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Review

Mannose: Good player and assister in pharmacotherapy

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ABSTRACT

Mannose is a monosaccharide widely distributed in body fluids and tissues, especially in the nerve, skin, testicles, retina, liver and intestines. It is used to synthesize glycoproteins and participate in immune regulation. In recent years, mannose has been applied more and more widely in the biomedical context as people have a deeper understanding of its biological effects. This review introduces the use of mannose in treating various diseases (including cancer, urinary tract infections, type 1 diabetes, and diabetic wounds), preventing pancreatic fistula, and improving magnetic resonance imaging for acute pancreatitis. We also demonstrate that mannose has the potential for clinical applications.

1. Introduction

Mannose is a monosaccharide and its molecular formula is $C_6H_{12}O_6$. Mannose receptor is found on many cells, including macrophages and dendritic cells. Mannose receptor can induce these cells to uptake antigens [1]. By taking advantage of this, some studies have reported that nanoparticles (NPs) are modified with mannose to target macrophages or dendritic cells to activate the immune response [2,3]. Mannose is also combined with conventional chemotherapy for better efficacy by taking advantage of the feature that the transporters of mannose and glucose are the same on cancer cells [4]. Mannose can affect bacteria by combining with FimH protein, which is the type 1 pilus adhesin of *Escherichia coli* (*E. coli*) [5]. Several researchers have made use of these characteristics to develop drugs that can highly bind to FimH protein [6]. Mannose can also improve intestinal microecology and prevent obesity caused by high-fat diet [7]. Mannose has many medicinal functions (Table 1). This review introduces the recent progress of medicine studies on mannose and indicates the potential of mannose in clinical applications.

2. Mannose and anti-cancer

2.1. Mannose and chemotherapy

Gonzalez et al. [4] found that the glucose levels in tumor cells treated with mannose increased, but the rate of cell growth decreased. The mechanism is that mannose can accumulate in tumor cells in the form of mannose-6-phosphate which can inhibit hexokinases and phosphoglucose isomerase. These enzymes are involved in the first and second steps of glycolysis, respectively. Therefore, mannose can prevent glycolysis, affect the use of glucose by cells, and inhibit cell growth. To test whether other sugar had the same effect as mannose, they treated different types of tumor cells with mannose, galactose, fructose, fucose and glucose. The result showed that mannose can more effectively inhibit tumor cell growth than other sugars. When mannose was combined with cisplatin or doxorubicin to treat mice with tumors, the effect was better than with cisplatin or doxorubicin alone. Mannose enhanced the efficacy of conventional chemotherapy. In addition, they spotted that the sensitivity of different tumor cells to mannose depends on the levels of phosphomannose isomerase, and that tumor cells are more sensitive to mannose when phosphomannose isomerase levels are low.

Methotrexate (MTX) was originally used for the treatment of acute leukemia [8]. After years of exploration of this drug, there are studies showing that MTX combined with NPs and chemotherapy can tackle cancer [9–11] or treat rheumatoid arthritis [12–14]. Fan et al. [15] synthesized carrier-free NPs, MTX-Man NPs, which consist of MTX and mannose (Table 1). And mannose is linked to MTX by ester bonds, which lead to the hydrolysis of ester bonds between MTX and mannose when MTX-Man NPs enter lysosomes through endocytosis, thereby releasing MTX and killing tumor cells (Fig. 1). They also set up the

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Table 1
Mannose-modified drugs and applications.

Mannose-modified drugs	Characteristics	Application	References
MTX-Man NPs	Mannose is linked to MTX by ester bonds. Carrier-free nanoparticles.	Chemotherapy	Fan et al. J Mater Chem B (2020)
BTM-NMs	Three-arm are conjugated with mannose. In combination with Tween 80.	Photodynamic therapy	Zhang et al. Chemistry (2017)
MSN-M6C-Man	M6C-Man is a compound with a mannose residue.	Photodynamic therapy	Bouffard et al. Int J Mol Sci (2019)
NP-R@M-M	Load with a receptor agonist and coating with cancer cell membranes.	Immunotherapy	Yang et al. ACS Nano (2018)
Multi-walled carbon nanotubes	Unique physical and chemical properties.	Immunotherapy	Dong et al. ChemistryOpen (2019)
M4284	100,000 times higher affinity for FimH protein than mannose.	Remove or kill *E. coli*	Spaulding et al. Nature (2017)
Man-PEI CPs	Less cytotoxicity to cells while higher selectivity to *E. coli*.	Remove or kill *E. coli*	Liu et al. Langmuir (2018)
KSiNPs	Promote the transformation of M1 macrophages into M2 macrophages	Accelerate wound healing	Gan et al. Biomaterials (2019)
M-Gd-NL	Enhance macrophages to uptake Gd-DTPA.	Improves ability of MRI to image acute pancreatitis	Tian et al. Int J Nanomedicine (2017)

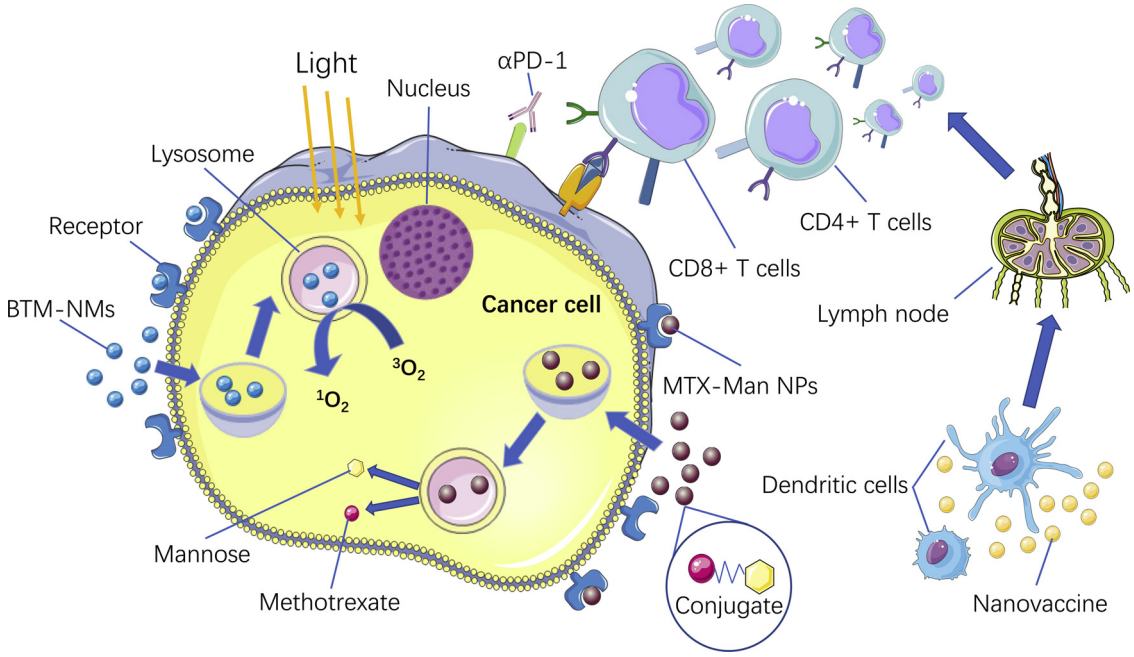

Fig. 1. The cancer uptake BTM-NMs into the lysosome, where 1O2 is produced under certain wavelengths of light. MTX-Man NPs enter the lysosome and hydrolyze into mannose and methotrexate. Dendritic cells uptake nanovaccine and migrate to lymph nodes to differentiate the naive T cells into CD4+ and CD8 + T cells.

experiments on mice and found that MTX-Man NPs treated McF-7 tumor-bearing nude mice better than MTX or mannose alone. Under fluorescence microscopes, more MTX-Man NPs adhered to tumor cells. This means that MTX-Man NPs may be a more effective option on treating tumors.

In comparison to conventional chemotherapy, mannose or MTX-Man NPs combined with chemotherapy is safer, more effective and tolerated in the treatment of tumors. However, it is necessary to obtain a larger amount of experimental data and verify its safety in a human body before they can be used in the clinic.

2.2. Mannose's application in photodynamic therapy

Photodynamic therapy is a therapy that transmits the energy to oxygen molecules via a certain frequency of light irradiation on a photosensitizer and produces reactive oxygen species with cytotoxicity, thereby killing cancer cells [16] (Fig. 1). In recent years, to reduce the damage to normal cells in photodynamic therapy, the photosensitizer has been modified to improve the selectivity of the photosensitizer to cancer cells. Zhang et al. [17] synthesized a photosensitizer, BODIPY, which is modified with mannose (Table 1). And they assembled it with Tween 80 to form a kind of nanomicelles (BTM-NMs), making it stable in water. Then they treated MDA-MB-231 breast cancer cells, MDA-MB-231 cancer cells and ordinary MCF-10A cells with BTM-NMs. They found that MDA-MB-231 breast cancer cells with high expression of the mannose receptor and more BTM-NMs attached to their surface. Bouffard et al. [18] made use of the characteristics of the cation-independent mannose 6-phosphate receptor, which is overexpressed in prostate cancer cells. They linked dimannoside-carboxylate (M6C-Man) to mesoporous silica NPs (MSNs), whereas M6C-Man is a compound with a mannose residue, which enables MSNs to more actively target prostate cancer cells. They also established experiments *in vitro* and found that MSN-M6C-Man makes a better result compared to other drugs in inhibiting the growth of prostate cancer cells (Table 1). The mannose-modified photosensitizer improves selectivity to cancer cells, which could make photodynamic therapy safer and less harmful than conventional chemotherapy.

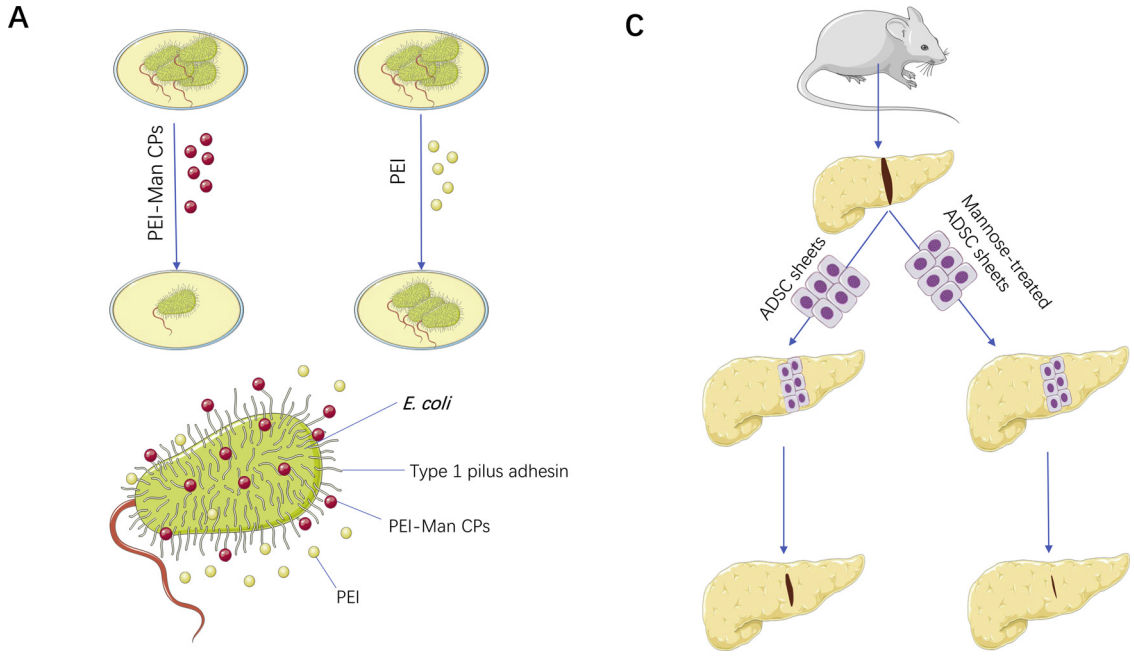

Fig. 2. (A) PEI-Man CPs has stronger damage and affinity for *E. coli.* (B) A 38.465mm2 wound is created on the back of the mouse. KSiNP can transform the M1-like macrophages into the M2-like macrophages and then M2-like macrophages release cytokines that reduce inflammation. (C) A section is created on the pancreas of mice.

2.3. Mannose-modified nanovaccine

Min et al. [19] utilized antigen-capturing NPs combined with radiotherapy to enhance killing tumor cells. The mechanism is that radiotherapy causes tumor cells to release antigens, then NPs capture antigens and present antigens to dendritic cells, which migrate to lymph nodes [20] and activate CD4 + T cells and CD8 + T cells. In combination with αPD-1, which can more effectively clear tumor cells (Fig. 1). To further improve the efficacy of NPs in the treatment of cancer, a few studies show that they modified NPs with mannose, which make use of the feature that the mannose receptor can induce dendritic cells to uptake antigens. Yang et al. [21] coated NPs with cancer cell membranes and loaded them with a receptor agonist, imiquimod (R837). Then they modified the NPs with mannose to produce a nanovaccine that would enhance the dendritic cells uptake of antigens. And abbreviation for this drug is NP-R@M-M (Table 1). Dong et al. [22] took advantage of multi-walled carbon nanotubes of the unique physical and chemical properties, they oxidized their surfaces, modified with mannose and loaded with ovalbumin (Table 1). In the experiments they set up, the new nano vaccine was able to promote the maturation of dendritic cells and induce an anti-tumor immune response.

We can see progress in the field of nanovaccine that from capturing antigens with NPs to load antigens onto mannose-modified nanomaterials. It is believed that nanovaccine will be one of the safer cancer treatment options.

3. Mannose and anti-bacteria

3.1. Mannose in combination with other drugs to treat urinary tract infection

Cranberry can inhibit urinary tract infection (UTI) caused by *E. coli* [23], and this effect is associated with cranberry which contains mannose. Russo et al. [24] divided 40 postmenopausal women who underwent cyst surgery into two groups in a 1:1 ratio. One group received two weeks of oral administration of nutrients containing cranberries, D-mannose and anti-inflammatory drugs, while the other group received no nutrients. Though the results showed that the women in the two groups scored almost no difference on the questionnaire, those receiving the supplements scored lower on the uncomfortable symptoms. Genovese et al. [25] divided 72 adult women with uncomplicated cystitis into three groups and treated them with a combination of mannose and drugs which derived from different plants. Group A was treated with berberine, arbutin, birch and D-mannose. Group B was treated with berberine, arbutin, birch, forskolin and D-mannose, and group C was treated with proanthocyanidins and D-mannose. After 12 weeks, the researchers spotted that all three combinations had positive effects on treating UTI. Milandri et al. [26] evaluated the effect of D-mannose, hibiscus sabdariffa, and lactobacillus plantarum on the prevention of urinary tract infection after urodynamic examination. And 100 adult women that underwent urodynamic were treated with D-mannose, hibiscus sabdariffa and lactobacillus plantarum. After 14 days of treatment, only 13 % of patient developed urinary tract infections. These studies suggest that mannose combined with other drugs can effectively treat urinary tract infections while reducing medical costs.

3.2. Mannose against E. coli

In fact, most UTIs are caused by uropathogenic *Escherichia coli* (UPEC) in the urinary tract [27]. UPEC adheres to the surface of the bladder by combining FimH protein with mannose [5]. Then UPEC multiplies, resulting in UTI. Spaulding et al. [6] made use of the feature that FimH protein can bind to mannose. They modified mannose to obtain mannoside (M4284), which has 100,000 times higher affinity with FimH protein than mannose (Table 1). They also fed mice with M4284 and spotted that the amount of UPEC in the gut and bladder of mice was significantly reduced. Polyethylenimine (PEI) is a highly cytotoxic compound. Liu et al. [28] modified PEI with mannose to make PEI more selective for *E. coli*. In their experiments, they found that the sterilization rate of mannose-modified polyethylenimine copolymer particles (Man-PEI CPs) were 100 % which were synthesized from PEI and mannose with a mass ratio of 100:36, while with the mass ratio of 100:0, the sterilization rate is only 10 % (Table 1). Furthermore, they treated Hela cells with Man-PEI CPs and PEI. Results showed that PEI was more harmful to Hela cells (Fig. 2A). This indicates that Man-PEI CPs have less cytotoxicity to cells while higher selectivity to *E. coli*.

Using mannose's ability to bind to FimH protein, we can develop a drug that can make *E. coli* slide off the bladder surface or kill *E. coli* while reducing *E. coli* resistance to antibiotics.

4. Mannose inhibits type 1 diabetes

Zhang et al. [29] found that D-mannose promotes the expression of the gene *Foxp3* in naive T cells and induces T cells to differentiate into regulatory T cells (Treg cells). They believe that the transforming growth factor-β (TGF-β) signaling pathway is the key to D-mannose inducing T cells to differentiate into Treg cells. To further understand the mechanism, the researchers cultured the naive T cells from mice with anti-TGF-β or SB431542 (an inhibitor of TGF-β receptor). The results showed that D-mannose did not increase the levels of *Foxp3* mRNA in T cells when blocking the signaling pathway with anti-TGF-β or SB431542. They also cultured human T cells and got the same results. Moreover, they established type 1 diabetes mice model and the airway inflammation induced by ovalbumin mice model. They added mannose to drinking water for mice and results showed that the number of islet cells increased in type 1 diabetes mice and the number of eosinophils reduced in airway inflammation mice. This suggests that D-mannose plays a positive role in both. Mannose induces T cells to differentiate into Treg cells, thereby reducing the harm done by immune cells, which provides a new treatment for patients with autoimmune diseases.

5. Mannose accelerates wound healing

Mannose can inhibit wound inflammation and reduce the number of neutrophils [30]. This may be related to the fact that mannose inhibits the synthesis of hyaluronic acid and the mechanism is that hyaluronic acid can be bound to CD44 receptor on neutrophils while mannose can deplete UDP-GlcNAc, which is the raw material of hyaluronic acid [31,32]. Jokela et al. [33] implanted a hollow sterile viscose fiber sponge tube under the skin of the mouse back, injected mannose solution of different concentrations into it and analyzed the liquid in the sterile viscose fiber sponge tube after a time. The number of neutrophils decreased as the amount of hyaluronic acid in the wound decreased. Gan et al. [34] modified NPs with mannose, konjac glucomannan-modified SiO2 (KSiNPs), which can accelerate the wound of diabetic mice as their previously study showed (Table 1). The mechanism is that the mannose modified NPs bind to the mannose receptor on macrophages and promote the transformation of phenotype M1 macrophages into phenotype M2 macrophages (KSiNPs form clusters on the M2 and activate the ERK signaling pathway, then M2 release cytokines: IL-10 and TGF-β. Thus, M2 has anti-inflammatory effects [35].) In the experiments, they created a 38.465 mm^2 wound on the back of the mice and treated mice with Konjac glucomann (KGM) or KSiNPs for 21 days. The results showed that mice treated with KSiNPs recovered the fastest (Fig. 2B). Using mannose to speed up wound healing may provide an effective treatment for diabetics whose wounds are difficult to heal.

6. Mannose improves ability of MRI to image acute pancreatitis

Acute pancreatitis (AP) is a disease whose extent is difficult to be diagnosed [36]. Studies have shown that the more severe the acute pancreatitis, more macrophages in the pancreas [37]. Tian et al. [38] developed a drug which can improve the ability of MRI to image AP (Table 1). They loaded gadolinium-diethylenetriaminepentaacetic (Gd-DTPA) in mannose modified liposomes (M-Gd-NL), which can target the mannose receptor on macrophages and induce macrophages to uptake, whereas Gd-DTPA is an imaging agent used in MRI [39,40]. Furthermore, they established varying degrees of AP mouse models and healthy mice models. Then these mice were injected with M-Gd-NL, scanned them with MRI at different time points. Result showed that serve AP mice Δ signal-to-noise ratio more than mild AP mice while healthy mice are minimal. Besides, they spotted that M-Gd-NL did not show toxicity in mice in the experiment. These findings indicate that M-Gd-NL may be a great choice to diagnose the extent of AP. This is significant in the clinical treatment of AP.

7. Mannose prevents pancreatic fistula

Pancreatic Fistula (PF) is a serious postoperative complication with a high incidence after pancreaticoduodenectomy [41,42]. Rupture of the pancreatic duct causes ulceration of the orifice of the fistula and dehydration in the patient, with a significant increase in the levels of amylase and lipase in the ascites. At present, treatments for pancreatic fistula include pancreaticojejunostomy [43], pancreaticogastrostomy [44], chemical substances blocking the pancreatic duct [45], and triple-drugs therapy [46]. Kaneko et al. [47] found a different approach to deal with PF. They cut off the pancreas of mice and adhered adipose-derived stem cell sheets (ADSC sheets) to the pancreas, whereas ADSC sheets were treated with mannose. They spotted that treated mice had significantly lower levels of ascites and serum lipase and amylase than untreated mice (Fig. 2C). Additionally, they found higher levels of fibroblast growth factor 2 (FGF2) in mannose-treated ADSCs while FGF2 can stimulate cell proliferation. This may explain mannose-treated ADSC sheets are more effective than ADSC sheets. This indicates that the treatment of pancreatic fistula with mannose-treated ADSC sheets is effective and has a broad prospect in clinical application.

8. Mannose prevents obesity caused by a high-fat diet

Sharma et al. [7] fed the weaned mice either a high-fat diet (HFD) or a normal diet (ND) and added mannose to their drinking water. Within 12 weeks of weaning, the weight of HFD mice was almost the same as ND mice, while HFD mice that did not add mannose to their drinking water gained weight in another set of experiments. They analyzed the serum and feces of HFD mice that drank water containing mannose, found that levels of glucose and insulin in their serum were close to ND mice. Additionally, the ratio between Bacteroidetes and Firmicutes in the gut of these mice increased. In other studies, the ratio of Bacteroidetes to Firmicutes in the intestines of obese mice or humans changed similarly [48–50]. Though mannose can increase the number of Bacteroidetes and Bacteroidetes can convert complex glycans to monosaccharides, glycosyl hydrolases are inhibited and there is higher fecal energy, which is probably why HFD mice that drink water containing mannose don't gain weight. In order to verify whether other sugar plays the same role as mannose, they added galactose to drinking water for HFD mice and the result showed that HFD mice were obese. Besides, they also spotted that adding mannose to drinking water for 3-week-old HFD mice helped prevent obesity, while mannose was added at 8-week-old, the mice remained obese. Although mannose can prevent obesity in HFD mice and increase the ratio between Bacteroidetes and Firmicutes in the gut of mice, its mechanism is still unclear and further exploration is needed.

9. Conclusion and perspectives

Mannose can interfere with the metabolic pathway of glucose, inhibit the growth of cancer cells, whereas mannose receptor induces endocytosis. People use these characteristics to develop drugs for different diseases. For instance, mannose-modified NPs can accelerate wound healing and kill *E. coli*, which is good news for diabetics. Mannose-modified nanovaccine and photosensitizer can enhance the efficacy of immunotherapy and photodynamic therapy while less harmful than traditional drugs. Although effects of mannose are exciting, there are still problems to be settled. For example, mannose was combined with chemotherapy to treat cancer but the effective dose in humans is unknown. The side effects of mannose in the treatment of urinary tract infections are unknown. Mannose-treated fat stem cell

tablets were used to treat pancreatic fistula in mice, but there were differences between human and mice in physiological structure. Thus, we need further investigation of mannose.

In summary, mannose as a monosaccharide, plays an important physiological role in living organisms. In the future, we will hope to find out more about the mechanism of mannose, so that mannose can play a more active and important role in clinical treatment.

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Declaration of Competing Interest

The authors declare that there are no conflict of interests.

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