

Present Status and Future Prospects of Functional Oligosaccharide Development in Japan*

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Abstract: This paper reviews the present status for the development of functional oligosaccharides in Japan and looks over the future prospects of these saccharides. Since 1970, several novel microbial enzymes producing specific oligosaccharides have been discovered. Using these new enzymes, it is now possible to produce on an industrial scale various oligosaccharides such as glycosylsucrose, fructooligosaccharides, maltooligosaccharides, isomaltooligosaccharides (branched-oligosaccharides), galactooligosaccharides, xylooligosaccharides, palatinose (isomaltulose), lactosucrose and so on. Recent developments in industrial enzyme-utilization technology have made possible a series of new oligosaccharides such as β -1,6-linked gentiooligosaccharides, α, α -1,1-linked trehalose, α -1,3-linked nigerooligosaccharides, branched-cyclodextrins, maltosyltrehalose, cyclic difructose and cyclic tetrasaccharide. The development of novel and highly functional oligosaccharides with physiological properties is now continuing and the market is expanding gradually. Recent human intervention and animal studies have revealed that foods are able to modulate the functions of innate or aquired immunity. In the near future, the development of oligosaccharides as immune system modulators including prebiotics is expected, and these saccharides may play an important role, especially in the reduction of lifestyle-related diseases as well as the maintenance and improvement of human health.

Key words: functional oligosaccharide, starch oligosaccharide, sucrose-related oligosaccharide, lactose-related oligosaccharide

Starch oligosaccharides, which represent the fragments of original polysaccharides, are composed of α -D-glucopyranosyl units linked by α -1,4 and/or α -1,6 bonds. Oligosaccharides containing only α -1,4-glycosidic linkages are called maltooligosaccharides, while those containing both α -1,4- and α -1,6-glycosidic linkages are called branched-oligosaccharides or isomaltooligosaccharides in Japan.¹⁾ Cyclodextrins are cyclic α -1,4-linked maltooligosaccharides containing 6–12 glucose units. The discovery of novel enzymes that produce specific oligosaccharides such as maltotriose, maltotetraose, maltopentaose and maltohexaose has made possible the production of syrup with a high content of each maltooligosaccharide.²⁾ Furthermore, recent developments in industrial enzyme-utilization technology have made possible a series of new starch oligosaccharides such as β -1,6-linked gentiooligosaccharides,³⁾ α, α -1,1-linked trehalose,^{4,5)} α -1,3-linked nigerooligosaccharides,^{6,7)} α -1,2-linked kojooligosaccharides including selaginose⁸⁾ and branched-cyclodextrins having glucosyl and maltosyl residue.^{9,10)}

The various types of oligosaccharides have been found as natural components in many common foods including fruits, vegetables, milk, honey and traditional Japanese foods such as sake and sweet sake used as seasonings. Oligosaccharides are functional food ingredients that have

a great potential to improve the quality of many foods. In addition to providing useful modifications to physico-chemical properties of foods, it has been reported that these oligosaccharides have various physiological functions such as the improvement of intestinal microflora based on the selective proliferation of *bifidobacteria*, stimulation of mineral absorption, non- or anticariogenicity and the improvement of both plasma cholesterol and blood glucose level.¹⁾

Production, properties and applications of oligosaccharides.

Research on the production of oligosaccharides for foods was started around 1970–1975 in Japan, and several oligosaccharides such as starch-related, sucrose-related, and lactose-related oligosaccharides and other oligosaccharides derived from several polysaccharides as the raw materials have been developed as shown in Table 1.¹⁰⁾

Xylooligosaccharides, agarooligosaccharides, mannoooligosaccharides and chitin/chitosan oligosaccharides have been produced from various polysaccharides such as xylan, agar, mannan, chitin and chitosan as raw materials. Recently, a difructose anhydride^{11–13)} has been developed from inulin as the raw material. Functional properties evaluated until now are summarized in Table 2.¹⁴⁾ Nigerooligosaccharides and agarooligosaccharides have been especially developed as food ingredients with physiologically unique functions such as immunopotentiating and apoptosis induction activities.^{15–18)} It has also been revealed that trehalose and melibiose have new physiological functions such as superoxide dismutase-like activity¹⁹⁾

*This paper is dedicated to our mentors, the late Professors Dr. Michinori Nakamura, Dr. Susumu Hizukuri and Dr. Toshiaki Komaki, in memory of their numerous pioneering works and leadership in the field of starch and its related science.

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Table 1. Various kinds of oligosaccharides developed in Japan.

| | |
|---------------------------------|---|
| Starch-related oligosaccharide | Maltooligosaccharides: Maltose-maltoheptaose (G2–G7) |
| | Isomaltooligosaccharides: Isomaltose, Panose, Isomaltotriose |
| Sucrose-related oligosaccharide | Cyclodextrins (CDs): α -CD, β -CD, γ -CD, HP β -CD, Branched CDs |
| | Others: Trehalose, Maltitol, Gentiooligosaccharides, Nigerose Kojioligosaccharides, Maltosyltrehalose, Cyclic tetrasaccharide |
| Lactose-related oligosaccharide | Glycosylsucrose, Fructooligosaccharides, Palatinose (Isomaltulose), Lactosucrose, Xylsucrose, Raffinose, Stachyose, Trehalulose, Cellobiose, Glucosylxylose |
| Lactose-related oligosaccharide | Galactooligosaccharides, Lactosucrose, Lactulose, Lactitol |
| Others | Xylooligosaccharides, Agarooligosaccharides, Mannooligosaccharides, Chitin/chitosan oligosaccharides, Cyclofructan, Cyclodextran, Cycloinulooligosaccharides, Difructose anhydride, Melibiose |

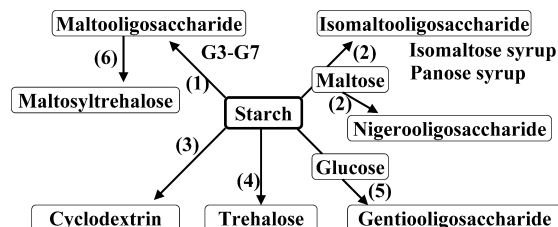
Table 2. Functional properties of oligosaccharides.

| | |
|--------------------------|--|
| Physicochemical property | Sweetness, Bitterness, Hygroscopicity, Water activity, Stabilization of active substances (protein, flavor, color, etc.) Inclusion capacity, Reinforcement agent for drinks, etc. |
| Biological property | Digestibility, Non-digestibility, Non-cariogenicity, Anti-cariogenicity, Bacteriostatic action, Selective proliferation of bifidobacteria, etc. Improvement of serum lipids and blood glucose, Effects on the absorption of minerals, Superoxide dismutase-like activity, Improvement of atopic dermatitis, Immunopotentiating activity, Apoptosis induction, Reduction of allergic reaction, etc. |
| Other property | Specific substrate for enzyme, Enzyme inhibitor, Elicitor, etc. |

Table 3. Several microbial enzymes developed since the 1970s.

| Enzyme | Product | Microbial origin* |
|-------------------------------------|-----------------------------------|--|
| Maltotriohydrolase | α -Maltotriose | <i>Streptomyces griseus</i> <i>Bacillus subtilis</i> |
| Maltotetraohydrolase | α -Maltotetraose | <i>Microbacterium imperiale</i> <i>Pseudomonas stutzeri</i> <i>P. saccharophila</i> <i>B. circulans</i> |
| Maltopentaose-forming amylase | α -Maltopentaose | <i>B. licheniformis</i> <i>B. subtilis</i> <i>B. cereus</i> <i>Pseudomonas</i> sp. |
| Maltohexaohydrolase | α -Maltohexaose | <i>Klebsiella pneumoniae</i> <i>B. subtilis</i> <i>B. circulans</i> F-2, G-6 |
| β -Fructofuranosidase | Fructooligosaccharides | <i>A. niger</i> |
| β -Glucosidase | Lactosucrose | <i>Arthrobacter</i> sp. |
| Cyclodextrin (CD) | β -Glucosyloligosaccharides | <i>A. niger</i> |
| Glucanotransferase (CGTase) | β -CD | Alkalophilic <i>Bacillus</i> sp. |
| α -Glucosidase | γ -CD | <i>B. clarkii</i> 7364 |
| MTSase (Glycosyltransferase) | Nigerooligosaccharides | <i>Acremonium</i> sp. |
| MTHase (α -Amylase) | Trehalose | <i>Arthrobacter</i> sp. |
| Fructotransferase | Difructose anhydride | <i>Sulfolobus</i> sp. |
| 6- α -Glucosyltransferase | Cyclic tetrasaccharide | <i>Arthrobacter</i> sp. |
| 3- α -Isomaltosyltransferase | | <i>Arthrobacter globiformis</i> A19 <i>B. globisporus</i> C11, N75 |

*References are shown in the text.

**Fig. 1.** Currently produced starch oligosaccharides.

(1) Maltooligosaccharide-forming amylase, (2) α -Glucosidase, (3) Cyclodextrin Glucanotransferase (CGTase), (4) Maltooligosyltrehalose Synthase (MTSase), Maltooligosyltrehalose Trehalohydrolase (MTHase), (5) β -Glucosidase, (6) MTSase.

and the improvement of atopic dermatitis,²⁰ respectively. At present, these oligosaccharides have been widely utilized in food, beverage and confectionery processing, applying these various functional properties of oligosaccharides as shown in Table 2.

Starch-related oligosaccharides.¹⁾

Since 1970, several novel microbial enzymes producing specific oligosaccharides have been discovered as listed in Table 3.¹⁴⁾ Using these new enzymes, it is now possible to produce several brand-new sweeteners from various raw materials on an industrial scale. Among these microbial enzymes, a maltotriohydrolase from *Microbacterium imperiale*, a maltotetraohydrolase from *Pseudomonas stutzeri* and a maltopentaose-forming amylase from *Bacillus licheniformis* are used for the production of maltotriose, maltotetraose and maltopentaose syrups, respectively.

The industrial production method of trehalose has been developed using two kinds of glycosidases such as maltooligosyltrehalose synthase (MTSase) and maltooligosyltrehalose trehalohydrolase (MTHase).^{4,5)} MTSase is a kind of glycosyltransferase and MTHase should be classified as an α -amylase.²¹⁾ A brand-new starch oligosaccharide, maltosyltrehalose has been developed.⁵⁾ A nigerooligosaccharide-containing syrup has been developed using the trans-

fer reaction of α -glucosidase from *Acremonium* sp.⁶⁾ Cyclodextrins are produced from starch due to the action of cyclodextrin glucanotransferase (CGTase) from various origins such as *B. macerans*, *B. stearothersophilus*, *B. coagulans* and Alkalophilic *Bacillus*.⁹⁾ Takada *et al.*²²⁾ found a novel microorganism origin CGTase, which produces γ -CD mainly as the reaction product from starch.

Both isomaltooligosaccharide (branched-oligosaccharide)-containing syrup and nigerooligosaccharide-containing syrup are produced from maltose as a raw material using the transfer reaction of α -glucosidase. Recently, Yamamoto *et al.*⁷⁾ revealed the formation mechanism of nigerooligosaccharides from maltose using *Acremonium implicatum* α -glucosidase. Furthermore, gentiooligosaccharide-containing syrup is produced from glucose using the condensation and transfer reaction of β -glucosidase. The oligosaccharides being currently produced are shown in Fig. 1.

Various kinds of maltooligosaccharide (G3–G7)-containing syrups are products having low sweetness. They impart resistance to retrogradation of starch gel and prevent the crystallization of sucrose, and have begun to be used as property enhancers for various foods, powdering materials, saccharides for dry milk, liquid diets for patients and viscosity-increasing agents for refreshing drinks.

Cyclodextrins are capable of forming an inclusion complex with various organic compounds by incorporating them into the cavity of their cyclical structure. This can lead to desirable changes in the physical and chemical properties of the incorporated compounds. Using these specific properties, cyclodextrins have been utilized for various foods.

Branched-oligosaccharide syrups are mildly sweet and have relatively low viscosity, high moisture-retaining properties and lower water activity, which reduces microbial growth. Isomaltose, panose and isomaltotriose cannot be digested by yeast. Therefore, these syrups are effectively used for traditional fermented foods in Japan. The intake of these syrups not only improves the consistency of feces but also increases the *Bifidobacterium* count in human intestine, thus effecting an improvement in colonic conditions as prebiotics. Branched-oligosaccharides such as isomaltose and panose inhibit the synthesis of water-insoluble glucan from sucrose, and these syrups are effectively used as anticariogenic saccharides.^{23,24)} With these specific characteristics as background, it can be understood why these syrups are used in various field of foods and beverage processing such as baking, confectionery, soft drinks, sake making, seasonings, *etc.*

Trehalose has a wide application to food products utilizing its physicochemical properties.⁵⁾ Gentiooligosaccharide-containing syrup having the unique property of bitter taste is used for beverages as a taste-improving saccharide. It has been revealed that gentiooligosaccharides have improving effects on human intestinal microflora and also on the absorption of calcium.²⁵⁾ A brand-new nigerooligosaccharide-containing syrup has begun to be used for various kinds of foods and beverages as a taste-improving and color-stabilizing saccharide.^{10,14)} Recently, a unique cyclic tetrasaccharide has been developed from

starch using two kinds of enzymes and new applications for healthy foods have been studied.^{26–28)}

Sucrose-related oligosaccharides.¹⁾

Various sucrose-related oligosaccharides such as glycosylsucrose (maltooligosylsucrose), fructooligosaccharides, palatinose (isomaltulose), lactosucrose, and so on have been developed.

Glycosylsucrose is produced by subjecting the mixture of starch hydrolysate and sucrose to the action of cyclodextrin glucanotransferase (CGTase). Because the saccharides contain a small amount of reducing sugars, it induces less Maillard reaction with protein. It is an anticariogenic sweetener that not only hardly induces dental caries but also inhibits the cariogenicity of sucrose.

Fructooligosaccharides are produced from sucrose by the transfructosylation of fungal β -fructofuranosidase. These saccharides have been efficiently produced by a continuous reaction using an immobilized enzyme system. It has been verified that the saccharides are nondigestible sweeteners and have low cariogenicity. The saccharides are selectively utilized by human intestinal *Bifidobacterium* to improve the microflora as prebiotics. Furthermore, it has been revealed that the saccharides have physiological properties such as cholesterol reduction and the improvement of constipation.

Palatinose (isomaltulose) is an isomer of isomaltose, and the production of the saccharide from sucrose has been carried out using immobilized α -glucosyltransferase from *Protaminobacter rubrum*. The process yields two kinds of products, crystalline palatinose and palatinose syrup. It is generally accepted that these two products are effective as sucrose substitutes for caries prevention, and that these saccharides are suitable for children because palatinose is digestible in the small intestine without any diarrhea and flatulence. There are also soybean oligosaccharides including raffinose and stachyose having the same physiological and functional properties as fructooligosaccharides. Moreover, Kitaoka *et al.*²⁹⁾ reported that cellobiose is produced in a high yield from sucrose by the sequential action of three enzymes such as sucrose phosphorylase, xylose isomerase and cellobiose phosphorylase.

Lactose-related oligosaccharides and others.¹⁾

Several kinds of oligosaccharides such as galactooligo-

Table 4. Production levels of oligosaccharides in Japan.

| Oligosaccharide | Production level (metric tons/year) |
|--|--|
| Maltooligosaccharide | 15000 |
| Isomaltooligosaccharide | 15000 |
| Cyclodextrin | 4000 |
| Trehalose | 30000 |
| Palatinose | 5000 |
| Fructooligosaccharide | 3500 |
| Galactooligosaccharide | 6500 |
| Glycosylsucrose | 2000 |
| Lactosucrose | 2500 |
| Gentiooligosaccharide | 500–1000 |
| Nigerooligosaccharide | 500–1000 |
| Others (Xylooligosaccharide, raffinose, <i>etc.</i>) | 1000–2000 |

saccharides, lactosucrose, lactulose and lactitol have been developed from lactose as a raw material. Almost all of these saccharides have the same characteristics as those produced from sucrose. Other oligosaccharides such as xylooligosaccharides, agarooligosaccharides, mannoooligosaccharides and chitin/chitosan oligosaccharides are produced from various polysaccharides using microbial enzymes. Xylooligosaccharides are low digestible sugars and utilized by most *Bifidobacterium* species. Kawamura and Uchiyama³⁰⁾ reported that an extracellular enzyme from *Bacillus circulans* produced cyclinuloooligosaccharides such as cyclinulohexaose, cyclinuloheptaose and cyclinulooctaose. New markets for foods applied utilizing the novel oligosaccharides such as agarooligosaccharides, mannoooligosaccharides and chitin/chitosan oligosaccharides have been developed.¹⁰⁾ Furthermore, it is well known that the new disaccharide, melibiose, is contained in honey and soybeans, and it has been revealed that the saccharide may be useful for atopic dermatitis.²⁰⁾

The production levels of oligosaccharides in Japan are presumed to be as shown in Table 4. Among these oligosaccharides, the demand for starch oligosaccharides is the largest, as is their production level. Also, at present, the market for oligosaccharides is expected to be more than 20 billion yen/year.³¹⁾

Future prospects of functional oligosaccharides.

As mentioned above, the research on the production of oligosaccharides for foods was started around 1970–1975 in Japan and several oligosaccharides were produced on an industrial scale from the early 1980s to the late 1990s. The research and development of novel oligosaccharides with physiologically functional properties is now continuing. The market for oligosaccharides continues to expand gradually. Among the markets, the production level and sales volume of starch oligosaccharide is the highest.

Since the 1980s, as the aging society began to manifest itself in many countries of the world, the rapid increase in lifestyle-related diseases has become a matter of public concern. Under these circumstances, in 1984, a national research project started under the sponsorship of the Ministry of Education, Science and Culture to investigate the interface between food and medicine. In this project, several beneficial functions including modulation of the immune, endocrine, nerve, circulatory and digestive systems in the body were evaluated.³²⁾ At the same time, the Japanese government passed a law on Foods for Specified Health Use (FOSHU), taking the initiative in the world in 1991.³³⁾ In 2002, FOSHU increased the total to 324 items of which more than 50% incorporate oligosaccharides as the functional components. The sales volume of FOSHU reached about 600 billion yen/year in 2004. Recent human intervention and animal studies have revealed evidence that some food constituents are able to modulate the function of immunological system.³⁴⁾ Furthermore, the importance of the intestinal immune system has been recognized because the intestine represents the largest mass of lymphoid tissue and functions as the frontier immune system.³⁵⁾

With increasing health consciousness among consumers and the rapid progress of physiologically functional foods,

the future profile of products containing oligosaccharides with biological activities seems to be greatly promising. In the near future, the development of oligosaccharides as mucosal immune system modulators including prebiotics is expected, and these oligosaccharides may play an important role, especially in the reduction of lifestyle-related diseases as well as the maintenance and improvement of human health.

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日本における機能性オリゴ糖開発の現状と将来

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日本におけるオリゴ糖開発の現状と将来についてレビューする。1970年以來、特殊なオリゴ糖を生産する微生物由来の酵素が相次いで見出され、これを利用してグリコシルスクロース、フルクトオリゴ糖、マルトオリゴ糖、イソマルトオリゴ糖(分岐オリゴ糖)、ガラクトオリゴ糖、キシロオリゴ糖、パラチノース(イソマルチュロース)、ラクトスクロースなどの種々のオリゴ糖が工業的スケールで生産されるようになった。最近の工業用酵素の利用技術の進展により、 β -1,6結合のゲンチオオリゴ糖、 α , α -1,1結合のトレハロース、 α -1,3結合のニゲロオリゴ糖、分岐シクロデキストリン、マルトシルトレハロース、環状ジフルクトース、環状四糖など一連の新しいオリゴ糖生産が可能になってきた。さらに、新しい高次の生理機能をもったオリゴ糖の開発も継続的に行われており、オリゴ糖市場もしだいに拡大しつつある。最近のヒト介入試験あるいは動物試験により、食品にはヒトに本来備わっている免疫あるいは獲得免疫機能を調節する機能があることが明らかにされてきた。近い将来、プレバイオテックスを含めて、免疫システムを調節する機能を有するオリゴ糖の開発が期待される。それによって、オリゴ糖は人々の健康の維持・増進はもとより、生活習慣病の減少にも貢献できるものと予測される。