Analysis of Development Trends in Glycoengineering (Postprint)

Authors: Wang Zhuo, Liu Hongtao, Yin Heng, Du Yuguang

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Abstract

Glycoengineering is a discipline that investigates the structure, function, preparation technologies, and applications of carbohydrates. Over the past three decades, continuous advancements in research techniques for glycan function have led to the elucidation of numerous glycan structures and their biological functions, gradually revealing the intimate relationship between glycans and processes of growth, development, and disease. Consequently, basic and applied research in glycobiotechnology has flourished, establishing itself as the most prominent new biotechnology field following genetic engineering and protein engineering. Currently, glycoengineering research is burgeoning both domestically and internationally; while review papers in this field are not uncommon, most emphasize discussions of basic theoretical research. This article focuses on introducing the status of glycoengineering technologies and industrial development, with particular emphasis on discussing major glycoengineering products in China in recent years, market conditions, domestic and international R&D trends, and technological innovation in glycoengineering. It also examines the opportunities and challenges confronting the development of glycoengineering in China, providing a reference for scholars, researchers, and industrial technicians engaged in glycoengineering teaching, scientific research, and application development.

Full Text

Preamble

Current Trends in Glycoengineering

Zhuo Wang[1], Hongtao Liu[1], Heng Yin[2], Yuguang Du[1*]

[1] State Key Laboratory of Biochemical Engineering, Institute of Process Engineering, Chinese Academy of Sciences, Beijing 100190, China

[2] Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, Liaoning 116023, China

Abstract

Glycoengineering is a discipline that investigates the structure, function, preparation technology, and application of carbohydrate substances. Over the past three decades, continuous advancement in glycan functional research methodologies has led to the elucidation of numerous glycan structures and their biological functions. The intimate relationship between glycan variations and growth, development, and disease processes has been gradually revealed. Consequently, basic and applied research in glycobiotechnology has flourished, establishing itself as the most compelling new biotechnology field following gene and protein engineering. While reviews on glycoengineering are not uncommon, most focus on fundamental theoretical research. This paper emphasizes the technological and industrial development of glycoengineering, specifically addressing major products, market conditions, domestic and international R&D trends, and technological innovations in China' s glycoengineering sector. We also discuss the opportunities and challenges facing China' s glycoengineering development, providing valuable references for scholars, researchers, and industrial technicians engaged in glycoengineering education, research, and application development.

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Funding: National Natural Science Foundation of China (31670809)
Corresponding Author: Yuguang Du, E-mail: ygdu@ipe.ac.cn

Carbohydrates constitute one of the three major classes of biological macromolecules alongside proteins and nucleic acids, representing the most abundant biological resource in nature. They primarily exist as polysaccharides such as cellulose and chitin, or as monosaccharides and disaccharides including glucose, fructose, and sucrose. Additionally, glycoconjugates are formed through covalent linkages between sugars and proteins, lipids, nucleic acids, or other small molecules. The conversion of sugars into products closely related to human life constitutes the main research content of glycoengineering. Current R&D in glycoengineering can be categorized into four main areas based on product characteristics: (1) extraction, separation, and purification of naturally occurring polysaccharides, followed by structural analysis and biological activity studies for product development, such as chitosan and lentinan, which feature natural, non-toxic, and environmentally friendly properties; (2) hydrolysis or cleavage of polysaccharides into oligosaccharides composed of 2-20 sugar residues, which offer improved water solubility and higher biological activity, making them a current research hotspot; (3) production of functional monosaccharides such as allulose, tagatose, and fucose through synthesis or conversion, which often participate in energy metabolism while exhibiting antioxidant, antiviral, and antitumor activities; and (4) preparation and activity studies of glycoconjugates including aminoglycoside antibiotics and glycoprotein vaccines. More broadly, the conversion of abundant natural sugars like glucose, sucrose, and cellulose into bioenergy and bio-based chemicals such as ethanol, butanol, and succinic acid also represents an important component of glycoengineering.

Although carbohydrates are the most abundant organic compounds in nature, their structural complexity and limited research methodologies have caused glycan research to lag significantly behind that of proteins and nucleic acids. For a long time, carbohydrates were understood merely as structural materials or energy storage molecules. In the 1960s, glycoconjugates were discovered densely packed on cell surfaces, leading to speculation that their glycan chains functioned in molecular recognition during life processes. During the 1970s, the establishment of physicochemical determination methods and the application of specific endo- and exo-glycosidases in structural analysis revealed the astonishing complexity and diversity of glycan chains, whose information content exceeds that of proteins and nucleic acids by several orders of magnitude. In the late 1980s, the cloning of glycosyltransferases responsible for glycan synthesis revealed that glycan structural diversity is regulated at both the genetic and protein levels. These breakthroughs laid a solid foundation for glycan structure-function studies, drawing increasing attention to carbohydrates as important biological macromolecules. By the 1990s, with the application of molecular and cell biology techniques in glycan functional research, particularly through interdisciplinary integration with carbohydrate chemistry, numerous glycan structures and biological functions were elucidated. Following gene and protein engineering, glycobiotechnology (glycoengineering) emerged as a discipline studying the structure, function, metabolic regulation, and development of glycoconjugates (glycan chains), gradually rising worldwide. In 2012, the U.S. National Research Council mapped out a roadmap for glycoscience, elevating glycoengineering research to new heights. Carbohydrate-based drugs such as vancomycin, Tamiflu, and heparin are widely used to treat inflammation, tumors, viral/microbial infections, and glycometabolic diseases. Additionally, oligosaccharide drugs for diabetes treatment and anti-rejection applications have been approved for market or entered clinical trials. Currently, international R&D priorities in glycoengineering focus on carbohydrate drugs and vaccines, functional sugar foods, carbohydrate biopesticides and fertilizers, and carbohydrate feed additives.

China' s glycoengineering development began in the 1980s, nearly simultaneously with other scientific powerhouses. In recent years, China' s glycoscience has advanced rapidly, establishing several research centers with substantial foundations, including the National Glycoengineering Technology Research Center at Shandong University, the Ministry of Health Key Laboratory of Glycoconjugates at Fudan University, the Ministry of Education Key Laboratory of Carbohydrate Chemistry and Glycobiology at Jiangnan University, and the Liaoning Provincial Key Laboratory of Glycobiology at Dalian Medical University. Over the past decade, China's continuous development in basic and applied glycoengineering research has fostered a thriving industry. For instance, the "Functional

Sugar City" in Yucheng, Shandong, has become a model for China' s bulk functional sugar product industry. China' s glycoengineering industry, centered on glycobiotechnology, has demonstrated rapid growth with an annual growth rate of approximately 20% in recent years, and its compound annual growth rate is expected to exceed 40%. Glycoengineering technology has been designated as a key field and frontier technology in the National Medium- and Long-Term Science and Technology Development Plan (2006-2020). As an important component of industrial biotechnology, glycoengineering research and industrialization have achieved fruitful results over the past decade, with the continuous emergence of high value-added products such as carbohydrate drugs, glycan-based plant vaccines, and functional sugar foods, nurturing a glycoengineering industry covering multiple fields and closely related to the health industry. This has led to the creation of numerous polysaccharide and oligosaccharide pharmaceutical and healthcare products, particularly the promotion of polysaccharides and oligosaccharides in planting and breeding applications, placing China at the forefront of glycobiotechnology product industrialization and application worldwide. Consequently, a regionalized, clustered sugar industry has begun to form, integrating functional sugars, carbohydrate drugs, and traditional sugars, guided by basic research, driven by market demands, and ultimately aimed at national health improvement. Glycoengineering products now cover various aspects including food healthcare, disease prevention and control, feed additives, energy supply, and crop safety [Figure 1: see original paper].

[Figure 1: see original paper]

By 2017, the glycoengineering industry had achieved a domestic output value of 80 billion yuan, accounting for approximately 10% of the global sugar industry total output value, serving society across food, medicine, animal husbandry, pest control, crop safety, and daily chemical applications. In 2015, China had approximately 256 glycoengineering-related enterprises. With the promotion of relevant industries during the 13th Five-Year Plan period, the number of enterprises continued to grow, reaching about 263 in 2016 and 272 in 2017. In 2016, China's total functional sugar output reached 3 million tons, with sugar alcohols accounting for 76.7% of total output value (2.3 million tons), oligosaccharides accounting for approximately 10% (300,000 tons), and microbial polysaccharides accounting for about 4% (120,000 tons).

China possesses vast polysaccharide and oligosaccharide resources and a long history of using them as medicines. Building upon this profound foundation, fully tapping resource potential to develop novel polysaccharide and oligosaccharide drugs, healthcare foods, and agricultural green formulations holds significant importance for safeguarding national health and environmental security.

2. Main Products

Carbohydrate products can be categorized into several major types based on different application purposes:

2.1 Carbohydrate-Based Drugs

Carbohydrate-based drugs generally refer to pharmaceuticals containing sugar structures, including monosaccharides, oligosaccharides, polysaccharides, and their modified compounds or derivatives. Carbohydrate substances constitute important modification components of cell membrane proteins and play crucial roles in biological processes such as signal recognition and immune response. Currently, carbohydrate-based drugs account for only approximately 0.2% of all FDA-approved drugs. However, due to their natural chirality and structural diversity combined with low toxicity and side effects, carbohydrate drug R&D has become a focal point for many pharmaceutical companies. Among the world' s top ten pharmaceutical companies, eight are actively developing carbohydrate drugs with related products already on the market. Clinical indications for carbohydrate drugs include tumors, viruses, thrombosis, diabetes, rheumatoid arthritis, neurological disorders, and gastrointestinal diseases. Currently, marketed carbohydrate drugs both domestically and internationally fall into four main categories: (1) polysaccharide drugs and their derivatives, such as heparin, hyaluronic acid, chondroitin sulfate, and fungal polysaccharides; (2) sugar or sugar-containing small molecule drugs, such as acarbose and active components from traditional Chinese medicine; (3) glycoprotein drugs, such as erythropoietin and interferon; and (4) carbohydrate vaccines, such as tumor vaccines and bacterial vaccines. Table 1 lists some clinically approved carbohydrate drugs from abroad.

Leveraging China' s long history of traditional Chinese medicine usage, domestic carbohydrate drug R&D has primarily focused on extracting polysaccharide components from herbal medicines. Developed lentinan has been approved for cancer adjuvant therapy. Additionally, Ocean University of China has developed sodium alginate polysaccharide derivatives for ischemic cardiovascular and cerebrovascular diseases based on marine polysaccharides. Shanghai Green Valley Pharmaceutical Co., Ltd. has developed mannose oligosaccharide diacid (GV-971), which can significantly inhibit the aggregation of amyloid- , a key pathological molecule in Alzheimer' s disease, and improve patients' cognitive function. The drug is currently undergoing Phase III clinical trials. Numerous other pharmaceutical companies also recognize the potential value of carbohydrate drugs from traditional Chinese medicine. Table 2 lists some clinically used carbohydrate drugs approved by the China Food and Drug Administration (CFDA).

2.2 Functional Sugars

In recent years, domestic enterprises producing functional sugars with healthcare, plant protection, and animal protection activities have continuously emerged, with some reaching considerable production scales (see Table 3). As these enterprises expand their product varieties, they will undoubtedly drive the rapid development of the functional sugar industry.

(1) Functional Sugar Foods

China has successfully developed dozens of functional oligosaccharide foods, though only a few have achieved large-scale production, mainly including isomaltooligosaccharides, fructooligosaccharides, xylooligosaccharides, galactooligosaccharides, chitosan oligosaccharides, and sugar alcohols.

Isomaltooligosaccharides are a type of starch sugar obtained through enzymatic or acid hydrolysis of starch, containing 40-90% isomaltose. They offer a glucose-like taste but cannot be directly absorbed by the small intestine, providing beneficial effects on intestinal flora. Fructooligosaccharides are primarily extracted from Jerusalem artichoke or converted from sucrose, and are applied as additives in processed foods such as baked goods, vinegar, and jelly, with products mainly divided into fructooligosaccharide syrup and refined fructooligosaccharides. Xylooligosaccharide products, primarily derived from corn cobs, are used as additives in food and dairy products, representing the most effective commercial functional sugar for promoting beneficial bifidobacteria in the intestine. Galactooligosaccharides play important roles in regulating intestinal flora in infants and have been widely applied in infant formula foods. Chitosan oligosaccharides, extracted from shrimp and crab shells, exhibit hypoglycemic and immune-enhancing functions, with broad applications in human healthcare, animal husbandry, and crop cultivation, and were approved as a new food ingredient in 2014. Sugar alcohols, which have a sweet taste but are completely non-metabolizable, hold significant application value and mainly include sorbitol, xylitol, maltitol, and erythritol.

(2) Functional Sugar Feed Additives

The feed industry, crucial for animal husbandry development, generates approximately 10 billion USD in annual global market sales. Functional sugars can enhance animal immunity, improve production performance, reduce disease incidence, and improve livestock product quality. Multiple functional sugars have been developed as feed additives and applied in animal husbandry with significant effects. Currently marketed functional sugar feed additives primarily include chitosan oligosaccharides, xylooligosaccharides, mannan oligosaccharides, and fructooligosaccharides, which have achieved good market responses in livestock, poultry, and aquaculture applications. Functional sugar feeds align with the concept of "green farming" and can reduce antibiotic usage. However, due to the short development history, only limited varieties have obtained Ministry of Agriculture certification numbers and achieved comprehensive promotion in China (see Table 4), resulting in insufficient product diversity compared to other feed additives. Additionally, limited promotion efforts have led to relatively shallow awareness among farmers, necessitating intensified marketing efforts in future feed markets.

(3) Functional Sugar Pesticides

Carbohydrate-based biopesticides primarily function to induce plant disease resistance and stress tolerance. Internationally, chitosan products have been approved in the United States as "alternative products to conventional fungicides" and "plant resistance regulators" for use on cucumbers, grapes, potatoes, strawberries, and tomatoes. The French National Center for Scientific Research has developed IODUS40 "laminarin" oligosaccharide, which has obtained a usage license from the French Ministry of Agriculture, primarily targeting wheat diseases.

China's functional sugar pesticide R&D currently ranks at an internationally advanced level, with some products even leading globally. According to the revised "Pesticide Management Regulations" implemented on August 1, 2017, carbohydrate biopesticides are mainly classified as natural plant resistance inducers and natural plant growth regulators. In terms of active components, China has registered far more polysaccharide and oligosaccharide biopesticides than foreign countries. By the end of 2017, multiple functional sugar biopesticides had been developed and obtained pesticide registration numbers, such as lentinan-based formulations, chitin and its derivative formulations, OS-oligosaccharins (pectin oligosaccharides), and amino oligosaccharins (chitosan oligosaccharides), demonstrating rapid development (see Table 5). Registered oligosaccharide biopesticides mainly include amino oligosaccharins and oligosaccharins, with amino oligosaccharins accounting for the absolute majority. There are 64 registered amino oligosaccharin products, including two technical materials (7.5%, 80%), one active ingredient (85%), and 61 formulated products with 0.5-5% content (18 mixtures and 43 single formulations). In 2017, amino oligosaccharin annual output reached approximately 1,300 tons, with large-scale promotion and application achieving certain practical results in agricultural production.

(4) Functional Sugar Fertilizers

In recent years, carbohydrate biostimulants such as sodium alginate, chitosan oligosaccharides, and sodium alginate oligosaccharides have attracted widespread market attention and application due to their comprehensive functions in disease resistance, stress tolerance, and growth promotion. Additionally, naturally sourced polysaccharides such as chitosan, carboxymethyl cellulose, starch, calcium alginate, and pectin exhibit film-forming and biodegradable properties, attracting considerable interest for preparing slow-release fertilizers through coating, which can reduce fertilizer application rates, improve efficiency, and protect the environment. The rapid development of polysaccharide and oligosaccharide biopesticides and biofertilizers has received corresponding policy support and standardization in China. The first domestic standard "Seaweed Acid Fertilizers" was officially implemented on April 1, 2017, marking a new stage of standardized development for China' s seaweed acid fertilizer industry. Carbohydrate fertilizers currently mainly include polysaccharides such as sodium alginate and chitin, primarily registered as organic water-soluble fertilizers. In China, numerous seaweed-processed polysaccharide biofertilizers have been registered, mainly distributed in coastal provinces such as Shandong and Jiangsu, while small amounts of oligosaccharides compounded with other active substances are registered as amino acid water-soluble fertilizers or micronutrient fertilizers. In recent years, with the emerging concept of biostimulants, carbohydrate biostimulants represented by sodium alginate, chitosan oligosaccharides, and sodium alginate oligosaccharides are rapidly entering the market, becoming a new growth point for carbohydrate agricultural preparations.

3. Market Analysis

3.1 Functional Sugars and the Health Industry

Functional sugars constitute an important component of functional foods, with main varieties including fructooligosaccharides, oligofructose, galactooligosaccharides, and mannan oligosaccharides. The global functional sugar market reached approximately 3.5 billion USD in 2016 and is projected to exceed 7 billion USD by 2024 (Table 6).

3.1.1 Sugar Alcohols Sugar alcohols refer to polyols produced by hydrogenation of corresponding reducing sugars, with major varieties including sorbitol, mannitol, erythritol, xylitol, and maltitol.

China has become the world' s largest sorbitol producer and exporter with continuously improving output and quality. While sorbitol was previously mainly used as a raw material for vitamin C production, its applications have gradually expanded to pharmaceuticals, chemicals, food, and daily chemicals in recent years.

The primary application of xylitol is as a substitute for sucrose or other sweeteners in chewing gum, ice cream, and other mass-market foods, with enormous international market demand. In 2015, China' s total xylitol output exceeded 100,000 tons, with annual exports accounting for only 15% of the international xylitol market.

Mannitol is listed as a national essential drug in the Chinese Pharmacopoeia and classified as a dehydrating agent in the "Newly Compiled Pharmacology." Clinically, mannitol can eliminate cerebral edema and vasculitis symptoms and is used to produce diuretics and vasodilators.

In summary, as low-calorie functional sweeteners, sugar alcohol products can prevent prevalent diseases such as obesity, dental caries, and diabetes, offering broad application prospects in the international food and beverage industry. Sugar alcohol products also have multiple pharmaceutical applications in the medical industry, with promising domestic and international market development expected in the coming years.

3.1.2 Oligosaccharides Although oligosaccharides have only a decade-long history internationally, they have developed rapidly into an emerging industry applied in food, medicine, feed, and chemical industries. The current oligosaccharide market reaches millions of tons with 25 commercial varieties and nearly

100 developed varieties, still growing at 10% annually. Functional oligosaccharides are primarily used as food additives in the dairy, healthcare product, beverage, and sugar-free functional food industries. Over the past three years, major domestic products including galactooligosaccharides, fructooligosaccharides, and isomaltooligosaccharides have grown at an average annual rate of 30%, indicating extremely broad market prospects. Galactooligosaccharides have been extensively added as important prebiotics in infant formula foods, representing vast market potential. However, compared to foreign enterprises, China' s production scale in the galactooligosaccharide field remains limited, with annual output of only several thousand tons.

3.1.3 Rare Sugars As a class of sugars with low natural abundance, rare sugars have proven important healthcare functions, mainly including D-allulose, tagatose, and L-arabinose. Currently, China' s industrialization of D-allulose and tagatose remains in the preliminary R&D stage, representing a blue ocean field for rare sugars. L-arabinose has been listed as an anti-obesity over-the-counter drug or nutritional supplement, but current domestic annual output is low and costs are high, leaving the potential market untapped. According to 2017 research reports from the Chinese Center for Disease Control and Prevention and other units, if added at 3.5%, Chinese household tables would require 17,500 tons of arabinose annually, yet current domestic market supply is less than 100 tons, indicating very broad market prospects for L-arabinose.

3.2 Functional Sugars in Agriculture

Currently, the global pesticide market is dominated by chemically synthesized products. According to the "2017-2022 China Biopesticide Market Monitoring and Investment Prospects Research Report" released by Bosi Data, biopesticides accounted for 5% of the global pesticide market in 2016 and are projected to reach over 7% by 2022, demonstrating strong growth potential. According to the "Forward Industry Research Institute Biopesticide Industry Report," North America and Western Europe will maintain the largest market shares, accounting for approximately 60-70% of the total market, but the greatest opportunities lie in developing countries. China will become the strongest and fastest-growing biopesticide market, with biopesticides expected to replace over 20% of conventional pesticides within the next decade.

[Figure 2: see original paper]

Carbohydrate-based biopesticides and biofertilizers constitute important components of biopesticides and biofertilizers, particularly as China has registered far more oligosaccharide-based products than foreign countries. Seaweed-based biofertilizers also account for a significant proportion of biofertilizers. China has formed representative and dynamic glycoengineering enterprises and industrial clusters, with Yucheng, Shandong, earning the reputation of "China' s Functional Sugar City." Representative enterprises include Shandong Longlive, Dalian Glycobio Biotechnology Co., Ltd., Dalian Chemphy Chemical Co., Ltd., Beihai

Gofar Marine Biological Industry Co., Ltd., and Hainan Zhengye Zhongnong High-Tech Co., Ltd., whose products have been promoted and applied on a large scale. Domestic enterprises with oligosaccharide biopesticide sales exceeding 100 million yuan have already emerged.

4. R&D Trends

Carbohydrate compounds exhibit vast diversity in monosaccharide composition, glycosidic bond types, and degree of polymerization, making their structural complexity far greater than the other two biological macromolecules, proteins and nucleic acids. Currently, most glycoengineering products are polysaccharides and oligosaccharides with simple monosaccharide compositions and glycosidic bond types, such as chitin, chitosan, chitosan oligosaccharides, sodium alginate, and glucan. Developing polysaccharide and oligosaccharide biological products with more complex structures represents a future growth point. Due to their superior solubility, bioavailability, and compatibility compared to polysaccharides, oligosaccharides have attracted widespread attention and application as functional foods, biopesticides, and biofertilizers both domestically and internationally. Developing more types of efficient enzymes with specific degradation characteristics to convert more polysaccharides into oligosaccharides through green processes remains important research content in glycoengineering. Microorganisms from extreme environments have become a research hotspot as enzyme resources, with novel extremozymes such as low-temperature, alkaline, and salt-tolerant enzymes offering unique catalytic properties that could significantly broaden the application scope of glycosidases and potentially generate important impacts in the glycoengineering industry.

Glycoengineering research has continued to gain momentum in recent years, with over 100,000 relevant publications in the past decade (2008-2017). The annual distribution of research papers in the glycobiotechnology field over the past ten years (Figure 3) shows a steady growth trend, with an average annual increase of nearly 400 papers. Polysaccharide research accounts for the largest proportion, followed by glycosides and oligosaccharides. In terms of research directions, the primary focus is biochemistry and molecular biology, with substantial publications also in applied chemistry, food science, and polymer materials research. Regarding patents, 41,313 patents were applied for in the glycoengineering field over the past five years, with polysaccharides being the most applied area and oligosaccharides ranking second.

[Figure 3: see original paper]

Using article keywords, we analyzed research hotspots in glycoengineering. In polysaccharide research, antioxidant activity is the most studied function, appearing in keywords of over 15% of polysaccharide research articles. The most studied polysaccharides are chitosan and cellulose, accounting for 15% and 11% of polysaccharide research articles, respectively. Numerous articles also address polysaccharide extraction processes and nanomaterial fabrication. Emerging research hotspots in the past two years (2016-2017) include hepatoprotective activity and opsonization modulation of polysaccharides, with increased attention to gums from Astragalus and Ulva. In glycoside research, antioxidant activity remains the most studied function, involved in 47% of glycoside articles, while flavonoid compounds dominate this field (61% of glycoside articles). In the past two years, research on glycosides for diabetes and colitis treatment has significantly increased, becoming a new hotspot. In oligosaccharide research, interactions between oligosaccharides and microorganisms have received substantial attention, with studies on antibacterial activity and intestinal flora regulation accounting for about half of all research. Chitosan oligosaccharide is the most studied oligosaccharide, representing about 1/10 of total articles, while inulin accounts for 6%. Antigen presentation and rhizosphere regulation have emerged as new hotspots in the past two years. Research on glycolipids, monosaccharides, and sugar alcohols is relatively limited overall. Glycolipid research mainly involves biosurfactants and T-cell killing, accounting for 33% and 29% respectively, with over 23% of articles addressing -galactosides. In monosaccharide research, antioxidant activity remains the most important direction, representing 63% of studies. Sorbitol is the most studied sugar alcohol (40%), followed by erythritol and mannitol, with primary research directions focusing on biomass energy.

Our analysis of major research directions in glycoengineering reveals that in carbohydrate drug development, drug delivery and antioxidant activity are the primary research focuses, with extensive research on polysaccharides due to their potential in drug delivery and medical nanomaterials, as well as considerable research on flavonoids and chitosan oligosaccharides. In the food industry, antioxidant, antibacterial, and flora modulation activities represent major research directions, with substantial research on polysaccharides and oligosaccharides. In feed research, glycan studies as prebiotics receive significant attention. In carbohydrate biopesticide research, the insecticidal and antibacterial activities of chitosan oligosaccharides and polysaccharides occupy important positions.

Regarding patent technology market distribution, mainland China is the most active region for patent applications in glycoengineering, with 29,748 patents, followed by the United States, Japan, South Korea, and Canada. Analysis of major countries' technology markets shows that Canada, the United Kingdom, and Australia have the most significant overseas patent applications with extensive patent layouts. China' s patents are primarily domestic applications, and awareness of overseas layout needs strengthening. In terms of patent holders, the Chinese Academy of Sciences ranks first globally with 393 patents in this field, with the Dalian Institute of Chemical Physics being the major secondary research institution with 86 patents. Regarding patent classification, applications in medical, dental, or toiletry preparations represent the primary application direction, with specific therapeutic activities of compounds or pharmaceutical preparations and specific uses of cosmetics or similar toiletry preparations being the main contents. Applications in food, foodstuffs, or beverages rank second in patent numbers.

In recent years, local governments have actively promoted the rapid and stable development of the sugar industry based on local resources. In 2016, the Shandong Provincial Department of Science and Technology established the "Shandong Provincial Sugar Industry Science and Technology Key Laboratory Alliance" by integrating 10 provincial key laboratories from enterprises, research institutions, and universities to drive Shandong' s sugar industry toward the goal of a 100-billion-yuan industrial cluster. In May of the same year, the National Biochemical Engineering Technology Research Center of the Chinese Academy of Sciences' Institute of Process Engineering signed an agreement with Xiangcheng High-tech Industrial Development Zone to jointly build the "Suzhou Industrial Base of the National Biochemical Engineering Technology Research Center, Chinese Academy of Sciences." The "Polysaccharide Bioengineering Industrial Park" project, jointly promoted with the Suzhou local government, has been listed as a key scientific and technological innovation project for Suzhou' s 13th Five-Year Plan.

5. Independent Innovation

Compared with foreign glycoengineering industries, China' s glycoengineering industry possesses certain comparative advantages and development potential. China has abundant raw carbohydrate material reserves, with rich sugar and corn resources providing sufficient production raw materials, while unique traditional Chinese medicine and marine biological resources offer convenience for functional sugar development. Additionally, national policies have strongly supported glycoengineering development in recent years. These conditions provide excellent support for glycoengineering product R&D and industrialization, further accelerating China' s glycoengineering industry development.

In terms of glycoscience research, China currently has 8 national glycoengineering technology research centers and state key laboratories, 1 national joint research center, and 8 provincial/ministerial key laboratories. In terms of publication numbers in the glycoengineering field in recent years, China has published 10,062 articles with over 30,000 total citations, ranking first globally, while the United States ranks second with 5,536 articles (Table 8). These data demonstrate that China' s research volume and overall influence in glycoengineering have achieved a leading global position. However, it should be noted that China' s citation percentage is only 62%, ranking ninth globally, indicating that overall paper quality still needs improvement. In terms of publishing institutions, the Chinese Academy of Sciences ranks first globally with 1,104 articles, while Zhejiang University and Jiangnan University also rank in the global top ten (Table 9). Regarding overall influence among the top ten institutions by publication number, the Chinese Academy of Sciences ranks second with 3,938 total citations. In terms of average academic level, Zhejiang University, the Chinese Academy of Sciences, and Jiangnan University have relative disciplinary influence values of 1.12, 1.0, and 1.0, ranking sixth and seventh respectively.

Currently, numerous glycoengineering products in China have achieved industrial production, with domestic enterprises and research institutes conducting extensive research on process links for different glycoengineering products and achieving a series of independently innovative research results.

5.1 Sugar Alcohol Industry

China' s starch sugar production enterprises have basically achieved domestic production of main equipment and technology, developing a series of new products and technologies. For example, Baolingbao' s three projects— "New Technology for Efficient Erythritol Fermentation and Waste Liquid Purification," "Fructose (Solid) Production Process from Wheat Starch," and "Research on Preparing Oligosaccharide Feed from Starch Sugar Processing By-products" —have all passed achievement appraisal and acceptance. Longlive' s multiple projects, including "Two-Step Process Technology for Furfural Production from Biomass Straw," "Co-production Process Technology for Cellulose Oligosaccharides and Lignin,"and "Microbial Enzymatic Process Technology for High-Purity Galactooligosaccharides," have passed on-site appraisal and acceptance. Among these, the production of cellulosic ethanol from corn cob processing residues won a national patent award. China's crystalline maltitol has successfully established multiple 10,000-ton-scale production lines through independent production technology. China' s xylitol industry has created an entirely new production process over decades of development, making China a world leader in xylitol production.

5.2 Functional Oligosaccharides

China' s functional oligosaccharide research began in the 1980s and achieved industrialization during the Ninth Five-Year Plan period. Due to their good water solubility and high biological activity, oligosaccharides have been widely applied in food and health industries, with main products including maltooligosaccharides, xylooligosaccharides, and chitosan oligosaccharides.

Xylooligosaccharides are the most effective oligosaccharides for bifidobacteria among functional oligosaccharides. Shandong Longlive Bio-technology Co., Ltd. jointly developed industrial production technology for xylooligosaccharides with China Agricultural University. In 2014, Longlive' s functional sugar products obtained carbon footprint certification, green labeling, and U.S. FDA certification.

Baolingbao and Jiangnan University jointly completed the research project "Key Technologies and Industrialization of Functional Oligosaccharide Biological Processing," which was the first in China to screen high-yield strains of galactosidase, fructosyltransferase, and transglucosidase, achieving more than 10-fold improvement in enzyme efficiency. The project won the first prize of Shandong Provincial Science and Technology Progress Award in 2012.

The Microbial Resources Team of the Qingdao Institute of Bioenergy and Bioprocess Technology, Chinese Academy of Sciences, focused on converting inulin into functional food fructooligosaccharides, establishing a yeast fermentation process for high-purity fructooligosaccharide production. This technology can produce fructooligosaccharides through fermentation at 40°C, substantially increasing yield.

In 2016, Fujian Shaxian County, relying on cooperation with the Energy College of Xiamen University, developed oxidation-separation reactions and mild biological enzymatic hydrolysis technology to extract and produce xylooligosaccharide products from abundant local bamboo resources and bamboo processing residues, achieving efficient and circular utilization of biomass resources.

In 2017, Glycobio (Suzhou) Biotechnology Co., Ltd., supported by the National Biochemical Engineering Technology Research Center (Beijing) of the Institute of Process Engineering, Chinese Academy of Sciences, established a 500-ton annual automated production line using chitin and shrimp/crab shells as raw materials through a proprietary green and clean production process, developing a new generation of chitosan oligosaccharide food additives, feed additives, and glycan-based plant vaccine products with clearly defined and controllable structures, leading international development of such products.

Compared with foreign-registered active components in carbohydrate biopesticides and biofertilizers, China' s most distinctive feature is that oligosaccharide-type products constitute the vast majority, developing a series of oligosaccharide biopesticides represented by amino oligosaccharins. In chitosan oligosaccharide production technology, the Dalian Institute of Chemical Physics, Chinese Academy of Sciences, has developed an efficient and green enzymatic hydrolysis-membrane separation process that ranks at a world-leading level. Systematic research on the mechanism of action and key application technologies of oligosaccharide biopesticides has led to the pioneering concept of "glycan-based plant vaccines" worldwide. Beyond traditional disease-inducing activity, new activities such as stress resistance and pesticide residue degradation have been discovered, expanding the application scope of oligosaccharide biopesticides.

In the polysaccharide biopesticide field, besides developing biopesticides such as chitin and glucan in parallel with international efforts, China has developed a series of biopesticides using lentinan as the active component based on domestic resource characteristics, expanding the R&D and application scope of polysaccharide biopesticides. For glucan, biopesticides using glucan oligosaccharides as active components have been developed, creating new glucan-based biopesticides.

In 2009, Shanghai Green Valley Pharmaceutical Factory accepted the transfer of research results on anti-Alzheimer' s disease drug GV-971 (mannose oligosaccharide diacid) from the Shanghai Institute of Materia Medica (GV-971 can cross the blood-brain barrier, inhibit A aggregation, promote A disaggregation, inhibit A neurotoxicity, and improve Alzheimer' s disease symptoms). Phase II clinical trials involving 255 patients with mild-to-moderate AD were completed in 2013, showing that 6-month GV-971 treatment was safe and well-tolerated, with an overall improvement rate of 92.77% in patients' cognitive dysfunction.

Currently, Phase III clinical trials have been initiated, with the potential to become the first carbohydrate drug for Alzheimer' s disease treatment.

6. Conclusion

As the glycoengineering industry continues to develop, it plays an increasingly important role in China' s food, healthcare, pharmaceutical, and food safety sectors. Functional sugars and carbohydrate-based drugs can effectively improve human health and are significant for enhancing quality of life, supporting related industries worth hundreds of billions of yuan. The glycoengineering industries of sugar alcohols, functional oligosaccharides, and rare sugars have entered a new era of rapid development, with enormous market demand and broad prospects for new carbohydrate feed additives both internationally and domestically. Carbohydrate-based drugs such as heparin, hyaluronic acid, carbohydrate vaccines, and glyco-adjuvants play irreplaceable roles in treating and preventing major diseases. The glycobiotechnology industry plays an important role in national economic and social development, representing a crucial force for leading future economic and social development with broad prospects.

The origin and development history of glycobiotechnology is relatively short, and the glycoengineering industry has only a twenty-year history internationally, but it has developed rapidly into an emerging industry applied in food, medicine, feed, and chemical industries, with a market scale reaching millions of tons, 25 commercialized varieties, nearly 100 developed varieties, and continuing to grow at 10% annually. Through nearly 30 years of unremitting efforts by domestic and international glycoscience researchers, the biological functions of glycan chains are being continuously revealed. Glycan chains are closely related to growth, development, and disease processes, triggering international competition in carbohydrate-based drug development that will undoubtedly drive glycoengineering research and industry development.

While China' s independent innovation capabilities and industrial standards in glycoengineering continue to strengthen, we should also recognize existing deficiencies: (1) Core production technologies for carbohydrate products are not yet mature. Although Chinese enterprises have accumulated some experience, many key enzymes in production still rely on imports. Future efforts should strengthen collaborative R&D between enterprises and research institutions to improve the quality of domestic enzyme products, such as systematically developing tool enzymes required for biological preparation of glycoengineering products and establishing specific glycosidase libraries for different glycan structures and glycosidic bond types. (2) Industry product standards are not well-established. Current bottlenecks in carbohydrate research include qualitative and quantitative analysis of glycan chains and structure-activity relationship elucidation, with some key technologies yet to be breakthrough. Meanwhile, China currently lacks unified glycoengineering product standards, resulting in uneven quality of some marketed glycoengineering products (especially functional oligosaccharides) and significant differences in product efficacy. The development of industry standards for glycan structure analysis and glycoengineering product quality control should be accelerated. (3) Existing resources are not fully exploited. China possesses vast forestry resources, crop waste, traditional Chinese medicine resources, and marine resources. How to fully tap these resources and truly develop high value-added products will be a key step in promoting innovative development of China' s functional sugar industry.

Contributing Experts: Zhuo Wang, Hongtao Liu, Heng Yin, Yuguang Du

Note: Figure translations are in progress. See original paper for figures.

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