EPI into KB cells by EPI-loaded NPs [123]. Amphiphilic α-tocopherol pullulan self-assembled nanomicelles was anchored with 10-hydroxycamptothecin, led to fast delivery into cell nuclei and enhanced cytotoxicity compared to drug alone. Enhanced assimilation of nanomicelles was an actin polymerization and energy-dependent endocytic process [124].

A pullulan derivative, *para*-aminobenzoic acid-quat188-pullulan has been used to develop stabilized gold NPs (AuNPs@PABA-QP) and explored as excellent nanocarriers to deliver doxorubicin (DOX) for improved anticancer activity and safety. AuNPs@PABA-QP-Dox displayed a 2.1-times superior anticancer effect against human bronchogenic carcinoma cells as compared to DOX and exhibited a lesser amount of toxic against normal Wi-38 cells. This effect was due to trigger late-apoptosis and S/G2-M cell arrest event [125]. Recently, novel organic and inorganic nanocomposits of pullulan derivative and AnNPs (FA-PABA-Q188-PUL@AuNPs) have been developed to enhance the specificity and efficiency of DOX. The nanocomposites revealed the 4.8-fold enhanced anticancer action of DOX against Chago-k1 cancer cells compared to DOX alone. The nanocomposites also triggered cells death by enhancing late apoptosis event by 26.4%

and by inhibiting the cell cycle at S/G2-M stages [126]. Pullulan displays inherent targeting efficacy to receptor of hepatocytes, therefore a reducible cholesteryl-pullulan-loaded DOX nano-construct (rCHP/DOX) was developed. The rCHP/DOX effectively inhibited HepG2 cells growth and attenuated the tumor volume in a murine model of hepatoma. Moreover, the rCHP/DOX prominently accumulated in tumor cells and released the DOX in reduction-sensitive manner [127]. 5-Fluorouracil (5-Fu) and folic acid-loaded pullulan stabilized AuNPs (5-Fu@PAuNP-Fa) was examined for targeted delivery and toxicity of 5-Fu as well as tissue imaging using *Danio rerio* embryo as an in-vivo model. The NPs exhibited much lower IC_{50} value against HepG2 cells in comparion to free components of nanomaterial. Biodistribution analysis confirmed that elevated degree of Au was internalized in cells as compared to other organs, suggesting that pullulan stabilized AuNPs are suitable for targeted delivery [128]. Fullerene (C60)-pullulan conjugates act as photodynamic antitumor therapeutics exhibited a higher affinity with the asialoglycoprotein receptors to target HepG2 cells [129].

Folate-coated maleilated pullulan–DOX and pyrrolidinedithiocarbamate-loaded NPs (FA-MPDOX/PDTC+DOX NPs) exhibited higher cytotoxicity against A2780 DOX resistance cells by co-transporting a greater extent of DOX within cells by endocytosis process. Releasing of drugs by nanocarriers was sustainable and pH dependent [130]. Folic acid-decorated cholesteryl-pullulan (CHP) NPs were explored as potential carrier of DOX that remarkably prevented tumor progress investigated in both human epidermal carcinoma KB cells and nude mice xenograft model [32]. The o/w-emulsion was prepared using cholesteryl pullulan (CHP) and trioctanoylglyceride (TriC8) with α-linolenic acid (ALA) and stabilized by bovine serum albumin (BSA). CHP/ALA/TriC8-emulsion showed greater cytotoxicity in RPMI4788 cells of colon cancer in comparision to free ALA. Authors did not observe significant difference in cell internalization efficiency of ALA in two forms [131]. To improve amphiphilicity and pH-sensitive properties, both urocanic acid and cholesterol succinate were grafted to pullulan and the developed nanoassemblies (UCPA-1-NPs)

583 to load higher extent of DOX. NPs showed superior cytotoxicity of DOX in MCF-7 cells by
584 intracellular delivery of DOX [51].
585 Selective and sustinable drug delivery is necessary in order to enhance the potency of
586 chemotherapeutics to the target site without inducing a toxic effect. XG has the tremendous
587 potential in sustainable drug liberation due to its gelling nature and ability of capturing the molecule
588 within the gel. DOX-loaded XG-based AuNPs (DXGP) showed 3-fold higher anticancer activity
589 in A549 cells compared to DOX alone [132]. Besides, AuNPs of XG and ascorbic acid (CPX-
590 AuNPs) exhibited higher cellular uptake with decreased cell viability of B16F10 cells [133].
591 Recently, Alle and co-workers prepared the DOX-carboxymethylated XG capped AuNPs using
592 was ultrafast synthesized by microwave irradiation that inhibited cell proliferation of LN-229 cells
593 [134]. XG-containing hydrogel nanocapsules (NC $(PhSe)_2$) were developed to deliver cutaneous
594 diphenyl diselenide in resistant melanoma SK-Mel-103 cells. The NC $(PhSe)_2$ showed superior
595 antimelanoma activity as compared to $(PhSe)_2$ alone [135]. Prepared XG-based hydrogels and
596 microspheres released omega-3 polyunsaturated fatty acids in colorectal cells. The results displayed
597 that α-linolenic acid increases the ability of prepared materials to attenuate the proliferation of
598 colorectal cancer cell lines. In contrast, docosahexaenoic acid carrying hydrogel had no enhanced
599 anti-neoplastic effect [136].
600 Superior cellular internalization and anticancer property of hydrophobic polyphenols, including
601 curcumin and naringenin conjugated with GG using dicyclohexylcarbodiimide and
602 dimethylaminopyridine reaction were reported against human ovarian cancer cell lines [137].
603 Moreover, GG/glucosamine conjugated with clioquinol (CQ) has been reported for the treatment
604 of oral cancer patches through modulation of EGFR expression and inhibition of tumor progression
605 in both cell line and animal systems [138]. GG nanohydrogel system (NH) containing anticancer
606 (paclitaxel) and anti-inflammatory (prednisolone) drugs synergistically showed enhanced the
607 anticancer effect in various tumor cell lines, such as MDA-MB-231, A2780, and Skov-3 [139]. 5-
608 Fu-containing calcium (Ca)-zinc (Zn)-gellan and Ca-Zn-gellan-ethyl cellulose microbeads

exhibited enhanced anticancer property against human colon cancer HT-29 cells [140]. Sophorolipid-combined AuNPs with reduced GG (SG-AuNPs) revealed higher efficacy in killing the human glioma LN-229 cells and glioma stem HNGC-2 cells [141]. Curcumin-loaded chitosan-GG based nanogels displayed enhanced anticancer activity against astrocytoma–glioblastoma U373MG cells [142]. IL-12-loaded chitosan (CS) NPs (CS/IL-12 NPs) were synthesized through tripolyphosphate, a crosslinking agent to transform the toxic nature of IL-12. The synthesized NPs showed inhibition of tumor metastasis by increasing the penetration of T-cells and NK cells and prevented the colorectal cancer liver metastasis in comparision to the CS-TPP-treated animals [143]. Curcumin loaded self-assembled glycyrrhetic acid (GA)-modified pullulan NPs (Cur-GAP NPs) showed higher cytotoxicity against HepG2 cells; it might be greater degree of cellular uptake and pH-responsive sustained release of curcumin [144]. DOX-loaded carboxymethyl XG-capped AuNPs (DOX@CMXG@AuNPs) nanocarriers were designed for efficient DOX delivery to tumor cells. It has been reported that the free DOX could be internalized in presence of ionophore because it builds an acidic surroundings in a healthy cell, through generation of the hydrogen ions in interchange of potassium ions [145]. DOX@CMXG@AuNPs in the combination of nigericin (ionophore) showed 4.6-fold higher cytotoxicity against human glioma cells (LN266) than free DOX. The pH-responsive liberation of DOX was also seen in DOX@CMXG@AuNPs treated cells [145]. Recently, SPG (EA/SPG-NP) and chitin (EA/Ch-NP) NPs loaded with ellagic acid have been investigated for their strong antitumor effect at concentration of 60 μg/mL against human breast cancer MCF-7 cells[146].

Camptothecin (CPT), an alkaloid of *Camptotheca acuminata* exhibits anticancer potential against various human cancers, including ovarian, breast, colon, melanoma, lung and pancreatic by promoting apoptosis and hampering angiogenesis. The lack of aqueous solubility, weak stability in physiological medium, and indefinite severe side-effects creat serious barrier for its clinical application. Liu and colleagues, consequently, encapsulated camptothecin using N-trimethyl chitosan (CPT-TMC) via micro-precipitation and sonication techniques to enhance its anti-tumor

response. CPT-TMC showed superior inhibition of B16-F10 cells growth and notable apoptotic cell death compared to free CPT. CPT-TMC also enhanced the survival of B16-F10 melanoma xenografted mice and ultimately displayed the possibilty of CPT in melanoma treatment [147]. All-trans retinoic acid (ATRA)-conjugated methoxy poly(ethylene glycol) (MPEG)-grafted CSNPs were designed via electrostatic interaction between ATRA and CS. The ATRA-MPEG-CSNPs efficiently inhibited invasion of tumor cells in comparision to ATRA alone, assessed by matrigel-based invasion test [148].

Gemcitabine-loaded chitosan magnetic nanoparticles (Gem-CsMNPs) were made through in-situ coprecipitation technique and investigated for anti-proliferative activity and pH-responsive drug release characteristics. Gem-CsMNPs exhibited 1.4-fold and 2.6-fold higher anti-proliferative activities against SKBR-3 and MCF-7 cells, respectively as compared to drug alone [149]. Self-assembled glycol CSNPs was developed and tailored with 5b-cholanic acid (HGC) for a prolonged and sustained delivery of RGD, an antiangiogenic peptide. RGD targets integrin $\alpha v\beta 3$, a glycoprotein membrane receptor, highly expressed on angiogenic endothelial cells. Intratumoral treatment of RGD-HGC considerably reduced tumor growth than natural RGD peptide by hampering fibroblast growth factor-dependent angiogenesis in matrigel matrics [150]. Alginate-based microparticles containing cyclophosphane and 5-Fu were synthesized for the controlled delivery of anticancer agents to cure intraocular carinoma. The synthesized microparticles exhibited 5-8-fold superior efficiency as compared to free drugs [151]. In continuation, carboxymethyl cellulose (CMC)-fasicinated porous Calcium carbonate ($CaCO_{3)}$ microparticles were layered by alginate and chitosan for the sustainable delivery of DOX. The DOX release rate from the developed microparticles at less than 5 pH was comparatively high within the first 15 h, and can be continued to >150 h but concurrently, the extent of free DOX at pH 5 was less [152].

Drug resistant is another major concern of available chemotherapeutics which occurs during prolong administration of chemotherapeutics. Urocanic acid possess imidazole ring, attributes to pH-induced hydrophilic-hydrophobic transition. It's conjugation to MPs produces pH-sensitive

composite for drug delivery system. A novel self-assembled and pH-sensitive O-urocanyl pullulan (URPA) NPs have been used as a potent vehicle for adriamycin (ADR) and studied the anticancer activity of ADR against drug-resistant MCF-7/ADR cells. URPA-NPs efficiently improved cellular uptake and significantly deliverd drug molecule to the nucleus of MCF-7/ADR cells for superior anticancer activity [153]. In addition, URPA was also found suitable as an excellent drug carrier for two chemotherapeutics, combretastatin A4 (CA4) and methotrexate (MTX). Intravenous injection of CA4-loaded MTX-URPA NPs to PLC/PRF/5 (hepatoma) bearing nude mice showed the improved antineoplastic and anti-angiogenic properties as well as the long-lasting distributions in both liver and tumor [51].

6. MPs as micro/nanocarriers for RNAi-mediated cancer therapy

Imbalanced homeostasis among proto-oncogenes and tumor-suppressive genes resulted in cancer. RNA interference (RNAi) therapy can be implemented to suppress tumor-progressive gene expressions [154]. NPs act as vectors for gene delivery and are more effective than viral-mediated gene delivery. The advantage of NPs-mediated gene delivery is the protection of RNAi molecules from immune recognition and enzymatic cleavage, and higher accumulation in cancerous tissues in comparision to normal tissue through enhanced permeability and retention (EPR) effect. Besides, the appropriated surface-functionalization of NPs and their size can prevent them from renal excretion. Organic NPs, including cationic polymer NPs and lipid-based systems, have gained considerable attention to precisely delivering RNAi at a tumor site. Several neutral and cationic MPs have been functionalized with selecting ligands on the basis of the target organ using polyetheleneglycol and other moieties (Table 3). For instance, curdlan, a neutral polymer extensively studied for an efficient siRNA nanocarrier for cancer therapy. Carboxymethylated-curdlan exhibits antitumor activity was hydrophobically modified with a sulfonylurea to prepare self-assembly. Aminate curdlan (AC)-based NPs were self-assembled with iRGD, a tumor-specific and tumor-penetrating cyclic peptide, and further complexed with siRNA. iRGD-functionalized

curdlan/siRNA particularly shipped the siRNA to integrin-expressing tumor cells through clathrin-mediated-endocytosis. In HepG2 cells, a gene Plk1 was successfully blocked using siRNA carried by AC-iRGD-NPs, suggesting that AC-iRGD-NPs may provide a biocompatible nano-platform for siRNA shipment [155]. Wang and colleagues optimized the lactobionic acid-conjugated curdlan-triornithine nanocarrier/SiRNA gene complex to enhance the higher transfection efficiency to ASGPR receptors over-expressing HepG2 cells [156].

Cationic polymers such as aminated curdlan can be alkylated to improve self-assembly for particle formation, enhance cell membrane permeability, and reduce cytotoxicity. In a study, alkylated 6-Amino-6-deoxy-curdlan/siRNA NPs efficiently delivered RNAi against STAT3 in mouse melanoma cell line B16. An increased apoptotic phenotype has also been detected in mouse melanoma cell line B16 when treated with the prepared NPs [157]. Prepared a copolymer containing folate–chitosan-graft-polyethylenimine (FC-g-PEI) to deliver the gene to inhibit lung tumorigenesis. The developed copolymer exhibited an exellent ability to condense Akt1 shRNA and provide good protection of shRNA from enzymatic attack. A stable formed complex of FC-g-PEI/ Akt1 shRNA could be used to efficiently inhibit Akt1-dependent cell growth and metastasis [158]. The CD73-siRNA encapsulated into chitosan-lactate NPs was developed to alter 4T1 breast tumor cells' immune system. CD73 is the cell surface ectonucleotidase, which assists in the secretion of immunosuppressive factor adenosine. Delivering the SiRNA against adenosine generating molecules through nano-cargoes may be considered an excellent tumor therapy approach [159]. Folate-conjugated chitosan-modified PLGA NPs were prepared to co-delivery of SiRNA against STAT3 and anti-inflammatory agents, flurbiprofen. Higher cellular uptake and apoptotic induction were detected in folate-conjugated chitosan-modified PLGA NPs treated groups of cancer cells, namely A549, MDA-MB231, and MCF-7 [160].

In the tumor microenvironment (TME), glycoprotein 130 (GP130)/IL6, sphingosine-1-phosphate (S1P)/S1P receptor 1, and signal transducer and stimulator of STAT3 have an unified network, which resulted into tumor development. Both IL-6/GP130 and S1P/S1PR1 pathways get

phosphorylated and subsequently trigger STAT3, led to provoke the S1PR1 expression and IL-6 level in a affirmative response circle. Blocking of this circle could arrest the neoplastic activity of cancer cells. In a recent study, knock down STAT3 upstream targets, namely GP130 and S1PR1 in colon cancer CT26 cells, breast cancer 4T1 cells, and melanoma B16-F10 cells using siRNA-decorated alginate-anchored trimethyl chitosan (ATMC) NPs. This was the first study which targeted this affirmative response circle and reduced the tumor size via downregulating the HIF-1α, IL-10, and SOCS3. This adjuvant approach offers a new way to treat cancer [19].

PEG-modified chitosan (PEG-CS) was synthesized using the ionic gelation method to successfully deliver anti-survivin siRNA. Application of PEG-CS/siRNA reduced tumor development and prevented metastasis in 4T1 tumor model by silencing the survivin gene, a member of apoptotic inhibitors encoded by the BIRC5 in human [161]. Spermine-introduced pullulan was condensed with RNAi to deliver the miR-181a in chronic myeloid leukemia (CML) cells, including the $CD34^+$ cells from clinical isolates. The miR-181a selectively inhibits the proliferation of CML $CD34^+$ cells, possibly via attenuation RALA (V-ral simian leukaemia viral oncogene homolog A). As expected, the miR-181a delivery improved the sensitivity of imatinib mesylate (IM) towards $CD34^+$ cells. IM is a specific blocker of the BCR-ABL fusion gene, which is the molecular hallmark of CML [162].

β-glucan SPG is a ligand for β-glucan receptor dectin-1 expressed on lung cancer cells and antigen-presenting cells. β-glucan SPG with antisense oligodeoxynucleotides dA40 (AS-ODN-dA40/SPG) sequence, especially targeting K-ras gene, led to suppress the growth of cancer cells [163]. Gemcitabine has binding affinity with dA40, so gemcitabine was combined with dA40 which showed potent cytotoxic activity in comparison to dA40 alone [164]. Moreover, SPG conjugated with folate and antisense poly (dA) that possessed effective anticancer activity in KB cells [165]. Mesenchymal stem cells (MSCs) are potential biological system for shipping of drug candidates in cancer treatment. Genetic engineering of MSCs by non-viral vector, spermine-pullulan was established to deliver IL-12 gene. MSCs harbouring IL-12 gene were injected in

B16F10 tumor bearing mice model through intratumorally and intravenously to investigate their antitumor efficacy. MSC-IL-12 significantly prevented lung metastases in B16F10 metastasis tumor bearing mice. Intratumoral injection of MSC-IL-12 cells noticeably reduced tumor growth in subcutaneous B16BL6 tumor mice, while intravenous injected did not arrest the tumor growth. It was might be due to distribution ability of MSCs in lungs [166].

7. MPs as bifunctionalized micro/nanocarriers

The integrated delivery of therapeutic RNA interference and a chemotherapeutic agent to cancer cells is interesting platform among other cancer therapies, which could deal superior cell killing latent and reduce side-effects (Fig. 3; Table 3). Chen and coworkers designed new folate-decorated amphiphilic bifunctional pullulan-modified (FPDP/DOX/shBeclin1) nanomicelles in 2018 for efficient targeted delivery of DOX and Beclin1 in folate receptor positive HepG2 cells. FPDP/DOX/shBeclin1 nano-micelles showed superior anticancer activity than non-folate targeted nano-micelles [167]. Similarly, carboxymethyl dextran (CMD) chitosan NPs (ChNPs) were fabricated for the co-delivery of siRNA against snail and DOX in HCT-116 cell lines. Snail genes promote cell survivability and induce epithelial to mesenchymal transitions (EMTs). The synthesized bi-functionalized (ChNPs-drug/siRNA/DOX) agents significantly inhibited metastsis and induced the apoptosis in HCT-116 cells [168]. Thiolated chitosan (TC) and trimethyl chitosan (TMC) NPs were decorated with HA (hyaluronic acid) and HIV-1-derived TAT peptide to enhance encapsulation efficiency of SiRNA. The dual blockade of signal transducer and stimulator of transcription 3 (STAT3) and programmed death-ligand 1 (PD-L1)by HA-TAT-TMC-TC NPs, led to impressive anti-tumor responses, including prominent arrest of growth, relocation, and angiogenesis of melanoma and breast cancer cells [169].

High expression of apoptosis inhibitors in tumor cells increases the resistance of cancer cells against chemotherapy. Therefore, cholesterol-grafted chitosan micelles (CCM) as a nanovehicle tool was synthesized for simultaneous shipment of both siRNA and curcumin to cancer cells

765 through siRNA condensation. The higher siRNA condensation efficiency of CCM was examined
766 by electrophoretic mobility shift assay and ethidium bromide dye exclusion assay. [170]. Nikkhoo
767 et al. designed carboxymethyl dextran-anchored trimethyl chitosan (TMC-CMD) NPs decorated
768 with BV6 and NIK/STAT3-specific siRNA to synchronously accelerate apoptotic cell death in
769 cancer cells, namely breast, colorectal and melanoma. In addition, the developed combination
770 decreased growth, cell relocation, colony formation, and angiogenesis of tumor cells through
771 interfering in gene expression of HIF and IL-10 [171]. Similarly, the hyaluronate-PEG-chitosan-
772 lactate (H-PCL) NPs were designed for the concurrent delivery of BV6, a apoptotic inhibitor and
773 IL-6 specific siRNA and evaluated the anti-tumor properties in cell line and animals systems. The
774 rdata revealed that H-PCL NPs increased apoptosis and concomitantly reduced the tumor forming
775 events in 4T1 and CT26 cells such as proliferation, migration, colony formation, and angiogenesis
776 as well as suppressed cancer formation in tumor-bearing mice [172].

777 Cancerous cells synthesize HIF-1α in the depletion of oxygen to adapt the hypoxic
778 microenvironment. HIF-1α regulates the expression of progression and metastasis-related genes of
779 tumor cells. HIF-1α/COX2/PGE2/EP4 signaling cascade seem to be significantly involved in
780 tumorigenesis. Thus, HA, and N,N,N-trimethyl chitosan (TMC) recoated superparamagnetic iron
781 oxide NPs (SPIONs) loaded with HIF-1α-silencing siRNA and EP4 antagonist (E7046) was
782 designed to inhibit growth, metastasis and colony formation of the tumor cells. SPION-TMC-HA-
783 siRNA NPs displayed the capacity to deliver siRNA for attenuating HIF-1α/EP4 axis which
784 remarkably reduces the cancer cells growth [173]. Similarly, knockdown of CD73/HIF-1α axis
785 using siRNA-loaded TAT-chitosan-SPION NPs led to potently inhibit the tumor growth and
786 angiogenesis [174].
787 D44, a trans-membrane glycoprotein is an early marker for neoplastic stem cell proliferation. CD44
788 facilitates the cell division, migration, and adhesion of cancer cells upon binding with its primary
789 ligand HA [175]. Therefore, HA recoated TMC-NPs were designed to specifically deliver the
790 siRNA against IL-6 and STAT3 in CD44-expressing tumor cells. The synthesized NPs having HA

and TMC potentially reduced cancer cell progression and these NPs can be used as nanovectors for gene-mediated combinational cancer therapy [176]. IL17RB/IL17B signalling activates a considerable enhance in the growth, proliferation, and relocation of cells by triggering of NF-κB and by upregulating of Bcl-2. Vahideh Alinejad and colleagues prepared carboxymethyl dextran (CMD) ChNPs for the encapsulation of IL17RB siRNA and DOX as well as examined their efficacy in MDA-MB361 cells. IL17RB-siRNA/DOX-CMD- ChNPs halted cell proliferation and migration via knock down of Bcl-2 and NF-κB gene expression [177]. A novel drug delivery system was developed by inducing chemically cross-linking among pullulan and poly(β-amino) ester (PBAE) for the combine delivery of methotrexate (MTX), and plasmid DNA expressing green fluorescent protein (pEGFP). MTX was linked with ester bond to pullulan and cationic nature PBAE facilitated the compression of the pEGFP. MTX-linked pullulan was decorated on the upper layer of PBAE/pEGFP polycomplex, led to synthesized MTX-PL/PBAE/pEGFP NPs. A strong tumor targeting property of NPs were examined agiant hepatoma at both vn-vitro and in-vivo systems [178]. A nanoplatform, PPEICD was developed to attain simultaneous delivery of mitoxantrone (MTO) and tumor suppressor gene, p53 by coupling β-cyclodextrin and polyethyleneimine to pullulan. The hydrophobic core of β-cyclodextrin retained MTO, while polyethyleneimine, a cationic molecule condensed pDNA. PPEICD nanocomplex-treated HepG2 cells exhibited higher apoptotic phenotypic characters compared to MTO and anti-p53 siRNA individually treated cells. These studies confirmed that the PPEICD nanostructures could powerfully and targeted deliver of p53 and MTO to tumor HepG2 and C6 cells and induce high cell death [179]. A novel amphiphilic dual-featured pullulan derivative (PDP) was assembled by decorating branched polyethylenimine and hydrophobic desoxycholic acid onto the parent chain of pullulan and assessed as a nano-driver for the combine delivery of DOX and p53 for efficient treatment of tumor. The obtained results demonstrated that synthesized PDP-DOX/p53 micelles were biocompatibility and less cytotoxic, exhibiting improved antitumor efficacy [30].

8. MPs as cancer diagnostic and theranostic agents

MPs-coated NPs are emerged as great tumor-homing agents. Specific ligand assemblies can be conjugated to the $–NH_2$ group and many other ligands to diagnose tumor. In this context, chitosan NPs loaded with 5-ALA (CNA), a ultimate fluorescent vector to specific delivery of 5-ALA in colorectal carcinoma were synthesized for endoscopic diagnosis of colorectal tumor. CNA have ability to prevent own self from engulfing by *E. coli* in the gastrointestinal which gravely hinders the outcomes of endoscopic evaluation. The results have confirmed that CNA can engulf by Caco-2 cells but not uptake by *E. coli* [180]. Similarly, cholesteryl pullulan of microbes was modified through incorporation of $–NH_2$ groups exhibiting a greater extent of fluorescence in cancer cells than common quantum-dots-liposomes [181, 182].

In recent years, SPIONs have come out as potent diagnostic agents in cancer biology field because of their exceptional features, mainly the enhanced magnetism that allows non-intrusive MRI and their promising in-vivo applications, including tumor hyperthermia in the existence of an external electromagnetic field [183]. However, poor stability in aqueous media of ferri-magnetic iron oxide NPs and undesirable accumulation to other tissues restrict their wide used as MRI and therapeutic agents although they exhibit higher contrast and hyperthermia. Therefore, ferri-magnetic iron oxide NPs are factionalized with MPs, and other ligands to improve aqueous medium dispersity and tissue-specific accumulation. For example, ferromagnetic nanocubes encapsulated and conjugated to bladder cancer-targeting peptide chitoson NPs for both MRI and NIRF imaging exhibited prolong blood circulation and tumor specificity [184]. A novel tumor diagnostic vehicle, FAPLCS/SPIONs was developed through decoration of SPIONs in self-assembled polymeric folate-anchored N-palmitoyl chitosan (FAPLCS) micelles and their cancer-targeting efficiency was elucidated in both cell line and animal systems. Specific ability of micelles to bind with folate receptor-overexpressed HeLa cells and their biocompatible nature make them as efficient MRI contrasting materials for detecting tumor that over-express folate receptors [185]. Ma and colleagues also engineered designed SPIONs stabilized with alginate (SPIONs-alginate) as a MRI

contrast agent which enhanced the detection of hepatocarcinoma [186]. A simplistic one-step synthesis technique has been optimized to develop biodegradable and biocompatible DOX and indocyanine green-conjugated magnetic chitosan nanospheres that could be useful for both fluorescence imaging and MRI guided chemo-photothermal intregated tumor therapy [187].

Water-soluble chitosan decorated ultrasmall superparamagnetic iron oxide (USPIO) NPs allow MRI-based chasing of single cell at cellular level in-vitro and in-vivo conditions. TEM and NMR relaxometry analysis varified the endosomal engulfment of chitosan–NP, subsequent endo-lysosomal escape, and cytosolic preservation by neural stem cells (NSC) [188]. A stable folate receptor decorated magnetite o-carboxymethyl chitosan NPs (FA-RITC-OCMC-SPIONs) anchored with rhodamine isothiocyanate (RITC), a bimodal nanoprobe that exhibit higher T_2-weighted negative contrast MRI in folate-positive HeLa [189].

Arachidyl chitosan (CSOAA)-based self-assembled nanoprobes were conjugated to diethylenetriaminepentaacetic dianhydride (DTPA) and gadolinium (Gd3+) to develop as a MRI contrast agent. A phantom investigation revealed a superior T_1-positive contrast-improving impact of the designed CSOAA-based nanoprobe than the marketed formulation (Gd-DTPA). No significant toxicity of nanoprobe was detected in head (Hep-2) and neck (FaDu) cancer cell lines [190]. Chitosan (CS) was cross-linked with gadopentetic acid (GA) and octadecanoic acid (OA) and loaded with chlorin e6 (Ce6) to prepare MRI directed photodynamic therapy (PDT) of cancer. Synthesize nano-construct, Gd-CS-OA/Ce6 exhibited higher contrast as compared to Gd-DTPA in MRI. Gd-CS-OA/Ce6 is proven to be a potent MRI-guided tumor ablating agent through PDT on *in situ* 4T1 tumor model [191]. A pH-sensitive Gd-loaded poly(L-lysine)/carboxymethyl chitosan NPs (Gd-PCNPs) designed as relaxivity-modulating MRI contrast agents that are nontoxic in B16 Cells. NPs selectively enhanced the relaxivity (10.008 mM^{-1}) at the PH 6 compare to Magnevist (3.924 mM^{-1}) in tumor area by disassembling in an acidic TME and subsequently enhanced the swap of protons among H_2O molecules and Gd^{3+} ions [192]. Moreover, gadolinium meso-tetrakis(4-pyridyl)porphyrin [Gd(TPyP)] loaded chitosan NPs were also

designed by passive adsorption for MRI. Relaxivities of Gd(TPyP)-CNs was detected to be increased with Gd concentration and it was 12-times superior in compariotion to Gd-DOTA [193]. Pullulan-conjugated gadolinium diethylene triamine pentaacetate (Gd-DTPA-Pullulan) was successfully synthesized as a hepato-targated T1 contrast agent for MRI application. Gd-DTPA-Pullulan provided three fold higher disparity of liver parenchyma in delayed MRI than Gd-DTPA-BMA (Omniscan) on orthotopic rat HCC. Gd-DTPA-Pullulan was also found comparative less toxic on normal liver cells than Gd-DTPA-BMA and Gd-DTPA [194]. Cobalt ferrite NPs (CFN) can also use as a effecient MRI contrast agent due to their superior saturation magnetization and magneto-crystalline anisotropy but their cytotoxic nature limits it utility in biomedical applications. Recently, Shakil and colleagues tried to overcome these challenges by coating a biocompatible polymer chitosan on the surface of CFN. The synthesized chitosan-coated cobalt ferrite NPs (CCN) were found to be biocompatible at the concentration of 20 mg/kg. A phantom MRI imaging analysis revealed that CCN were found to be potent T_2-weighted contrast agent and could be used as a potential agent for MRI contrast dye [195].

Multifunctional nanoplatforms that incorporate imaging and chemophotothermal treatment for superior cancer diagnosis and therapy have gained immense interest in recent years. Chitosan-conjugated magnetic graphene (CMG) NP has proposed as a biosafe multifunctional theranostics for synchronous drug/gene and SPIO delivery to tumor. CMG was found to be as a strong T_2 contrast-improving agent in phantom and *ex vivo* MRI analysis. In addition, DOX-loaded CMG NPs more efficiently combat the lung cancer cell proliferation (IC_{50} = 2 μM) compare to free drug (IC_{50} 4 μM), suggesting that CMG NPs provides an excellent strategy for simultaneous delivery of drug and gene as well as imaging of targeted site [196]. Theranostic polymeric NPs were designed with docetaxel and superparamagnetic iron oxide (SPIO) nanocrystals. Carboxy-terminated poly(lactic-co-glycolic) acid was conjugated to polymeric NPs using a single emulsion sovlent evaporation method. The synthesized NPs exhibited higher cellular engulf capacity and growth preventive effect on PC3 prostate tumor. In vitro MRI analysis confirmed that the NPs

895 behave as a contrast improving agents [197]. Very recently, a new multifunctional functional nano-
896 realm, SPION@Au-CS-DOX-FA NPs was prepared by cross linking between pH-sensitive
897 superparamagnetic iron oxide core-gold shell (SPION@Au), chitosan (CS), folate (FA), and DOX.
898 Tumor growth was remarkably stunted in NPs-treated mice by sustain drug release capability.
899 The NPs significantly induced apoptosis in SkBr3 cells by upregulating of BAX and BAK
900 expression and downregulating of Bcl-2 and Bcl-XL [198]. Acetylated pullulan-coated magnetic
901 NPs exhibit theranostic effect through magnetic flux-induced hyperthermia [181, 182]. Xie and
902 colleagues estabilised a chitosan/carboxymethylcellulose functionalized magnetic molybdenum
903 disulfide (mMoS2-CS/CMC) naocomposites as an efficient drug carrier for DOX. The mMoS2-
904 CS/CMC-DOX nanocomposites were examined as biocompatible, negligible toxic to normal cells
905 but highly accumulating materials in tumor tissue, exhibiting an excellent photo-thermal effect
906 [199]. Similarly, alginate-based theranostic (OAL-*g*-PEG-FA/RhB) nanogels were developed for
907 the cancer chemotherapy and diagnosis, by cross-linking the folate-linked PEG and rhodamine
908 B linked PEG subsequently covalent fusion of nanogels. The synthesized nanogel killed the tumor
909 cells potentially by releasing the chemotherapeutics in pH/reduction dependent manner and tissue-
910 specific manner. The attached rhodamine B group makes them suitable to locate cancer tissue
911 [200]. Thus, the entire study proposed that theranostic nanogels have ability to prevent cancer and
912 the real-time and non-invasive location tracking in cancer tissue.
913
914 **Conclusion and future prospects**
915 Intrinsic characteristics of MPs such as renewable, biocompatible, biodegradable and non-
916 immunogenicity are of significance for cancer therapy. The optimization of microbial growth
917 conditions could provide large scale production of specific polymer. To discovering a novel
918 polysaccharides with excellent absorption, distribution, metabolism, elimination and toxicity
919 (ADMET) properties and anti-tumor property, OSMAC (One strain many compounds) approach
920 can be apply through altering the microbial growth condition. However, lack of depth knowledge

921 in chemical structural elucidation of new MPs remains a blemish between the structural
922 relationships with bioactivity. Few scientific communities are focusing on identifying their
923 chemical structure, i.e. their biological activities are being systematically understood.

924 MPs exhibit not only synergy with cancer chemotherapeutics but also reduce their adverse
925 side effects. Mingling the cancer chemotherapeutics with MPs is an excellent paradigm to prevent
926 tumor growth and malignancy. Very few combination of polymers and anticancer agents has been
927 investigated upto date. An aggressive attention of researchers is needed in this dimension of
928 development of cancer chemotherapy. However, it is very exhaustive and cost consuming to screen
929 all possible combinations by experimental trials. It is documented that combining the anticancer
930 agents interfering on the same pathway through different target appear to be more likely to produce
931 synergistic effects. As discussed above, MPs exhibit inherent anti-neoplastic activity by altering
932 the different signalling pathways. Researcher can take an advantage of depth insight of anticancer
933 targets of MPs to develop novel therapeutics. Few polysaccharides are only reported for their only
934 preventing tumor growth but has not been explored for their mode of actions. Therefore, extensive
935 research efforts are essential to elucidate the targets of anticancer MPs.

936 The low oral absorption, large dose-requirements and short biological half-life is another
937 major concern for microbial polysaccharides showing anti-proliferative activity; restrict their
938 development into a commercial pharmaceutical formulation for clinical application. Precise
939 chemical modification of available MPs, therefore, is an important aspects of innovation to improve
940 their prolong blood circulation and reduce side effects. Chemically-modified polymers tend to
941 conjugate the hydrophobic moieties and self-assembled complex into hydrophobic inner core and
942 hydrophilic outer core by electrostatic interactions, possessing potential to resolve last-ditch
943 therapeutic challenges. Self-assembled MP-based nano-carriers are capable to hold higher amount
944 of drug and genes to be delivered, show large surface area and highly stability under physiological
945 conditions, higher specificity to tumor tissues and controllable dug release properties. Apart from
946 it, MPs based nano-carriers are also functionalized with specific receptors such as transferrin,

folate, and temperature and light responsive moieties for tissue-specific delivery. In last few years, numerour in-depth studies have been documented on the investigation of chemically modified MPs nano-carriers for their specificity and efficiency towards wide range of in vitro and in vivo model systems, indicating their efficacy for translation to clinical research. However, their large scale production and reproducibility is one of major concern among translation research. Feasible, cost effective and multi-functionalized polymers-drug/gene engineering approaches are toughest task.

This review provides a glimpse of recent trends, challenges and great opportunities in the direction of MPs contributing in cancer theranostics. The biosafe, biocompatibility characteristics of MP are fascinating and booming field for future breakthrough of cancer therapeutics and diagnostics. Besides, the precise use of MP based nano drugs will ultimately save breathes of cancer suffering human being in the future. However, innovative efforts are necessary to articulate ideal drug at the global level.

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Figure captions

Figure 1. Chemical structure of some important MPs.

Figure 2. Possible targets of MPs for prevention and therapy of cancer. MPs stimulate the both intrinsic and extrinsic apoptosis pathways in tumor cells. Extrinsic pathway is triggered by binding extracellular ligands to external death receptor and, subsequently caspase 8/3,7-mediated cell death programming occurred. The intrinsic apoptosis pathway involves activation of caspase 3 by cleaving bid, leading to mitochondrial dysfunction followed liberation of cytochrome c and stimulation of caspases-9 and caspases-3. Caspase-3 stimulates the emblematic apoptosis characteristics, including DNA fragmentation and cell death in several tissues. MP creates starving environment to tumor cells by preventing the endothelial cells proliferation through blocking the VEGFR signaling pathways. MP obstructs the NF-kB activity through locking the receptor tyrosine kinase (RTK) and downregulating the expression of intercellular adhesion molecule-1 (ICAM-1), which resulted into jammed epithelial-mesenchymal transition (metastasis)**.** MPs bind with specific receptors of immune cells and initiate their maturation to produce the different kinds of cytokines, which further stimulates cytotoxic T-cells proliferation and other signalling pathways. The stimulated cytotoxic T cells inhibits the the growth of cancer cells. MPes also improve the antitumor immunity activity through reshaping the gut microbiota.

Figure 3. Underlying strategies and mechanism of MPs decorated nano-construct mediated drug delivery. Microbial polymers are chemically modified with suitable reagent to improve their pharmacokinetics properties and bioavailability and link with therapeutic agents (drug, nucleic acid peptides) and diagnostic agents. Microbial polysaccharides based therapeutics/theranostics are mainly designed for passive targeting and active targeting. Tumor cells exhibit overexpression of specific receptors as compared to normal cells. Specific-ligands linked nanoparticles specifically pass into cancer cells via a receptor-mediated pathway. While passive targeted nano-constructs get accumulated to tumor cells through leaky vascular system of tumor. Drug/Gene therapeutics are then liberated into the cytosol escaping from the endo-lysosomes.

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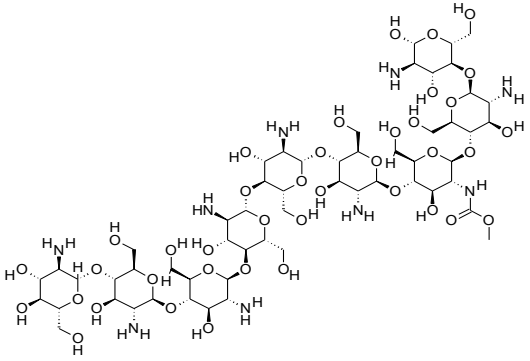

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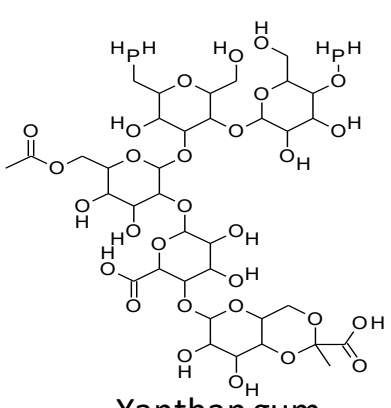
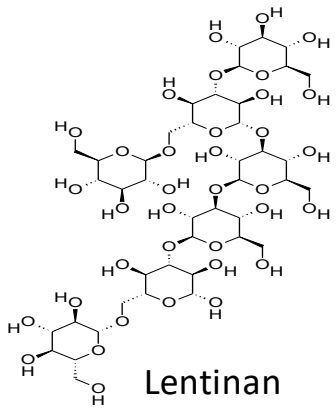
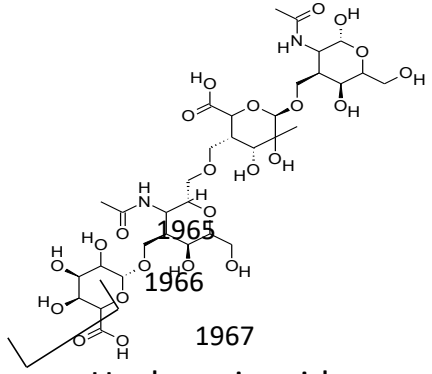


Xanthan gum



Lentinan



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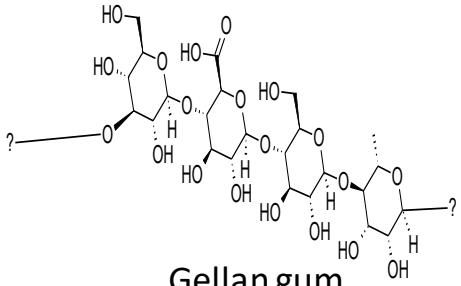
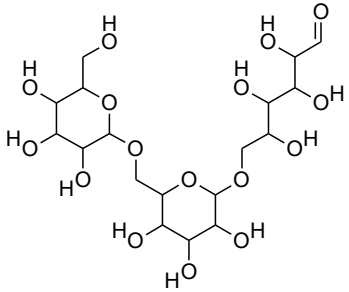
Hyaluronic acid



Gellan gum



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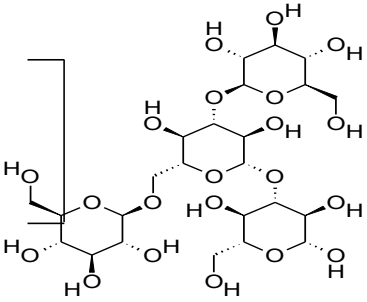
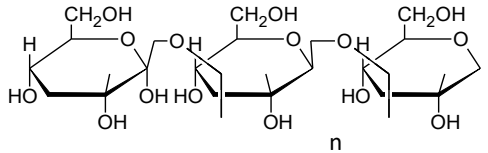


Schizophyllan



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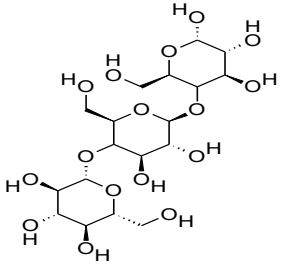
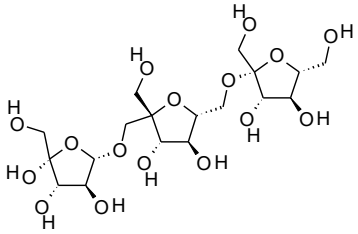
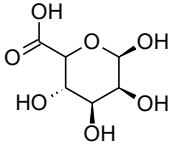
Curdlan



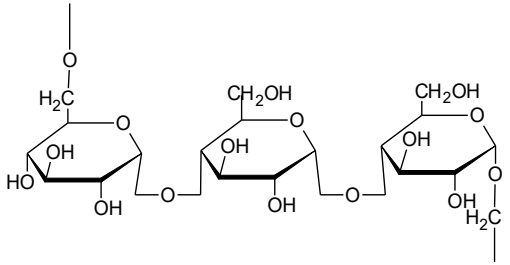
β-glucans



Levan



Alginate



Pullulan

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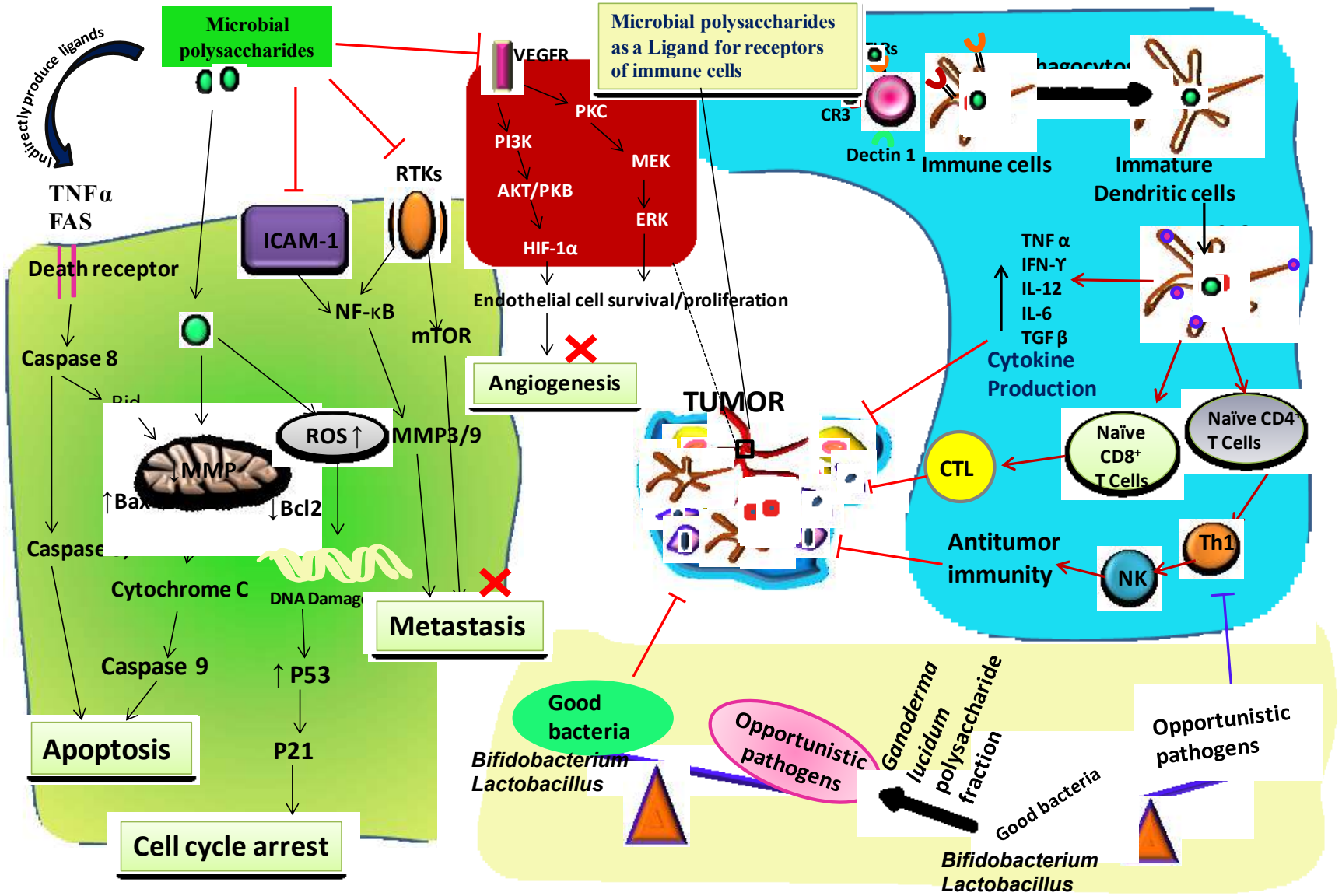
Microbial polysaccharides
Indirectly produce ligands
TNFα
FAS
Death receptor
Caspase 8
Caspase
Cytochrome C
Caspase 9
Apoptosis
Cell cycle arrest
ICAM-1
RTKs
NF-κB
mTOR
ROS↑
MMP3/9
↓MMP
↑Bax
↓Bcl2
DNA Damage
↑P53
P21
VEGFR
PKC
PI3K
MEK
AKT/PKB
ERK
HIF-1α
Endothelial cell survival/proliferation
Angiogenesis
Metastasis
TUMOR
Microbial polysaccharides as a Ligand for receptors of immune cells
CR3
Dectin 1
Immune cells
Immature Dendritic cells
TNFα
IFN-γ
IL-12
IL-6
TGFβ
Cytokine Production
Naïve CD8+ T Cells
Naïve CD4+ T Cells
CTL
Th1
NK
Antitumor immunity
Good bacteria
Bifidobacterium
Lactobacillus
Opportunistic pathogens
Ganoderma lucidum polysaccharide fraction
Good bacteria
Bifidobacterium
Lactobacillus
Opportunistic pathogens

Figure 2

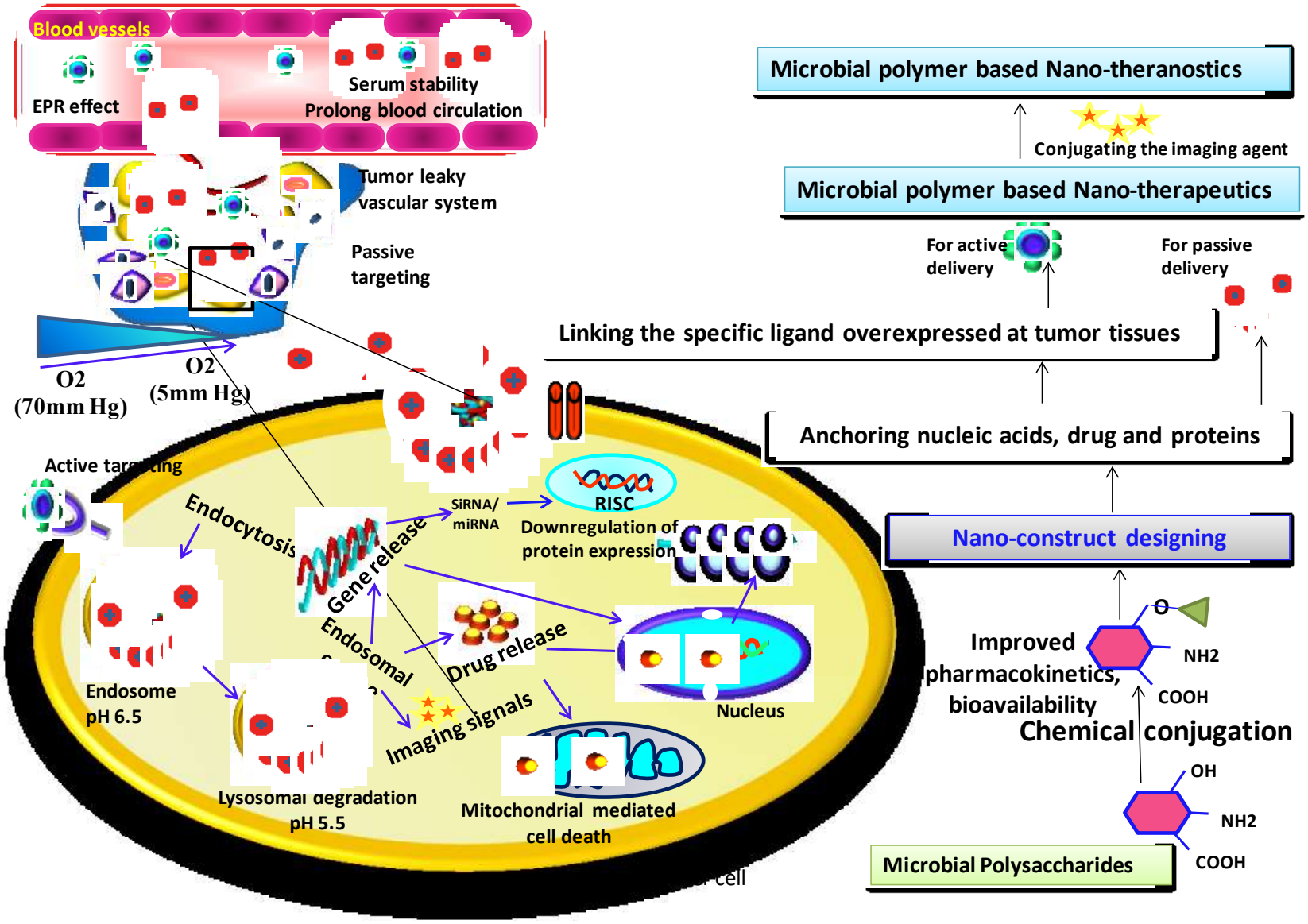
Blood vessels
EPR effect
Serum stability
Prolong blood circulation
Tumor leaky vascular system
Passive targeting
O2 (70mm Hg)
O2 (5mm Hg)
Active targeting
Endocytosis
Endosome pH 6.5
Gene release
Endosomal
SiRNA/ miRNA
RISC
Downregulation of protein expression
Drug release
Nucleus
Imaging signals
Lysosomal degradation pH 5.5
Mitochondrial mediated cell death
cell
Microbial polymer based Nano-theranostics
Conjugating the imaging agent
Microbial polymer based Nano-therapeutics
For active delivery
For passive delivery
Linking the specific ligand overexpressed at tumor tissues
Anchoring nucleic acids, drug and proteins
Nano-construct designing
Improved pharmacokinetics, bioavailability
Chemical conjugation
O
NH2
COOH
OH
NH2
COOH
Microbial Polysaccharides

Figure 3

2030 Table 1. MPs and their primary structure, origins and characteristics

Polysaccharide	Microbe	Major producer	Primary structure linkages	Characteristics	Ref.
Xanthan gum	Bacteria	*Xanthomonas campestris*	(1→4) linked β-D-glucose	Non-toxic, biodegradable, economical, pH, temperature, enzymatic cleavage resistant.	[201]
Gellan gum	Bacteria	*Sphingomonas elodea*	(1→4) rhamnose-(α-1→3)-d-glucose-(β-1→4)-d-glucuronic-(β-1→4)-d-glucopyranosyl-(β-1→ with O(2) l-glyceryl and O(6) acetyl substituents on the 3-linked glucose	Biodegradability and nontoxicity, pH, enzymatic cleavage resistant.	[202]
Alginate	Algea and bacteria	*Laminaria hyperborea*, *Ascophyllum nodosum*, *L. japonica*, *L. digitata*, *Macro cystis pyrifera*	β-1,4-linked D-mannuronic acid (M) and L-guluronic acid (G)	Biocompatibility, biodegradability, processability, low cost.	[203]
Dextran	Bacteria	*Leuconostoc*, *Lactobacillus*, and *Streptococcu*s	α-(1→6)-linked d-glucopyranosyl repeating units	Biocompatibility, biodegradability, nontoxic.	[204]
Curdlan	Bacteria	*Alcaligenes faecalis*	β-(1→3)-glucan	Inherent biological property, poor solubility, biosafe, thermo stable gel forming ability.	[39]
Lentinan	Fungi	*Lentinus edodes*	β-(1→3)-glucan with β-(1→6) glucopyranoside branches	Water soluble, heat stable, alkali labile, bioactive.	[205]
Pullalan	Fungi	*Aureobasidium pullulans*	α-(1→4)-maltotriosyl units	Neutral, homolinear, water soluble, low viscosity, non-toxic, non-immunogenic.	[206]
Schizophyllan	Fungi	*Schizophyllum commune*	β-(1→3)D-linked with β-(1→6)-D-glucosyl branches	Weak gelation at low temperature, restrict to enzymatic cleavage.	[207]
Chitosan	Fungi	Zygomycetes	β-1,4-D-glucosamine	Non-immunogenic, water soluble, Inexpensive, biocompatible, biodegradable.	[208]

Scleroglucan	Fungi	*Sclerotium* spp.	β-1,3-D-glucopyranosyl units	Non-ionic, resistance to hydrolysis, temperature, good emulsifying capability, bioactive.	[209]
Pleuran	Fungi	*Pleurotus ostreatus*	β-(1→3) and β-(1→6)-glucan	Bioactive.	[210]
Zymosan	Yeast	*Saccharomyces cerevisiae*	β-(1→3)-glucan	Insoluble in water.	[211]
Levan	Bacteria	*Lactobacillus* sp., *Halomonas* sp., *Acetobacter* sp., *Zymomonas* sp.,	β-(2→6)-fructan	low intrinsic viscosity value, emulsifying capacity, adhesive ability, no swelling capacity.	[212]
Hyaluronic acid	Bacteria	*S. zooepidemicus*	Glucuronidic β-(1→3) bond	Swelling capacity, biocompatibility, non-immunogenicity, biodegradability, viscoelasticity.	[213]

2031

2032 Table 2. Anticancer property of MPs and their mode of action

Polysaccharide	Source	Mechanism of action	Model	Dose	Ref.
EPS	L. *plantarum* GD2, L. *rhamnosus* E9, and L. *brevis* LB63	↑Bax, ↑caspase 3/9, ↓Bcl-2, ↓survivin	In-vitro	400 µg/mL	[214]
K5PS	*Escherichia coli*	↓Metastatis, ↓cell adhesion, ↓invasion	In-vitro, In-vivo	5 and 10 mg/kg	[73]
EPS-1	*Paenibacillus polymyxa* EJS-3	↓Cell proliferation	In-vitro	0.2-1.2 mg/mL	[40]
REPS	*Rhizobium* sp. N613	↓Tumour formation	In-vivo	5-120 mg/kg	[41]
Sulfated polysaccharides	*Ecklonia cava*	↑Apoptotic body, ↑PARP, ↑caspase 9	In-vitro	9.8-75 µg/mL	[215]
GF-1	*Grifola frondosa*	↓ Meth A	In-vivo	0.5-5 mg/kg	[80]
	G. frondosa	↑Body weight, ↑spleen cell number	In-vivo	1-4 mg/kg	[80]
Grifolan NNMF-5N	*G. frondosa*	↑Macrophage ↑cytotoxic T-cells	In-vivo	100-500 µg/mL	[82]
MaitakeZ	*G. frondosa*	↑NK-cells, ↑killer T-cells, ↑macrophages, ↑lymphokines, ↑IL-1	In-vivo	1 mg/kg/day	[79]
		↑Splenocyte proliferation, ↑peritoneal macrophage, ↑IL-12, ↑IL-2, ↑IFN-γ	In-vitro, in-vivo	0-400 µg/mL 8 mg/kg/day	[12, 79]
		↑DC-cells, ↑IL-12, ↑antigen specific Th1	In-vitro in-vivo	0-400 µg/mL 8 mg/kg/day	[79, 84]
GFPBW2	*G. frondosa*	↑ IL-6, ↑TNF-α, ↑macrophage activation	In-vitro	5-500 µg/mL	[86]
GFPBW2	*G. frondosa*	↑Macrophage activation, ↑splenocyte proliferation, ↑IL-6, ↑TNF-α, ↑Dectin-1/Syk/NF-κB signalling	In-vitro, in-vivo	5-500 µg/mL 0.2-5 mg/kg	[87]
GFP-A	*G. frondosa*	↑TLR-4,↑mitogen-activated protein kinases, ↑NFκB	In-vitro	40-160 µg/mL	[162]
GP11	*G. frondosa*	↑NO production, ↑TNF-α, ↑IL-1β, ↑TLR-4, ↑ spleen and thymus weight	In-vitro, in-vivo	62.5-1000 µg/mL 27-216 mg/kg	[88]
Se-GP11	*G. frondosa*	↑ TNF-α, IL-2, NO production, spleen and thymus weight	In-vitro, in-vivo	62.5-1000 µg/mL 27-216 mg/kg	[89]

Polysaccharide rich extract	*G. frondosa*	↑Neutrophil phagocytic activity, ↑CD11b expression	In-vitro	0.025-0.1 mg/mL	[90]
GF9801	*G. frondosa*	↑G2/M phase arrest, ↑Bax, c↑aspase-3 ↓Bcl-2, ↓mitochondrial membrane potential	In-vitro	30-120 µg/mL	[55]
S-GAP-P	*G. frondosa*	↑Apoptosis, ↓peritoneal macrophage, ↓proliferation of SGC-7901	In-vitro, in-vivo	10-100 µg/mL 50 mg/kg/day	[108]
	G. frondosa	↑ Sub-G_0/G_1 phase and cell apoptosis	In-vitro	10–50 µg/ml	[108]
S-GFB	*G. frondosa*	↑S-phase cell cycle arrest, ↑caspase-3/8 ↓Notch expression, ↓NF-B/p65 translocation, ↓FLIP	In-vitro	0-100 µg/mL	[86]
Sul-GFPW	*G. frondosa*	↓Endothelial cell proliferation, migration and invasion	In-vitro	100 µg/mL	[68]
Vitamin C and D-fraction combination	*G. frondosa*	↑Bax, ↑PARP, ↑cytochrome c, ↑G2/M phase arrest, ↓Bcl-2	In-vitro	0.2 mg/mL	[111]
D-fraction	*G. frondosa*	↑ Delayed type hypersensitivity	In-vivo	0.2-1.5 mg/mL	[79]
		↑NK cells, ↓metastasis	Clinical study	40-150 mg/patient	[79, 94]
		↑IL-12 production, ↑NK cells activation	In-vivo	8.7 mg/kg/day	[79, 94]
		↑Th-1/Th-2 differentiation, ↑IL-12, ↑p70, ↑IFN-γ	In-vivo	7.8 mg/kg/day	[95]
		↑IL-10, ↑MHC-II, ↑NO production, ↑IFN-γ	In-vivo	4 mg/kg/day	[93]
		↑IFN-γ, ↑IL-12, ↑p70, ↑IL-18	In-vivo	5 mg/kg/day	[79]
		↓Carcinogenesis, ↓cancer metastasis	In-vivo	1 mg/kg	[70]
		↑D-fraction, ↑cytochrome c	In-vitro	18-367 µg/mL	[79]
MD-fraction	*G. frondosa*	↑NK cells, ↓ICAM-1	In-vivo	8 mg/kg/day	[72]
MD-fraction with cisplatin	*G. frondosa*	↑ IL-12, ↑p70, ↑metastasis ↓Tumour formation	In-vivo	8 mg/kg	[84]
MD-fraction and mitomycin-C	*G. frondosa*	↑Th1 response, ↑IL-12; ↓tumour growth	In-vivo	0.25 mg/kg/day	[79]
Lentinan with oxaliplatin	*Lentinus edodes*	↓NF-κB, ↓STAT3, ↓survivin signalling	In-vitro, in-vivo	800 µg/mL & 20 µM 25 mg/kg & 10 mg/kg	[216]

SLNT1 and JLNT1	*L. edodes*	↑Apoptosis, ↑IL-2, ↑TNF-α	In-vivo	12.5-800 µg/mL 50-200 mg/kg	[217]
SLNT	*L. edodes*	↑Caspase-9/8, ↑ROS, ↑Bax, ↑cytochrome c, ↑TNF-α, ↓NF-κB, ↑Bcl-2	In-vitro, in-vivo	0.4-1.6 mg/mL 0.2-1 mg/kg	[217]
Active hexose correlated compounds	*L. edodes*	↑Neutrophils, ↑NK cells, ↑CD3/CD4 ↓Lymphocytes, ↓monocytes, ↓CD4/CD8	Clinical	3 gm/diet	[218]
LEP	*L. edodes*	↑SOD, ↑GSH-Px ↓IL-2, ↓TNF-α	In-vivo	100-500 µg/mL	[216]
LEP1	*L. edodes*	↑Caspases-3/9, ↑cytochrome c, ↑cleaved of PARP, ↑Bax, ↓MMP, ↓Bcl-2	In-vitro	100-400 µg/mL	[216]
WEP1	*L. edodes*	↑Cell proliferation, ↑G2/M phase arrest, ↑ROS production ↓Tubulin polymerization	In-vitro, in-vivo	50-200 mg/kg	[106]
β-glucan	*L. edodes*	↑T-cell, ↑$CD4^+$ T-cell, ↑neutrophils	In-vivo	1 mg/kg	[97]
MPSs	*L. edodes*	↑TLR4-NF-κB pathway	In-vitro	0.1-0.5 mg/mL	[98]
Se-Lentinan	*L. edodes*	↓Metastasis, ↓tumour growth	In-vitro, in-vivo	5-20 µg/mL 9-36 mg/kg	[67]
Lentinan	*L. edodes*	↑IFN-γ ↓Tumour growth, ↓angiogenesis	In-vivo	0.5-5 mg/kg	[63]
Lentinans	*L. edodes*	↓Tumour growth	In-vivo	1-100 mg/kg	[216]
Lentinan	*L. edodes*	↓Tumour growth	In-vivo	1 µg/gm	[216]
SLMs-1 and SLMs-2	*L. edodes*	↓Tumour cell proliferation	In-vitro	25-400 µg/mL	[106]
KS-2	*L. edodes*	↑Interferon production	In-vitro, in-vivo	0.1-140 mg/kg	[216]
Lentinan with mitomycin, tegafur, and 5-FU pyrimidine	*L. edodes*	↑Survival rate of patient	Clinical study	2 mg/week	[216]
Lentinan with fluoropyrimidine	*L. edodes*	↑Apoptosis and orotate phosphoribosyl Transferase, ↓Thymidylate synthase, ↓dihydropyrimidine dehydrogenase	Clinical	0.1 mg/kg/day	[107]
Coriolan	*L. edodes*	↓Sarcoma 180 tumor growth	In-vivo	5-100 mg/kg	[216]

PSK	*L. edodes*	↑MM46-tumour bearing survival rate	In-vivo	250 mg/kg	[216]
PBPs	*L. edodes*	↑ROS generation and JNK	In-vitro	100 and 200 µg/mL	[219]
Polysaccharide rich extract	*L. edodes*	↑E-cadherin epithelial marker ↓Cell proliferation, ↓MMP-2 enzyme activity, ↓oncogenic potential, ↓cell migration, ↓invasion	In-vitro	10-100 µg/mL	[220]
Tramesan	*L. edodes*	↓Leukemic cell growth	In-vitro	0.5-2 mg/mL	[221]
PSK	*L. edodes*	↑p38-MAPK, ↑caspase-3 activation ↓Cell proliferation, MMP	In-vitro	30 and 100 µg/mL	[222]
PSK with IL-2	*L. edodes*	↑G_0/G1-Phase arrest ↓Tumour cell proliferation	In-vitro	50 and 100 µg/mL	[223]
CVPs-B	*L. edodes*	↑Cell apoptosis, ↑cell proportion in G_0/G_1	In-vitro	0-100 µg/mL	[224]
PSP	*L. edodes*	↓Prostate tumour formation, ↓CD133, ↓CD44	In-vitro, in-vivo	0-500 µg/mL 200 & 300 mg/kg	[225]
PSP with camptothecin	*C. versicolor*	↑S-phase arrest ↓Cell proliferation	In-vitro	0-400 µg/mL	[226]
PSP with DOX and etoposide	*L. edodes*	↑S-phase arrest, ↑Bax, ↓BcL-XL	In-vitro	0-400 µg/mL	[227]
PSP with cyclophosphamide	*C. versicolor*	↑Plasma half-life ↓HepG-2 cell's viability, ↓renal drug clearance	In-vitro, in-vivo	1-10 µM	[228]
PSP with DOX and VP-16	*C. versicolor*	↑Bax, ↑cytochrome c, ↑cleaved PARP ↓Bcl-2, ↓survivin, ↓ERK, ↓p65 gene	In-vitro	0.1-1 mg/mL	[229]
PSP	*C. versicolor*	↑S-phase arrest, ↑cyclin E, ↑caspase-3	In-vitro	25-100 µg/mL	[230]
PSP	*C. versicolor*	↑AP-1, ↑EGR1, ↑IER2, ↑IER5, ↑GADD45A/B, ↑TUSC2 ↓NF-kB, ↓phosphatases, ↓kinases	In-vitro	400 µg/mL	[231]
PSP with radiation therapy	*L. edodes*	↑Blood and serum lymphocyte proliferation, ↑NK cells, ↑granulocytes	In-vitro, in-vivo	2 mg/injection	[232]
RPSP	*L. edodes*	↓Tumour growth and mass	In-vivo	IC_{50} = 243 µg/mL	[233]

PSK with cisplatin	*L. edodes*	↑Cell cytotoxicity ↓Cell proliferation	In-vitro	100 µg/mL	[233]
PSK	*L. edodes*	↑SOD mimicking activity	In-vivo & clinical	50 mg/kg 3 gm/patient/day	[233]
SPCV	*C. versicolor*	↑Cell cytotoxicity, ↑WBC, ↑IgG level ↓ Tumour growth and mass	In-vitro, in-vivo	50-200 µg/mL	[233]
PSK with docetaxel	*L. edodes*	↑Apoptosis, ↑$CD4^+$ and $CD8^+$ T-cell infiltration at tumour site, ↑splenic NK cell cytotoxicity, ↑ IFN-γ ↓Tumour proliferation	In-vivo	300 mg/kg	[234]
PSP	*C. versicolor*	↓Angiogenesis, ↓VEGF, ↓vascular density, ↓tumour growth	In-vivo	50 µg/kg	[5]
PSP	*C. versicolor*	↓Survival time of rats	In-vivo	250 mg/kg	[233]
PSP	*C. versicolor*	↓Cell proliferation, ↓metastasis, ↓tumour growth	In-vitro, in-vivo	25-100 mg/kg	[235]
PSP with CPA	*L. edodes*	↑Lymphocyte proliferation, ↑NK-cell function, ↑WBC, ↑ spleen and thymus weight, ↑IgG, ↑IL-2 production	In-vivo	2g/kg/day	[233]
PSK	*L. edodes*	↑Inhibition of Meth A induced fibrosarcoma	In-vitro, in-vivo	0-100 µg/mL 20 mg/kg	[5]
Yunzhi and Danshen	*L. edodes*	↑B-lymphocytes, ↑T-helper lymphocytes ($CD4^+$), ↑ ratio of T-helper (CD4+)/T suppressor and cytotoxic lymphocytes ($CD8^+$)	Clinical	50 mg/kg 20 mg/kg	[5]
PSP	*C. versicolor*	↑Blood leukocyte, ↑neutrophil counts, ↑IgG, ↑IgM	Clinical	340 mg/patients	[5]
PSP	*C. versicolor*	↑IL-6, ↑IL-2, ↑TNF-α, ↑TLR-4, ↑NF-kB, ↑AP-1, ↑IRF5, ↑phosphorylation of kinases, namely IRAK4, TAK1, IKKα, ERK, P38 & JNK	In-vitro	25 µg/mL	[86]
CVG	*C. versicolor*	↑IFN-α and -γ ,↑ IL-2, 4, 6, 10 & 17A,	In-vitro	40-200 mg/kg	[236]
PSK with mAb	*L. edodes*	↑NK-cell, ↑IFN-γ, ↑cell killing effect	In-vitro, in-vivo	0-400 µg/mL 100 mg/kg	[237]
PBP	*L. edodes*	↑TNF-α, ↑IL-1β, ↑IL-6 mediated lymphocyte proliferation ↓ MCF-7 cell growth	In-vitro	100 and 300 µg/mL	[238]
Chitosan	Numerous fungi	↑G1/S cell arrest	In-vitro	800 µg/mL	[59]

CPA, cyclophosphamide; CVG, natural anticancer glucan; CVPs-B, *C. versicolor* polysaccharide-B; EPS, exopolysaccharide; GF9801; anti-tumor polysaccharide fraction; GFP-A, neutral α-polysaccharide; GFPBW2, homogenous polysaccharide; KS-2, a new antitumor polysaccharide, extracted from culture mycelia of *L. edodes*; K5PS, O-sulfated polysaccharide; LEP, *L. edodes* polysaccharide; mAb, trastuzumab monoclonal antibody; MPSs, mucopolysaccharidoses; PBP, protein-bound polysaccharide; PSK, polysaccharide Krestin; PSP, polysaccharopeptide; REPS, rhizobium exopolysaccharide; RPSP, a refined polysaccharide peptide; Se-GP11, selenium polysaccharide; Se-Lentinan, selenium containing lentinan; S-GAP-P, chemically sulfated polysaccharide derived from water-insoluble polysaccharide; S-GFB, sulfated polysaccharide; SLMs, solid lipid microparticles; SLNT, a water-extracted polysaccharide; SPCV, small polypeptide from *C. versicolor*; Sul-GFPW, sulphated derivative of water soluble polysaccharide; WEP, water-extracted polysaccharide;

2058 Table 3. MPs-based micro/nanobiomaterials for anticancer application

Biomaterial	MP	Carrier drug/agent	Size (nm)	Cancer type	Mechanism of action	Model	Doses	Ref.
Ps/miR-181a NPs	PL	miRNA-181a	20–50	Leukemia	↑Imatinib mesylate sensitivity ↓RALA (V-ral simian leukaemia viral oncogene homolog A, ↓ras	$CD34^+$ cells	1.2-3.6 µg/mL	[162]
PPAA-p53	PL	Ascorbic acid p53	150	Glioma	↑Collagen synthesis ↓Metastasis	C6 cells	PPAA3:p53 (4:1)	[239]
CP-SUPA	PL	Cisplatin	-	Liver Lung	↑Cell killing effect, ↑apoptosis, ↑cell cycle arrest ↓Tumor growth	HepG2 and A549 cells Balb/c mice	0-200 µmol/L 3.5-30 µmol/kg	[240]
MTX-PL/PBAE/pEGFP NPs	PL	Methotrexate and plasmid DNA	< 200	Liver	↑Cell killing, ↓hepatoma development	HepG2 cells Balb/c nude mice	MTX-PL/PBAE/pEGFP in the ratio of 20:50:1	[178]
ADR-URPA NPs	PL	Adriamycin	157	Breast	↑pH-dependent release and accumulation of ADR in MCF-7 nucleus	MCF-7 and ADR cells	0.01-100 µg/mL	[153]
5-Fu@AuNPs-Fa	PL	5-Fu	71	Liver	↑Cell killing effect and accumulation in liver	HepG2 cells	3.2-208 µg/mL	[241]
rCHP/DOX NPs	PL	DOX	80 and 160	Liver	↑Cell growth inhibition, accumulation and internalization in tumor site	HepG2 cells Balb/c nude mice	0.0001-10 µg/L 10-40 mg/kg	[127]
Spermine-PL/DNA NPs	PL	IL-2	230	Skin	↑Tumor growth inhibition	MSC-IL-12 cells C57BL/6 mice	10-40 µg/mL	[166]
PPEICD NPs	PL	Methotrexate and p53	100-300	Liver Colon	↑Apoptosis, liver targeted drug delivery ↓Multidrug resistance problem	HepG2 and C6 cells	1-5 µM	[179]
6AC-iRGD/siRNA NPs	CU	siRNA Plk1	30 -70	Liver	↓Polo-like kinase	HepG2 and GES-1 cells	10-120 µg/mL	[242]
CTOL-GFP-pDNA NPs	CU	GAPDH	80	Liver	↑Transfection efficiency	HepG2 cells	10-100 µg/mL	[243]

CTL-PEG-FA/Bcl-2 siRNA NPs	CU	Bcl-2 siRNA	240	Liver	↑Apoptosis	HepG2 cells Female BALB/c nude mice	4-100 µg/mL 0.3 mg/kg	[244]
CUVa mediated siSTAT3 NPs	CU	siSTAT3	60-80	Liver	↑Apoptosis	HepG2 cells mouse melanoma B16 cells	10-140 µg/mL	[157]
siRNA-decorated and CS modified-PLGA NPs	CS	STAT3-siRNA and flurbiprofen	194-210	Lung Breast	↑Apoptotic cell death	A549, MDA-MB-231 and MCF-7	2.5-20 µg/mL	[160]
CHI-g-PEI mediated Akt1 siRNA NPs	CS	Akt1siRNA	150	Lung	↑Apoptosis	A549 cells	5-150 pMol	[245]
FC-g-PEI/shRNA complexes	CS	Akt1 ShRNA	<80	Lung	↑Apoptosis ↓Metastasis, ↓proliferation	A549 cells C57BL/6 mice	5-50 µg/mL 2.8 mg/kg	[158]
ChNPs /siRNA/DOX/CMD	CMD CS	DOX, and Snail siRNA	172	Colorectal	↑ E-cadherin, ↓ MMP-9, ↓vimentin proliferation, ↓malignancy, ↓metastasis	HCT-116 cells	2.5 µg/mL	[246]
CU-based Curimi polymers	CU	siRNA Plk1	85–105	Cervical Liver	↑Cellular uptake and silence the plk1 gene	HeLa and HepG2 cells	20-120 µg/mL	[247]
UCPA-1	PL	DOX	150 - 300	Breast	↑Cell killing	MCF-7 cells	5-100 µg/mL	[124]
CA4/MTX-URPA NPs	PL	MTX and CA4	187	Liver	↑Anti-angiogenic, ↑anti-tumor	HepG2 cells PLC/PRF/5-bearing nude mice	0-250 µg/mL 3-5 mg/kg	[86]
FA-MP-DOX/PDTC+DOX NPs	PL	Pyrrolidinedithiocarbamate and DOX	152	Lung	↑Cellular uptake, ↑cytotoxicity	A2780/DOX resistant cells	2 µmol/L	[130]
PA-PTFE	PL	Gemcitabine	-	Colon	↑Tumor regression	CT-26 cells CT-26 colon cancer bearing BALB/c mice	0.05-5 µg/mL 0.5 mg/kg	[248]

(NH2 PEG)-Pull-(Cyst-DOX) and (FA-PEG)-Pull-(Cyst-DOX)	PL	DOX	150 and 100	Breast	↑Cell killing, ↑blood stability	MCF-7 cells	IC_{50}=1.2 mu M and 3.1 mu M (MCF-7 cells) & 1.8 mu M and 1.1 mu M (KB cells)	[249]
FPA/EPI NPs	PL	Epirubicin	261	Skin	↑Cell killing	KB cells	0.01-10 mg/L	[123]
PUL-DO/bHis78 nanogels	PL	N-alpha-Boc-L-histidine and DOX	< 140	Breast	↑Cell killing	MCF-7 cells	1.2 μg/mL and 1 ng/mL to 10 μg/mL (DOX)	[250]
FA-CHP	PL	DOX	20–30	Skin	↑Cytotoxicity ↓Tumor volume	KB cells BALB/c nude mice	5 mg/L CHP 200 & DOX 2mg/kg	[32]
CHM-HER2	Cholesteryl group-bearing mannan	HER2 protein	20-30	Fibrosarcoma	↑Production of IgG antibodies against HER2	CMS7 and CMS 17 cells BALB/c mice	400 μg/mL	[251]
PL/FO-Pheo-A nanogel	PL	Pheophorbide-A	170	Cervical	↑Apoptotic cell death	HeLa cells Balb/C-nu mice	IC_{50} < 0.25 μg/mL	[31]
C-CCM/siRNA NPs	CS	Curcumin and siRNA	165	Lung	↑Clathrin-mediated endocytosis of siRNA	A549	100 μg/mL	[252]
TAT-TMC-TC-SPIONs	CS	HIF-1α and CD73 axis	133	Colon Breast Ovarian	↓VEGF, ↓FGF, ↓TGF-β, ↓angiogenesis	CT26, 4T1, and B16-F10 cells	50-100 μg/mL	[174]
CGO-TMC-HA NPs	CS	Hypoxia-inducible factor and Dinaciclib	95	Breast Colon Ovarian	↓MMP9, ↓MMP2, ↓Metastasis	CT26, 4 T1, and B16- F10 cells	0.5 mg/mL	[253]
TMC-CMD	CS CMD	STAT3 and BV6	105	Breast Colon Ovarian	↓VEGF, ↓FGF, ↓TGF-β, ↓angiogenesis ↓IL-10, ↓HIF, ↓cell migration, ↓colony formation	CT26, 4 T1, and B16-F10 cells	34.5 μM, 39 μM, and 9.5 μM	[171]

HA-PCL NPs	CS	anti-IL-6 siRNA and BV6	100	Breast Colon	↓Angiogenesis, ↓tumor growth	4T1 and CT26 cells	0.5 mg/ml	[172]
HA-TAT-TMC-TC NPs	CS HA	STAT3/PD-L1 siRNA	110	Melanoma Breast	↓VEGF, ↓FGF, ↓TGF-β, ↓angiogenesis	B16-F10 and 4T1 cells	80 pM siRNA	[169]
SPION-TMC-HA NPs	CS HA	HIF-1α, EP4 and antagonist (E7046)	126.9	Breast Ovarian	↓ Proliferation, Migration, Invasion, Angiogenesis, and Colony formation ↓ ki-67, Bcl-2, VEGF, FGF, TGF-β, MMP-9 and MMP-2	CT26, 4T1 and B16-F10 cells	20-40 nM	[254]
DOX-IL17RB siRNA-CMD-ChNPs	CMD CS	DOX, IL17RB siRNA	114	Breast	↓ Bcl-2, NF-kB	MDA-MB361 cells	6.5 μg/mL	[177]
CD73-siRNA-loaded ChLa NPs	CS	CD73-siRNA	100	Breast	↓ CD73	4T1 cells	25 nM	[159]
PEG-grafted CSNPs	CS	anti-catenin siRNA	100–150	Colon	↓Catenin expression	HCT-116 cells	100 pmol/μL	[255]
psi-Pgp-tGC NPs	CS	P-glycoprotein-targeted poly-siRNA	200-300	Breast	↓P-glycoprotein ↓Sanitize cancer cells	Adriamycin-resistant cancer cells	5 nM	[256]
HA-TMC NPs	HA CS	IL-6 and STAT3	110	Breast Colorectal Ovarian	↓Cancer cell progression, ↓angiogenesis, ↓migration	4T1, CT26 and B16-F10 cells	20 μg/mL	[257]
ALG-TMC NPs	ALG CS	S1PR1 and GP130	110	Breast Ovarian Colorectal	↓HIF-1α, ↓IL-6, ↓SOCS3	4T1, B16-F10 and CT26 cells	30 μg/mL	[19]
CS-HA NPs	CS HA	Bcl-2	100-120	Bladder	↓Bcl-2	T24 cells	5 μg/mL	[29]
PCA NPs	CS	A2AR and CTLA-4	72	Breast Colorectal	↓PKA, ↓SHP2, ↓PP2Aα	4T1 and CT26 cells	80 μg/mL	[258]
mPEGOSC	CS	PTX	104 – 111		↑Targeted efficiency of drug	Sprague–Dawley (SD) rats	10 mg/kg	[259]

MSN-APTES-CS NPs	CS	Methotrexate	75	Breast	↓Proliferation of breast cancer cells	MCF7	0.5 μM	[28]
FA-CL NPs	CS	CD73-siRNA and dinaciclib	147	Breast Colorectal Ovarian	↓Survivin, ↓XIAP, ↓Bcl-2	CT26, 4T1, and B16-F10 cells	10 μg siRNA and 40 mg/ kg dinaciclib	[260]
CS NPs	CS	Bcl-2 specific siRNA and DOX	301	Prostate	↓Bcl-2	PC-3	0.7 mg/kg of DOX and 1.2 mg/kg of siBcl2	[261]
PEG-PCL NPs	CS	A2AR-specific siRNA	100	Breast Ovarian Colorectal	↓PKA, ↓CREB ↑NF-κB, ↑p65	4T1, B16-F10 and CT26 cell lines	80 μg/mL	[262]
CS-based plumbagin microspheres	CS	Plumbagin	106.35	Melanoma	↓Tumor growth, ↓systemic toxicity	B16-F10 bearing C57BL/6J mice	6 mg/kg	[263]
CPT-TMC NPs	CS	Camptothecin	30-50	Melanoma	↑Intertumoral apoptosis ↓Intertumoral angiogenesis	B16-F10 bearing C57BL/6J mice	2.5 mg/kg	[147]
GO–CMC–FI–HA	CS HA	DOX	30	Cervical	↑Sustained drug release	CD44 over-expressed HeLa cells	4 μM	[264]
ATRA-mPEG-CS NPs	CS	All-trans retinoic acid	100	Colon	↑Apoptosis	CT-26 cells	10 and 20 μg/mL	[148]
RGD-HGC NPs	CS	RGD peptide	230	Ovarian	↓Angiogenesis	B16-F10 bearing C57BL/6J mice	10 mg/kg	[150]
CNA	CS	5-aminolaevulinic acid	100	Colon	↑Fluorescent endoscopic detection	Caco-2 cells	0.5 mg/mL	[180]
GC-DOX	CS	DOX	250	Mesothe-lioma	↑Anti-tumor effect	II45 cells	10 mg/kg	[265]
Pluronic F127- DOX CS NPs	CS	DOX	250-300	Breast	↑Anti-tumor effect	MCF-7 cells	10, 5 mg/kg	[266]
CS-NPs/NAR	CS	NAR	447	Lung	↓Cell proliferation	A549 cells	0.5 mg/mL	[267]

CLCs NPs	CS	CUR	197	Cervical	↑Apoptosis	HeLa cells	90-200 µg/mL	[268]
ALG-CS-PF127 NPs	ALG CS	CUR	100	Cervical	↓Cell proliferation	HeLa cells	14.34 µM	[269]
$CaCO_3$(CMC)/CS-ALG NPs	CS ALG	DOX	3 -14	Live	↑Apoptosis	HepG2	2 mg/kg	[270]
Cyclophosphane and 5-Fu loaded-ALG microparticles	ALG	Cyclophosphane and 5-Fu	-	Cardiac	↑Antitumor property	Malignant rhabdomyoma strain injected rat	1.7mg/100 g	Lin, and Fu et al., 2009
Gem-CsM NPs	CS	Gem	4	Breast	↑Antitumor property	MCF-7 and SKBR-3 cells	1.5 and 4.8 µM	[149]
CS entrapped DEX–DOX NPs	CS	DOX	100	Tumor cells	↑Anti-tumor efficacy	J774A.1 macrophage bearing Balb/c mice	15 mg/kg	[271]
ART-CSM NPs	CS	ART	349-446	Breast	↑Cell membrane shrinkage, ↑pyknotic bodies formation, ↑DNA fragmentation	4T1-breast tumor-bearing BALB/c mice mode	16.25 µg/mL	[272]
CS-AuNPs	CS	Au	3-10	Cervical Breast	↑Caspase-dependent cell death, ↑ROS production	HeLa, MCF-7 and PBMC	100 µM	[273]
PEG-CS/siRNA	CS	Survivin	100	Breast	↑Apoptosis	4T1 cells		[161]
GX1-DGC-DCT	CS	DCT	151	Glioma	↑Nuclear shrinkage and fragmentation	co-HUVEC cells	100 µM	[106]
PTX-NPs-PEG-Tf	CS	PTX	341	Lung	↑Pharmacokitenics	HOP-62 cells	0.3 µM	[119]
CS-TPP/IL-12	CS	IL-12	200	Colon	↑Infiltration of NK cells ↓CRC hepatic metastasis	CT26 cells Balb/c mice	0.2 µg	[143]
CENP	CS	CUR	235	Gastric	↑Apoptosis	MKN45 cells	3.4 µM 12.8 µM	[138]
PTX-loaded PLGA NPs	CS	PTX	200–300	Lung	↑Cytotoxic effect	A549 cells Lung-metastasized mice	10-40 µg/mL 10 mg/kg	[274]

Cet-PTX NPs/Cet-QUE NPs	CS	PTX and QUE	290	Lung	↑Cytotoxicity in cancer cells, ↑pAkt, ↑pERK ↓Tumor growth	A549 and A549/Taxol cells	2-16 μg/mL 10-80 μg/g	[276]
siRNA@CS-HAD NPs	HA CS	Bcl-2-targeted siRNA	100	Bladder	↑Targeted delivery in T24 cells and accumulation capacity of drug	T24 and 5637 cells	25-400 μg/mL	[29]
SNB-CS-NPs	CS	SNB	< 200	Breast	↑Sustained release	In vitro drug release assay	2-10 μg/mL	[277]
cRGD CS-Au NPs	CS	SNB	50	Breast	↓Tumor vasculature	MCF-7 and HUVEC cells	0.5-20 μM	[278]
5FU-CS NPs	CS	5-FU	324	Cervical	↑Antineoplastic activity, ↑ROS production, ↑apoptosis	HeLa cells	50-100 μM	[279]
5-FU-loaded CS–protamine NPs	CS	5-FU	116	Lung Cervical	↑Cytotoxicity, ↑apoptosis ↓Tumor growth	A549 and HeLa cells	3.75-35 μg/mL 5-Fu at 1.6 mg	[280]
HA–CH–IRN/5-Fu NPs	CS HA	5-FU and IRN	153.8	Gastric	↑Cytotoxicity ↓Tumor volume	MGC803 cells BALB/c nude mice	0-0.5 μM	[281]
5-FU-CS NPs	CS	5-FU-Hase enzyme	151-778	Colon	↑Cytotoxicity	HCT-116 cells	4-15 μM	[282]
5-FU-loaded CS NPs	CS	5-FU	320	Lung	↑Cytotoxicity	A375 cells	200 μg/mL	[283]
5-FU+DOX@CMC NPs	CS	5-Fu and DOX	112	Breast	↑Oxidative stress, ↑DNA fragmentation	MCF-7 cells	15-33.8 μg/mL	[284]
GC-FU/miR-122 NPs	CS	Liver-specific miRNA-122 and 5-Fu	100	Liver	↑Apoptosis ↓Proliferation of cells, ↓ADAM17, ↓Bcl-2	HCC and L02 cells	0.125-1 gm/L	[285]
CS-chondroitin NPs	HA	5-FU and nitroxoline	245	Liver	↑Cytotoxicity ↓Metastasis	HepG2 cells	3.31 to 0.17 μg/mL	[286]
Anti-HER2 conjugated OCP copolymer NPs	CS	DOX and anti-HER2 monoclonal antibody	< 49	Breast	↑Cytotoxicity	MCF-7 cells	0-10 mg/mL	[287]
DOX-loaded CS/ALG NPs	CS ALG	DOX	300	Ovarian	↑Cytotoxicity ↓Cell viability, ↓melanoma tumor growth	B16-F10 & B16-OVA Female C57B6 mice	1-100 μM 3 mg/kg	[288]

DOX@Cts-MS NPs	CS	DOX	440	Breast	↑Cell killing, ↑apoptosis, ↑cellular uptake	MCF-7 cells	0-100 µg/mL	[289]
Ce6-CS NPs	CS	Ce6 and DOX	90–130	Breast	↑Antiproliferation	MCF-7 cells	0-110 µg/mL	[290]
CPP-CS-co-PNVCL NPs	CS	Cell penetrating peptide and DOX	< 200	Breast	↑Life span ↓Tumor volume	MCF-7 & HUVEC cells BALB/c mice	0.001-10 µg/mL 7.5 mg/kg	[291]
D@HRGF NPs	CS	DOX	540. to 674.9	Lung Breast	↑Antitumor activity, ↑drug release under hypoxic condition	A549 & MCF-7 cells Athymic nude mice	0-100 µM 20 mg/kg	Jang et al., 2020.
DOX-CS-NPs	CS	DOX	300–550 nm	Cervical	↑Apoptosis, ↑G2/M, ↑S phase cell arrest	HeLa tumor cells	2-5 µg/mL	[292]
HA-GC-DOX/CXB	HA CS	DOX and CXB	150	Lung	↑Cytotoxic effect, ↑pH-dependent drug release ↓Tumor growth	PC-9, NCI-H1650-Luc & A549-Luc cells NSCLC xenograft mice	10 µg/mL 0.5-1.25 mg/kg	[293]
CMC-g-PA NPs	CS	DOX	274	Liver	↑Cellular uptake	HepG2 cells Wistar rat	5 mg/kg	[294]
CCM/CS/R-D NPs	CS	Ca_2^+ channel siRNA and DOX	122	Cervical	↑G0/G1 event arrest	HeLa and NIH3T3 cells tumor xenograft mice	2-50 µM 10−250 nM	[295]
LCN-TAM	CS	TAM	285	Breast	↑Cytotoxicity, ↑cellular uptake of TAM	MCF-7 cells Caco-2 cells	0-120 mg	[296]
pH-responsive drug delivery of CS NPs	CS	TAM	100–150	Breast	↑Apoptosis, ↑pH-dependent drug delivery, ↑anticancer effect	MCF-7 cells	0-60 µg/mL	[297]
CS-PA-grafted TAM polymeric micelles	CS	TAM	67 & 84	Breast	↑Cytotoxicity	MCF-7 cells	1 and 10 µg/mL	[298]
TAM-micelles	CS	TAM	81.48	Breast	↑Cytotoxicity	MCF-7 cells	9.8 µg/mL	[299]

TAM-PL	CS	TAM	169.66		↑Antitumor effect ↓Pgp efflux	Female Sprague Dawley rats	10 mg/kg	[300]
CGNCs	CS	TAM	232 & 248	Breast	↑Cytotoxicity	MCF-7 cells	10-60 µg/mL	[301]
HA-GEM/CH-Pt NPs	CS	GEM	187	Lung	↑Cytotoxicity, ↑antitumor effect	NCl-H460 cells BALB/c mice	5 mg/mL	[302]
LPHNP	CS	CUR and cisplatin	225	Ovarian	↑Cytotoxicity	A2780 cells	1.6-12.4 µg/mL	[303]
HA-CS-nanoCAP	CS	Cisplatin	193	Lung	↑Cytotoxicity, ↑CD44 receptors specific drug delivery, ↑pH-responsive drug release	A549 cells	0-3 µM	[304]
PTX/GNCP-ES	CS	PTX	110–180	Breast	↑Cytotoxicity, ↑apoptosis, ↑tumor inhibition	MCF-7 cells BALB/c nude mice	0.1-5 µg/mL 10 mg/kg	[275]
1,3β-Cs-PTX-NPs	CS	PTX	113	Glioma	↑Cytotoxicity	LN18 and C6 cells	0.39-12.5 ng/mL	[305]
PTX-CHN	CS	PTX	200	Lung	↑Cell proliferation, ↑apoptosis	A549 cells	5-500 µg/mL	[192]
PTX-CS-NP-10	CS	PTX	227	Breast	↑Cell proliferation, ↑apoptosis	MDA-MB-231 cells	0.156 -160 µM	[306]
DTX + PSS/DOXO-coated GNRs@HSA/CS hybrid NPs	CS	DTX and DOX	310	Breast	↑Cytotoxicity	MDA-MB-231 cells	0.0572 µM	[307]
DTX-Ag-NCPs	CS	DTX	190	Breast	↑Cytotoxicity	MDA-MB-231 cells	0-200 µg/mL	[308]
DTX-NPs	CS	DTX	158	Breast	↑Cytotoxicity, ↑oral bioavailability	MDA-MBB-231 cells	0.58 µg/mL	[309]
GX1-DGC-DCT NPs	CS	DTX	151	Glioma	↑Cellular uptake, ↑tumor inhibition	co-HUVEC cells BALB/c mice	25-200 µM	[310]
DTX-TPGS-g-CS-Trastz-NP	CS	DTX and trastuzumab	126-186	Breast	↑Cytotoxicity	SK-BR-3 cells	0.025- 25 µg/ml 7.5 mg/kg	[311]

PY-CS-PLA/PTX	CS	PTX	165	Colon	↑Antitumor activity, ↑oral bioavailability ↓Toxic effect	Caco-2 cells Heps tumor-bearing mice	20 mg/kg	[312]
PTX-CH-loaded LCS_NPs	CS	PTX	143	Breast	↑Apoptosis, ↑antitumor effect ↓Cancer growth, ↓metastasis	4T1 cells BALB/c mice	0.01-5 µg/mL 5 mg/kg	[313]
PTX-loaded rBG-NPs	CS	PTX	400	Cervical	↑Cytotoxicity	HeLa cells	0-500 ng/mL	[314]
CUR@CS-MCM-41	CS	CUR	180	Glioma	↑Cytotoxicity	U87MG cells	5-30 µg/mL	[315]
CUR/FA-AmCS-TPP	CS	CUR	175	Colon	↑Cytotoxicity	LS174T cells	5-40 µg/mL	[316]
6-TG-CNPs/CUR	CS	CUR	262	Breast Ovarian	↑Cytotoxicity, ↑G2/M phase arrest, ↑apoptosis	MCF-7 and PA-1 cells	3.125-100 µM	[317]
CUR-SA-PLGA NPs	CS	CUR	100–200	Glioma	↓Proliferation	U87MG cells	1 mg/mL	[196]
CMACPs	ALG CS	CUR	172–199	Breast	↑Cytotoxicity, ↑cellular uptake of the drug	MDA-MB-231 and HDF cells	0-30 µg/mL	[318]
CG-loaded CS/ALG NPs	ALG CS	CUR diglutaric acid	212 - 552	Colon Liver Breast	↑Anticancer effect, ↑cellular uptake of the drug	Caco-2, HepG2 and MDA-MB-231 cells	0.1-10 µg/mL	[319]
MTX-loaded FTC-NPs	CS	MTX	< 400	Cervical	↑Cytotoxicity, ↑cellular uptake of the drug	HeLa cells	0.1-10 µg/mL	[320]
MTX-loaded 5F/1C NPs	CS	MTX	300	Lung	↑Cytotoxicity, ↑apoptosis ↓Proliferation	A549 cells	180 µg/mL	[320]
MTX-PMX-PC NPs	CS	MTX and PMX	80	Lung	↑Antitumor activity, ↑intracellular uptake of the drug	A549 and LLC cells	0.05-500 µg/mL	[167]
MTX@AuNCs-CS-AS1411	CS	MTX and nucleolin targeting AS1411 aptamer	190	Lung	↑Anticancer effect, ↑accumulation of drug at tumor site ↓Tumor growth	A549 cells BALB/c mice	10-800 µg/mL 10 mg/kg	[321]

CLCs NPs	CS	CUR	197	Cervical	↑Lactate dehydrogenase activity, ↑cellular uptake ↓Lower ATP	SiHa, CaSki and HeLa cells	24 μM	[322]
CUR/FCt-NPs	CS	CUR	115	Lung	↑Apoptosis ↓Cell viability	HCT-116 and A-549 cells	150 μM	[323]

1,3β-Cs-PTX-NPs, 1,3β-glucan-paclitaxel loaded nano-structure; 5FU, 5-fluorouracil; 6-AC, 6-amino-6-deoxy curdlan; 6-TG , 6-thioguanine; ADR-URPA NPs, adrinomycine-loaded O-urocanyl pullulan NPs; ALG, alginate; AmCS, aminated chitosan; APTES, 3-aminopropyl) triethyoxysilane; APTES, 3-aminopropyl) triethyoxysilane; ART-CSM NPs, artemisinin-loaded CS magnetic NPs; ATRA, ll-trans retinoic acid; ATRA, ll-trans retinoic acid; AuNPs, gold NPs; bHis, nalpha-Boc-L-histidine; CA4, combretastatin A4; CAP, cyclophosphamide, doxorubicin and cisplatin; C-CCM/siRNA, siRNA/curcumin loaded NPs; CCM/CS, cancer cell membrane modified silica NPs; Ce6, chlorin e6; Ce6, chlorin e6; Cet, cetuximab; CG, curcumin diglutaric acid; CGNCs, chitosan-gellan nanocapsules; CGO, carboxylated graphene oxide; CHI-g-PEI, chitosan-graft-polyethylenimine; ChLa, chitosan lactate; CHM, cholesteryl group-bearing mannan; ChNPs, chitosan nanoparticles; CHP, cholesteryl group-bearing pullulan; CHP, cholesteryl pullulan; CLCs, cholesteric liquid crystals; CLCsNPs, curcumin loaded chitosan NPs; CMACPs, CUR loaded magnetic alginate/chitosan layer-by-layer NPs; CMC, carboxymethyl chitosan; CMC-g-PA, carboxymethyl chitosan-g-poly(acrylate); CMD, carboxymethyl dextran; CNA, click nucleic acid; CNA, click nucleic acid; CPP, cell penetrating peptide; CP-SUPA, cisplatin-pullulan monosuccinate; CPT-TMC, Camptothecin encapsulated N-trimethyl chitosan; cRGD, cyclic arginylglycylaspartic acid; CS, chitosan; CS-MCM-41, chitosan-capped MCM-41; CS-NPs/NAR, chitosan encapsulated naringenin NPs; CS-NPs/NAR, chitosan encapsulated naringenin NPs; CTL, curdlan with trilysine; CTOLs, lactosylated curdlan-triornithine nanocarriers; Cts, chitosan; CU, curdlan; CUR, curcumin; CUVa, curdlan derivatives; CXB, celecoxib; D@HRGF, DOX-loaded hypoxia-responsive glycol CS NP conjugated with FA; DCT, docetaxel; DCT, docetaxel; DEX, dextran; DGC, glycol chitosan; DGC, N-deoxycholic acid glycol chitosan; DOXO-GNRs, doxorubicin-modified gold nanorods; DTX-TPGS-g-chitosan, docetaxel-loaded D-α-tocopherol polyethylene glycol 1000 succinate conjugated CS NPs; F/C, fucoidan/chitosan; FA, folate; FC-g-PEI, folate-chitosan-graft-polyethylenimine copolymer; FCt, fungal chitosan; FI, fluorescein isothiocyanate; FPA/EPI NPs, folate-modified pullulan acetate NPs; FTC, folate redox-responsive chitosan; GA, glycyrrhetinic acid; GC, glycol chitosan; GC, GEM, gemcitabine; GEMs, genetically encoded multimeric NPs; GO, graphene oxide; GX_1, a gastric cancer angiogenesis marker peptide; HAD, hyaluronic acid dialdehyde; Hase, hyaluronidase; HER2, erbB-2/neu/HER2; HGC, 5beta-cholanic acid; HGC, 5beta-cholanic acid; HIF, hypoxia inducible factor; HSA, human serum albumin; IRN, irinotecan; LCN, lecithin/chitosan NPs; LPHNP, lipid-polymer hybrid NPs; MP, maleilated pullulan; mPEGOSC, PEG-modified *N*-octyl-*O*-sulphate chitosan micelles; MSN, mesoporous silica nanoparticle; MSN, mesoporous silica nanoparticle; MTX, methotrexate; MTX, methotrexate; OCP, O-succinyl chitosan graft pluronic F127; PA, palmitic acid; PA, pullulan acetate; PBAE, poly(β-amino) ester; PC, stealth nanocarriers; PCA, protocatechuic acid; PCL, polycaprolactone; PCL, poly-ε-caprolactone; PDTC, pyrrolidinedithiocarbamate; PEG, Poly (caprolactone); PEG, Poly (caprolactone); PEG, polyethylene glycol; pEGFP, plasmid DNA expressing green fluorescent protein; PF127, pluronic F127 (protein grade detergent); pgp, P-glycoprotein; Pheo-A, pheophorbide-a; PLGA, poly (lactic-co-glycolic acid); plk1, polo-like kinase; PMX, pemetrexed; PNVCL, poly(N-vinylcaprolactam); PPAA, pullulan–PEI–ascorbic acid; Ps, spermine-introduced pullulan; psi-pgp, Pgp-targeted poly-siRNA; PSS, poly(sodium-4-styrenesulfonate); Pt, platinum; PTFE, polytetrafluoroethylene; PTX, paclitaxel; PTX/GNCP-ES, paclitaxel-loaded estrone-modified glycol chitosan NPs; PTX-CH-loaded LCS_NPs,

paclitaxel–cholesterol complex-loaded lecithin–CS NPs; PTX-CHN, paclitaxel chitosan NPs; PUL-DO, pullulan-deoxycholic acid; PY-CS-PLA, a novel chitosan-based multifunctional NP; QUE, quercetin; rBG-NPs, reduced BSA and GC NPs; rCHP, reducible cholesterol-modified pullulan; RGD, a peptide; SA, sialic acid; SNB, sunitinib; SPION, superparamagnetic iron oxide; TAM, tamoxifen citrate; TC, thiolated chitosan; Tf, transferrin; tGC, thiolated glycol chitosan; TMC, trimethyl chitosan; TPP, tripolyphosphate; UCPA, pullulan derivatives