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Article

1-Deoxymannose: Orally Active FimH Inhibitor for Targeted Therapy in the Human Urinary Tract

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Abstract: Background: FimH inhibitors are anticipated to serve as preventive therapeutics against urinary tract infections. Consequently, multiple inhibitors—predominantly D-mannose derivatives—have been synthesized, and their binding affinities (determined by dissociation coefficient; K_D) to FimH have been examined *in vitro*. Nonetheless, their preventive efficacy in humans, including those governed by the rate of delivery of orally administered drugs to the urinary tract and the K_D values. Therefore, this study aimed at investigating the post-ingestion FimH inhibitory effects of DM and D-mannose in the urinary tract. Six participants were administered single 1-g doses of the samples in a crossover test. The D-mannose analog, 1-Deoxymannose (DM), reportedly exhibits an identical K_D to FimH as D-mannose. **Methods:** To estimate the post-ingestion FimH inhibitory effects of DM and D-mannose in the urinary tract, six participants were administered single 1-g doses of the samples in a crossover test. The sample concentrations in urine were measured 8 h after ingestion. **Results:** DM levels increased rapidly after oral intake; contrarily, D-mannose was detected in the urine before administration with no notable increase post-ingestion. The peak concentration ranges of D-mannose and DM in urine were 2.15–22.9 $\mu\text{g/mL}$ and 665–57,804 $\mu\text{g/mL}$, respectively, which are 66.3–707 and 3,600–31,200 times that of K_D , respectively. **Conclusions:** These results indicate that DM as a supplement is an orally active FimH inhibitor with substantial efficacy in the human urinary tract. Conversely, D-mannose is expected to exert comparatively milder effects.

Keywords: 1-deoxymannose; 1,5-anhydro-D-mannitol; urinary tract infection; FimH

1. Introduction

Urinary tract infection (UTI) is a disease stemming from an urinary tract infection, such as the bladder, predominantly attributed to uropathogenic *Escherichia coli* (UPEC). The number of patients affected is second only to pneumonia, and large medical expenses are incurred worldwide. Furthermore, even if cured, over 50% of the patients experience recurrence within a year of recovery [1]. This is extremely high compared to the recurrence rate of pneumonia, which is 18.3%, and reduces the patients' quality of life [2]. Antibiotics are generally administered to treat this disease, but the overuse of antibiotics can result in the development of resistant bacteria, making antibiotics less effective. Occasionally, it is impossible to treat. As mentioned above, appropriate use of antibiotics for the treatment of diseases is needed worldwide, and there is a need to develop alternatives to antibiotics for disease prevention. D-mannose (Man) is sold as a supplement to prevent tract tract infections [3]. Orally ingested Man reportedly reaches the urinary tract and binds to the FimH protein of UPEC, inhibiting infection [4]. However, a recent study concluded that humans were ineffective in preventing tract tract infections [5]. Furthermore, in a human study in which people who had experienced recurrent urinary tract infections ingested 2 g of Man, 12 showed no increase in urinary Man in the first hour after administration, while 7 showed an increase. Compared to before intake, the increase rate was 1.468 ± 0.248 [6].

UPEC has FimH at the tip of its type 1 pili, which recognizes the Man residue at the end of the sugar chain in the bladder epidermis, attaches to it, and causes infection [1,7,8]. Substances that bind

to FimH are expected to bind to the fimbriae of UPEC and inhibit infection of the urinary tract, and various FimH inhibitors have been synthesized and their K_D values to FimH have been investigated [9]. However, the amounts of most of these synthetic compounds that reach the urinary tract after oral administration in humans have not been investigated. The functions required for a preventive agent against tract infections are that it is safe for humans, that it reaches the urinary tract when administered orally, and that its concentration in the urine is high enough to inhibit the adhesion of FimH and Man sugar chains to bladder epidermal cells.

1-Deoxymannose (DM), also called 1,5-anhydro-D-mannitol, is the C1-deoxyform of Man; therefore, DM is a Man analog [10]. DM is synthesized with hydrogenation of 1,5-anhydro-D-fructose (1,5-AF) produced from α -glucan with Pd/C as a catalyst or *Saccharomyces cerevisiae* enzymatically reduce 1,5-AF in medium and release DM and 1,5-anhydro-D-glucitol, C2-epimer of DM, to medium [11,12]. The K_D value of DM for fixing H has already been reported [13]. The values for DM are lower than those for Man; therefore, DM is expected to be a FimH inhibitor [9]. Here, we prepared crystals of DM samples for human trials and compared the urinary DM concentration after oral ingestion of DM and K_D to examine their potential as FimH inhibitors with orally intake.

2. Results

2.1. Preparation of Test Material and Purities

A 1,5-AF aqueous solution was prepared from starch by enzymatic degradation with a purity of 94.8%. Seventy percent of the 1,5-AF was converted to DM after Hydrogenation. The purity of the collected crystals of DM was determined to be 98.2% by the high performance liquid chromatography (HPLC) which was sufficient for use in a human trial. The purity of the male supplements was 100%.

As a result of analysis of X-ray diffraction data of DM, the crystal was orthorhombic (rhombic), with space group: P212121 (19), lattice constants: $a = 7.906 \text{ \AA}$, $b = 9.460 \text{ \AA}$, $c = 9.918 \text{ \AA}$, $\alpha, \beta, \gamma = 90^\circ$. The X-ray diffraction profile is shown in Figure 1, and the peak search results are presented in Appendix A (Table A1). When observed under an optical microscope, the crystals are orthorhombic (rhombic) and octahedral (Figure 2).

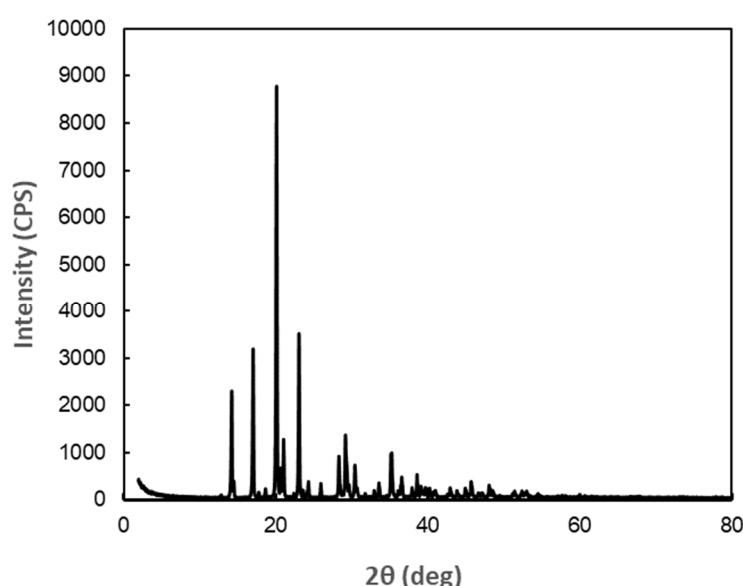


Figure 1. X-ray diffraction profile of 1-deoxymannose crystals.

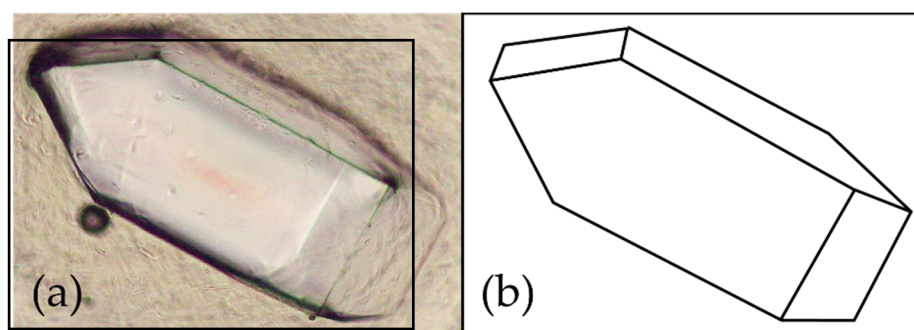


Figure 2. Crystal form of 1-deoxymannose. (a) Optical micrograph, (b) Model of crystal form.

2.2. Safety Analysis of DM

In a single oral gavage administration study of DM in mice, no deaths or abnormalities in general condition were observed in the DM-administered group, and no differences were observed between the control and DM-administered groups in body weight measurements 14 days after administration. Furthermore, no abnormalities were observed in the animals during necropsy. Based on the above results, it was determined that the LD₅₀ value of DM for female mice exceeds 2000 mg/kg.

As a result of the dose-finding test for the bacterial reverse mutation test in DM, no increase in the number of colonies, precipitation, or growth inhibition was observed in the test microorganisms, so this test was conducted at 5 concentrations (5,000 to 313 µg/plate) with a common ratio of 2, with the highest concentration being 5,000 µg/plate. Regardless of the presence or absence of S9MIX, no increase in the number of revertant colonies was observed in any of the test strains, and neither growth inhibition nor precipitation was observed. Based on these results, DM was considered negative.

2.3. Human Trial

Six subjects ingested a single dose of 1 g of Man dissolved in water, and we attempted to detect Man concentrations in the urine. These values were below the detection limit of HPLC (detection limit 0.1 mg/mL). Therefore, the determination was performed using gas chromatography-mass spectrometry. Figure 3 shows the individual changes before and after administration. Even before administration, urines of five subjects contained from 1.22 µg/mL to 11.3 µg/mL Man and one subject was 42.5 µg/mL. After administration, the number of subjects with the highest value decreased, whereas that of the other subjects did not change.

One week after the mannose trial, the same subjects ingested a single dose of 1 g DM dissolved in water; however, no abnormal symptoms such as diarrhea were observed. Figure 4 shows individual changes in urine DM concentration after ingestion. The DM concentration in the urine of all the participants was below the HPLC detection limit before ingestion. After ingestion, all DM content in the urine increased. In four out of six subjects, the peak concentrations in urine were at 2 h and ranged from 1.22 to 5.78 mg/mL. In the remaining two subjects, the peak values were 1.46 mg/mL and 0.665 mg/mL at the 3rd and 6th hour. The urinary recovery rate of DM was 43.3±9.05%. These results indicate that most of the orally injected DM was quickly excreted in the urine.

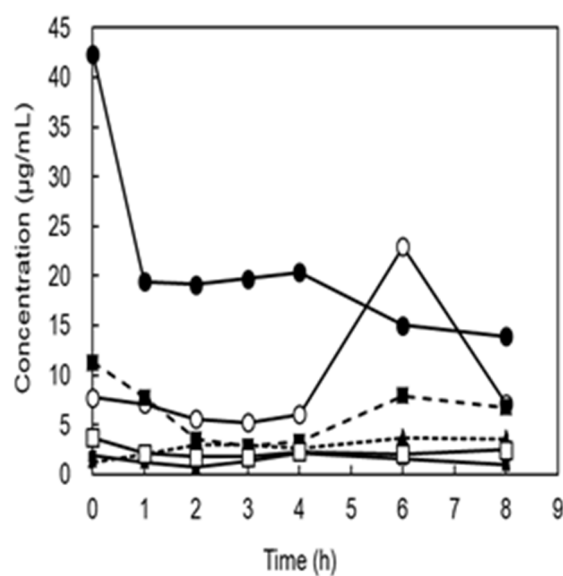


Figure 3. Changes in D-mannose concentration in urine after oral administration.

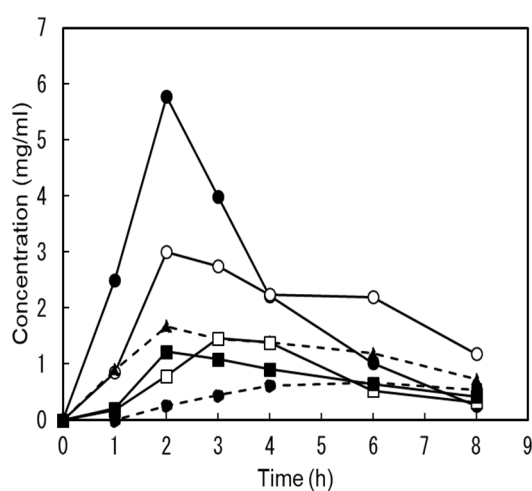


Figure 4. Changes in 1-deoxymannose concentration in urine after oral administration.

2.4. Utilization of Carbohydrates by *E. coli*

We evaluated the ability of DM by *E. coli* (NBRC 3301) was evaluated. The turbidity results are illustrated in Figure 5. No increase in turbidity was observed in the culture solution containing DM compared to that in the culture solution containing Man and glucose. DM is difficult, the use by *E. coli*.

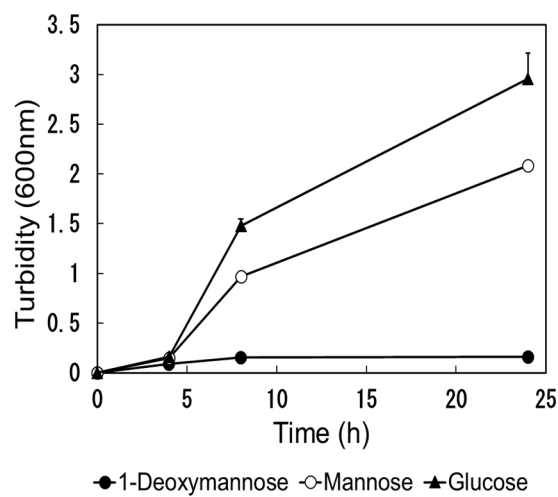


Figure 5. Utilization of 1-deoxymannose on the growth of *E. coli*.

3. Discussion

LD₅₀ of DM is more than 2000 mg/kg, and the bacterial reverse mutation test is negative. Therefore, DM can be regarded as safe for a single oral administration. Contrarily, in order to conduct long-term human trials on supplements, it is necessary to conduct a 90-d continuous oral administration test and micronucleus test to ensure safety.

Table 1 documents the K_D of each carbohydrate with FimH, as determined by isothermal titration calorimetry, and the urinary concentrations of DM and Man after oral intake. K_D of DM and Man are reported as 1.125 mM (0.185 μg/mL) and 1.672 mM (0.301 μg/mL) respectively [9,13]. In this Man trials, the average urinary Man concentration before ingestion was 11.4±15.7 μg/mL, which is higher than the K_D value of 0.301 μg/mL, so it may be thought that Man is constantly excreted in the urine, and that Man has an inhibitory effect on FimH and may has a function of UPEC. On the other hand, urinary Man concentration did not increase even when 1 g of Man was administered orally. A similar report was made in 2023, and it was reported that when 2 g of Man was orally intake, there were non-responders whose urinary Man/creatinine ratio did not change, and even in responders, the concentration increases by only about 40%. For these reasons, it is difficult to expect that even if Man is used as a supplement, its effect on the inhibition of UPEC adhesion will be enhanced. In 2024, a large-scale human trial was conducted on the effectiveness of Man in preventing tract infections and concluded that Man did not have any effect on preventing tract infections compared with a placebo [5]. Man in the urinary tract in both test groups may have been protected, but there may have been no difference in their effectiveness.

Table 1. Comparisons of K_D value to FimH and peak urine concentration.

	1-Deoxymannose	D-Mannose
K _D value (μM : μg/mL)	1.125 : 0.185	1.672 : 0.301
Peak urine concentration after oral intake (μg/mL)	665-5,780	2.15-22.9
Peak urine concentration/K _D	3,600-31,200	66.3-707
AUC (μg·h/mL)	437-2,240	1.43-19.3

After oral intake of DM, the concentrations of DM in urine rapidly increased dramatically, and the concentration was 3,600-31,200 times higher than that of K_D and the values were quite large compared with those of Man. One gram of DM is a realistic amount for supplementation.

The study involved six healthy individuals, both men and women, aged between 33 and 57 years. However, due to the limited sample size, restricted age range, and uneven gender ratio, caution is advised when generalizing the findings. It is essential to evaluate the applicability of the results to groups with different age ranges and gender distributions

Although the sequence identity is only 15% with *E. coli*, type 1 fimbrial FimH of *salmonella enterica* has the ability to mediate mannose-sensitive adhesion like *E. coli* [14]. Viruses and microorganisms that induce red blood cell agglutination have long been studied. The inhibitory activities of Man and DM have been evaluated in guinea pig red blood cells and *salmonella Shigella flexneri* [15]. Man and DM inhibit agglutination at 0.025% (250 µg/mL) and 0.013% (130 µg/mL) or higher when tested at 30 times the minimum bacterial concentration that causes hemagglutination. At a bacterial concentration of 1.9 times, those of Man and DM were both greater than 0.0016% (16 µg/mL). Comparing these values to the urinary concentrations from our human studies, DM is much higher than the 130 µg/mL of the 30 times test for *Salmonella* and Man is much lower than 250 µg/mL. At a bacterial concentration of 1.9 times, the concentration of Man was close to that of Man, which is constantly excreted in the urine. From these facts, it is assumed that the constantly excreted Man, although weak, slightly suppresses the adhesion of UPEC with type 1 fimbriae but cannot suppress adhesion when a large number of bacteria are present. Conversely, if DM is constantly taken as a supplement, it is likely to suppress infection even if the number of bacteria is large.

Therefore, an orally active FimH inhibitor is expected to be effective against the human urinary tract.

Although the relationship has not been clearly proven, when urinary glucose occurs in patients with diabetes, sugar may increase the chances of developing UTI [16,17]. Therefore, the carbohydrates in urine cannot be utilized for growth by *E. coli*. Since DM is not assimilated by *E. coli*, it is assumed that the risk of bacterial contamination is low, even when used as a preventive supplement for tract infections over a long period.

In human studies, the urinary recovery of DM was less than 50% after ingestion to 8 h. Therefore, the remainder may have reached the large intestine without being absorbed by the small intestine. In the intestine, UPEC reaches the urinary tract via the anus and vagina [1]. Oral mannoside intake in mice reduces UPEC in the intestine and urinary tract [18]. Therefore, DM not absorbed by the small intestine may reduce UPEC levels in the human colon. As discussed above, DM is a potent, orally active FimH inhibitor in the human urinary tract and may also be active in the intestine.

Therefore, alternatives to antibiotics are required to prevent UTIs. Therefore, DM has the potential to act as a highly active prophylactic agent. However, because both FimH and P fimbriae are involved in the adhesion of *E. coli* [1], there is some concern as to whether inhibitors of FimH alone have a preventive effect. In the future, it will be necessary to conduct safety studies on DM and evaluate its activity in long-term human ingestion prevention studies.

4. Materials and Methods

4.1. Test Materials

The compound 1, 5-AF was prepared per prior methodology [19]. DM was obtained by hydrogenation of aqueous 15%Bx of 1,5-AF a solution with 20% Raney Nickel of 1,5-AF solid content as catalyst at 40°C, 3 h under H₂ pressure 0.9 MPa. The reaction solution removed the catalyst was concentrated to 75%Bx. After added seed crystal of DM, the solution temperature controlled from 60°C to 40°C for 12 h with rolling with flask and crystallizing it. DM crystals were obtained by basket-type centrifugation.

The Man used pure powder for commercially available for supplements (NOW FOODS).

4.2. X-Ray Crystal Structure Analysis

We outsourced CLEARISE Co., Ltd. to perform the X-ray diffraction analysis of the DM crystal. The measurement device is Rigaku's wide-angle X-ray diffraction device: RINT2500HL, and the measurement was carried out under the following conditions; measurement wavelength: CuK α (0.15418 nm), X-ray output: 50 kV-250 mA, optical system: concentrated beam with monochromator, slit: DS 0.5 deg + 5 mmH, SS 0.5 deg, RS 0.15 mm, scanning axis: 2 θ / θ interlocking, scanning method: continuous scanning, scanning range: $2 \leq 2\theta \leq 80$ deg, scanning speed: 0.5 deg/min, sampling: 0.01 deg.

4.3. High Performance Liquid Chromatography Analysis

The high performance liquid chromatography (HPLC) device used was manufactured by JASCO Corporation, and the detector was a differential refractometer. The column was used with two MITSUBISHI MCI GEL CK 08S connections, the column temperature was at 60°C, the eluent was water, the flow rate was 1 mL/min, and the injection volume was 100 μ L. The obtained chromatogram was analyzed as a simple area percentage and was determined to be pure. The sample concentration was determined from the area ratio by using a standard substance of known concentration.

4.4. Gas Chromatography-Mass Spectrometer (GC-MS) Analysis

Zero point one five micro gram of adonitol was added as an internal standard to a 30 μ L urine sample that was diluted 10 or 100 times, and 60 μ L ethanol was added to remove the protein. After centrifuging at 15,000 rpm for 5 min, 60 μ L of supernatant was dried with a centrifugal evaporator. After adding 20 μ L of TMS-PZ (Tokyo Chemical Industry Co., Ltd.) to dried sample and allowing it to react for one hour at room temperature, the concentration of Man was measured by GC-MS. The measurements were performed using a TRACE 1610 gas chromatograph equipped TSQ 9610 mass spectrometer (Thermo Fisher Scientific K.K.) and TG-5SILMS column (Length:20 m, I.D.:0.18 mm, Film:0.18 μ m). Helium was used as the carrier gas, and the flow rate was maintained at 0.8 mL/min. One micro little sample was injected at a temperature of 250°C, and split ratio was 1:20. The column oven temperature was kept at 80°C for 2 min, and then gradually increased to 300°C at 20°C/min. The ion source temperature was 250°C, and mass spectra range was between 50 to 550 m/z.

4.5. Acute Oral Toxicity Test Using Female Mice

This research was outsourced to Japan Food Research Laboratories. The DM dose was 2000 mg/kg, and a control group was set up to receive water for injection, and each group consisted of 5 ICR female mice. The test animals were fasted for 4 h prior to administration. After measuring the body weight, the test group received the DM solution, and the control group received the injection solution in a single dose of 20 mL/kg using a gastric tube. The observation period was 14 d, with frequent observations on the day of administration and once daily thereafter. Body weight was measured on days 7 and 14 after administration. All the animals were necropsied at the end of the observation period.

4.6. Bacterial Reverse Mutation Test

The bacterial reverse mutation test was outsourced to Bozo Research Center Co., Ltd., and tested in accordance with good laboratory practice. The protocol followed the OECD Guidelines for Testing of Chemicals 471 for bacterial reverse mutation tests. The strains used in the test were Salmonella typhimurium TA100, TA1535, TA98, and TA1537, and E. coli WP2 uvrA. 2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide, sodium azide, CR-191, 2-aminoanthracene, and benzo [a] pyrene were used as positive controls.

4.7. Humane Trial

This study was reviewed and approved by the Ethics Committee of User Life Science Co., Ltd. (US L202203). Before the subjects participated in the study, the study director sufficiently explained the purpose and content of the study. After confirming that the subjects fully understood and agreed with the content, they obtained their voluntary written consent to participate in the study. The study was conducted on six healthy men and women aged 33–57 years.

A sample for oral intake was prepared by dissolving 1 g Man or DM in water to obtain a 20% w/w solution. In human studies, urine is collected before sample ingestion. The entire sample was ingested orally at 9:00, and the entire amount of urine was collected after 1, 2, 3, 4, 6, and 8 h. The subjects were allowed to eat breakfast before 9:00 a.m. and lunch at 12:00 p.m. during the test. After the urine volume was measured, the collected urine was stored in a freezer at -25°C until measurement. After thawing, Man concentration was measured by GC-MS for Man administration, and DM concentration was measured by HPLC for DM administration. The urinary recovery rate of each sample was calculated from the collected urine volume and urinary DM or Man concentration, and was divided by the administered dose to obtain the urinary recovery rate (%).

4.8. Carbohydrate Fermentation Test

E. coli (NBRC 3301) was shaken at 37°C for 17 h using 2 mL of M9 minimal medium (Difco™ M9 Minimal Salt supplemented with MgSO₄ and CaCl₂) containing 1% glucose to obtain a culture solution. Ten microliter of the above culture solution was added to 2 mL of M9 minimal medium containing 1% of each sugar (DM, Man, glucose), and cultured with shaking at 37°C. During the culture, 100 µL was taken out over time, and the turbidity (600 nm) was measured using a cell with an optical path length of 1 cm.

5. Conclusions

DM demonstrates binding affinity for FimH. After oral intake of DM, the concentrations of DM in urine rapidly increased dramatically, and the concentration was 3,600–31,200 times higher than that of KD and the values were quite large compared with those of Man. Upon oral administration, almost all of the ingested DM is excreted into the urinary tract. Therefore, it is an orally active FimH inhibitor in humans. It is necessary to conduct a 90-d continuous oral administration test and micronucleus test to ensure safety, and evaluate its activity in long-term human ingestion prevention studies.

6. Patents

This article is contingent upon data from two patents: “Urinary tract infection prevention/treatment agent containing 1-deoxymannose” (WO/2024/034495) and “1-deoxymannose crystals precipitated from an aqueous solvent” (Unpublished Japanese patents).

Author Contributions: Conceptualization, K. Y.; Investigation, H. H., N. M., T. K., and S. I.; Project administration, K. Y.; Project administration, K. Y.; Visualization, N. M.; Writing - original draft, H. H. and K. Y.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of User Life Science (ULS202203, 31/4/2022)."

Informed Consent Statement: Informed consent was procured from all participants involved in the study. Written informed consent was obtained from all patients for publication of this paper.

Data Availability Statement: The original contributions of this study are included in this article. Further inquiries can be directed to the corresponding authors.

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Conflicts of Interest: The authors (Yoshinaga K., Hayashi H., Miyazaki N. T.Kawakami and S. Izumi) are employees of SUNUS Co., Ltd., and the rest are joint researchers. This research presented in this paper was funded by SUNUS Co., Ltd. and the METI R&D Support Program for Growth-Oriented Technology SMEs (Grant Number JPJ005698). This study was performed as part of the professional duties of the authors. The views expressed in this article are those of the authors and do not necessarily reflect those of SUNUS Co. The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Abbreviations

The following abbreviations are used in this manuscript:

DM

Man

UPEC

UTI

1-Deoxymannose

D-Mannose

Uropathogenic *Escherichia coli*

Urinary tract infection

Appendix A

Appendix A.1

Table A1. Peak search results from X-ray crystallographic analysis of 1-deoxymannose.

Peak No.	Diffraction angle (deg)	Surface spacing (nm)	Intensity (cps)	Integrated intensity (a.u)
1	12.89	0.6862	51	5
2	14.26	0.6206	2253	374
3	14.54	0.6087	256	24
4	17.08	0.5187	3129	493
5	17.81	0.4976	103	15
6	18.71	0.4739	182	30
7	20.16	0.4401	8698	1438
8	20.75	0.4277	488	60
9	21.08	0.4211	1113	141
10	22.43	0.3961	78	11
11	23.1	0.3847	3435	530
12	23.64	0.3761	125	17
13	24.35	0.3652	329	61
14	25.97	0.3428	296	43
15	28.35	0.3146	867	175
16	29.21	0.3055	1268	307
17	29.67	0.3009	167	18
18	30.44	0.2934	667	138
19	30.74	0.2906	188	46
20	31.79	0.2813	83	14
21	32.97	0.2715	131	18
22	33.61	0.2664	292	51
23	35.2	0.2548	535	42
24	36.16	0.2482	83	17
25	36.61	0.2453	410	108
26	37.96	0.2368	192	34
27	38.61	0.233	454	69
28	39.13	0.23	173	29
29	39.79	0.2264	143	30
30	40.26	0.2238	157	33
31	41.01	0.2199	134	33
32	42.98	0.2103	171	53
33	43.87	0.2062	131	28
34	44.96	0.2015	183	38
35	45.72	0.1983	322	81
36	46.71	0.1943	73	14
37	47.14	0.1926	74	13
38	48.08	0.1891	252	60
39	48.54	0.1874	99	13

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